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The Supply of Medical Radioisotopes

Interim Report of the OECD/NEA High-level Group on Security of Supply of Medical Radioisotopes

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NUCLEAR ENERGY AGENCY
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

FOREWORD

At the request of its member countries, the OECD Nuclear Energy Agency (NEA) has become involved in global efforts to ensure a reliable supply of Molybdenum-99 (^{99}Mo) and its decay product, Technetium-99m (^{99m}Tc), the most widely used medical radioisotope. The NEA established the High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) in April 2009. The main objective of the HLG-MR is to strengthen the reliability of ^{99}Mo and ^{99m}Tc supply in the short, medium and long term. In order to reach this objective, the group has been reviewing the ^{99}Mo supply chain, working to identify the key areas of vulnerability, the issues that need to be addressed and the mechanisms that could be used to help resolve them.

Throughout the first year of its two-year mandate, the HLG-MR has examined the major issues that affect the short-, medium- and long-term reliability of ^{99}Mo/^{99m}Tc supply. The collective efforts of HLG-MR members and nuclear medicine stakeholders have allowed for a comprehensive assessment of the key areas of vulnerability in the supply chain and an identification of the issues that need to be addressed. This report, along with the two studies undertaken by the NEA Secretariat, identify these issues and provide some initial discussion on the mechanisms that could be used to address those issues.

The work of the HLG-MR and nuclear medicine stakeholders has demonstrated the increased understanding and information sharing by all stakeholders of the complexities of the supply chain. There are various viewpoints, perspectives and stakeholders requirements that the supply chain needs to accommodate. Through the HLG-MR meetings and follow-up actions, significant progress has already been achieved on improving the supply situation through such actions as increasing communication, co-ordinating reactor schedules and increasing understanding of demand-management opportunities. The work also points to the need for continued action on the part of all stakeholders to address the issues.

In this report, the current situation of reactors and processing capacities and constraints are discussed. It also discusses work that has been done related to communicating the supply situation to downstream stakeholders, the need for assessing future demand, and the issues around transportation within the supply chain. The report also provides the HLG-MR members' view on the economic situation of the supply chain and describes a review of alternative ^{99}Mo/^{99m}Tc production technologies. The report also discusses findings related to a related supply shortage of Iodine-131. Finally, the report provides the next steps of the HLG-MR and the NEA Secretariat in their efforts to support the long-term reliability of ^{99}Mo/^{99m}Tc supply.

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INTRODUCTION

1.1 The issue

Molybdenum-99 (^{99}Mo) and its decay product, technetium-99m (^{99m}Tc), the most widely used medical radioisotope, are used in medical diagnostic imaging techniques which enable precise and accurate, early detection and management of diseases such as heart conditions and cancer, all in a non-invasive manner. The imaging can significantly impact medical decisions, for example, by providing predictive information about the likely success of alternative therapy options or whether or not there is a need for surgical intervention.

^{99m}Tc medical imaging techniques account for over 80% of all nuclear medicine procedures, representing over 30 million examinations worldwide every year. Disruptions in the supply chain of these medical isotopes – which have half lives of 66 hours (^{99}Mo) and 6 hours (^{99m}Tc) respectively and thus must be produced continually – can suspend important medical testing services.

Historically, five research reactors commissioned between 43 and 53 years ago produce 90 to 95% of the total global supply of ^{99}Mo. Given the age of these reactors, there are issues related to their reliability with unexpected shutdowns occurring more often. In fact, these isotopes have been in short supply a number of times over the last few years due to unexpected and/or extended shutdowns. Most recently the Canadian National Research Universal Reactor (NRU) was unexpectedly shutdown in May 2009 as a result of a leak in the reactor vessel and only returned to service in mid-August 2010.

The ages of the major producing reactors also raise issues related to reactor availability given the need for extended shutdowns for planned maintenance work and possibly for unplanned maintenance. For example, in 2010 both the High Flux Reactor in the Netherlands and the OSIRIS reactor in France were scheduled to be down for extended maintenance periods.

There is also the fact that some of these reactors are expected to reach their end of life in the next six years. The OSIRIS reactor is planning to be retired from service in 2015 and Canada has indicated that it stop production of ^{99}Mo from the NRU reactor by 2016.

In addition to issues related to the reactors, there are also potential limits to processing capacity. This capacity is needed to extract and purify the ^{99}Mo from the irradiated targets, making bulk ^{99}Mo for use in ^{99m}Tc generators for medical procedures. The limitation of processing capacity is especially evident in regards to the geographical location of these facilities; there would be difficult transport problems and loss of product from decay if irradiated targets were to be transported long distances.

These issues have resulted in ^{99}Mo/^{99m}Tc supply that is currently unreliable. Actions have to be taken by all stakeholders to ensure the long-term reliability of these important medical radioisotopes.

1.2 OECD/NEA involvement

At the request of the Government of Canada, the NEA hosted a workshop of international experts and stakeholders in January 2009 to identify the challenges faced in providing a reliable supply of ^{99m}Tc and ^{99}Mo and measures that should be taken to ensure this supply. Over 90 participants were in attendance, with representatives from governments, universities, reactor operators, processors, generator manufacturers and distributors, industry associations, the medical community, international organizations and regulators.

At the workshop, participants discussed a wide variety of issues including challenges to the management of existing capacities, regulatory impediments and demand side management. They identified the need to develop, deepen and share, as appropriate, contingency plans for future supply disruptions. They also focused on the longer term and on the need to engage health authorities to reduce uncertainties regarding long-term demand and the means by which to encourage more investment in production and greater redundancy in the system.

In addition, there was unanimous support for the establishment of a working group to carry forward the conclusions of the workshop and to identify the practical measures that should be taken.

1.3 Formation of the High-level Group on Medical Radioisotopes

Following up on the workshop, the NEA Steering Committee established the High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) in April 2009. This group is currently comprised of 22 experts from 13 countries, the European Commission and the International Atomic Energy Agency, and is being funded by its members through voluntary contributions. The group oversees and assists, where necessary, efforts of the international community to address the challenges of medical isotope supply reliability. The NEA Secretariat supports the group and brings its expertise to the issue. Annex 1 provides the members of the HLG-MR as of June 2010.

The main objective of the HLG-MR is to strengthen the reliability of ^{99}Mo/^{99m}Tc supply in the short, medium and long term. In order to reach this objective the group has been reviewing the ^{99}Mo supply chain, working to identify the key areas of vulnerability, the issues that need to be addressed and the mechanisms that could be used to address those issues. The HLG-MR recognises that governments have the ultimate responsibility for establishing an environment conducive to investment and also for regulations related to the ^{99}Mo supply chain.

The HLG-MR is aware that there are a number of other on-going forums related to medical isotope supply reliability and is ensuring that efforts are not duplicated. The NEA's goal in getting involved in this issue is to add value to the ongoing work and to support member countries. Bringing the international community together to discuss, share and learn, and applying NEA expertise on nuclear issues and economic studies, represent important contributions to the current global effort.

1.4 Meetings of the HLG-MR

Since its formation, the HLG-MR has held three meetings, along with a number of conference calls. A small but representative group of medical isotope stakeholders, including representatives of the nuclear regulation community, the medical isotope industry and the nuclear medicine community were invited to the meetings. This format provided a useful information and idea sharing opportunity, allowing the HLG-MR to obtain insights from industry and the medical community.

At the first meeting (17-18 June 2009, in Toronto, Canada) the Terms of Reference for the group (provided in Annex 2) and the first instalment of the HLG-MR rolling action plan (provided in Annex 3) were agreed upon. The plan included undertaking an economic analysis of the supply chain, increasing useful and regular communications to users about ^{99}Mo and ^{99m}Tc supply availability, developing protocols to inform stakeholders of unanticipated events and co-ordinating reactor schedules. The action plan also included assessing options to increase short-, medium- and long-term production. These options include demand side management (e.g. promoting efficient patient scheduling, using alternative procedures) and producing ^{99}Mo via alternative reactors or technologies. In terms of bringing new supply to market, the action plan included work to identify regulatory issues, especially those related to the transportation of ^{99}Mo and ^{99m}Tc, and measures to address these issues.

At the second meeting of the HLG-MR (14-15 December 2009, Issy-les-Moulineaux, France) participants welcomed the positive actions that had been taken up to that time, such as the progress on the economic study, the development of communication protocols and the co-ordination and communication of reactor schedules. The presentations and ensuing discussions highlighted the complexity of the issues affecting the reliable supply of medical radioisotopes, especially those related to the economics of the supply chain.

Participants agreed to a list of actions to further improve the management of the 2009-2010 shortage and to work toward increasing reliable supply – the second instalment of the rolling action plan (provided in Annex 4). This list included developing and implementing communication protocols, sharing guidelines with the global health community on the efficient use of available supplies of ^{99}Mo and ^{99m}Tc and examining opportunities for securing longer-term medical radioisotope supply.

Most recently, the HLG-MR held their third meeting (24-25 June 2010, Paris, France). At that meeting new actions to produce medical radioisotopes from the Argentina, Brazil and Russian Federation were discussed. As well, two NEA studies, undertaken for the HLG-MR by the NEA Secretariat, were presented: one on the economics of the ^{99}Mo/^{99m}Tc supply chain and one that examines a wide range of current and emerging ^{99}Mo/^{99m}Tc production technologies. Along with finishing these two studies, the third instalment of the rolling action plan included items related to enhancing supply, improving regulation and communication, optimising use, supporting nuclear non-proliferation and studying future demand. This action plan is provided in Chapter 10.

The next meeting will occur in January 2011 and will focus on policy options for ensuring a long-term reliable supply of ^{99}Mo and ^{99m}Tc.

This paper presents the findings of the HLG-MR work to date (as of August 2010), including the main issues identified that affect the reliable supply of ^{99}Mo and ^{99m}Tc. This publication is timely as the HLG-MR passed the mid-term point of its two-year mandate in June 2010.

The paper discusses the current situation of reactors and processing capacities and constraints. It also discusses work that has been done related to communicating the supply situation to downstream stakeholders, the need for assessing future demand, and the issues around transportation within the supply chain. The report also provides the HLG-MR members' view on the NEA Secretariat economic study on the supply chain and describes the work the Secretariat is undertaking on reviewing alternative ^{99}Mo/^{99m}Tc production technologies. The report also discusses findings related to a related supply shortage of Iodine-131. Finally, the report provides the next steps of the HLG-MR and the NEA Secretariat in their efforts to support the long-term reliability of ^{99}Mo/^{99m}Tc supply.

Chapter 2

REACTOR IRRADIATION CAPACITIES

2.1 Current situation

Historically, there were only 5 reactors that produced 90 to 95% of global ^{99}Mo supply: three in Europe (BR-2 in Belgium, HFR in the Netherlands and OSIRIS in France), one in Canada (NRU), and one in South Africa (SAFARI-1). All these reactors are over 43 years old. In the past, the Cintichem reactor in the United States, the FRJ-2 reactor in Germany, the NRX in Canada and the SILOE reactor in France also produced ^{99}Mo for the global supply chain. However, all of these reactors have been shut down: Cintichem in 1989, NRX in 1992, SILOE in 1997 and the FRJ-2 in 2006.

There are also the OPAL reactor in Australia and the RA-3 reactor in Argentina, which predominately produce for their local markets but have recently been exporting small quantities of ^{99}Mo (IAEA, 2010). The OPAL reactor has the potential to increase production substantially but is currently limited by the local processing capacity.

The newest additions to the ^{99}Mo global supply chain are the MARIA reactor in Poland, which started producing ^{99}Mo for global distribution in February 2010, and the LVR-15 reactor in the Czech Republic, which started producing ^{99}Mo for global distribution in May 2010. There are also various reactors around the world that produce small quantities of ^{99}Mo for domestic use. Table 1 on the next page provides further information on the major ^{99}Mo producing reactors.

As mentioned above, the five main reactors were commissioned between 43 and 53 years ago. As the reactors age there is the requirement for longer downtime periods between production cycles to repair or replace ageing parts or to undertake additional inspections to determine the effects of ageing on the reactor. This requirement follows the increased likelihood of failures, as many components are not observable or serviceable without extended maintenance shutdowns (AECL, 2009). During these extended downtimes, the reactor is not irradiating materials to produce any ^{99}Mo.

In the past, the supply impacts of the regular downtime periods would normally be smoothed out by other reactors. The duration of the required extended maintenance periods has, however, created the need for longer-term expanded production at other reactors, leading to logistical issues (including difficulty in balancing reactor operations with other research projects). In addition, these extended periods have become more frequent, leading to situations where more than one reactor is shut down at the same time. For example, in summer 2010 the HFR, the NRU and the OSIRIS reactor were all down for extended periods. As a result, the impacts of these extended periods are often no longer able to be smoothed out, greatly affecting the downstream component of the supply chain, especially the final user – the patient.

A consequence of ageing reactors that is even more important for the reliable supply of ^{99}Mo is the increased occurrences of unexpected shutdowns at producing reactors. Between 2000 and 2010, there have been six unexpected shutdowns related to reactor safety concerns (Ponsard, 2010). Most recently the NRU was shut down in May 2009 as a result of a leak in the reactor vessel and it was returned to service in mid-August 2010, after an extended outage that lasted more than a year. These unexpected shutdowns disrupt the supply chain, especially when they occur at one of the two major production reactors (HFR and NRU); it is impossible for the other reactors to these situations at very short notice by adding an additional production cycle or increasing production capacity.

Table 1: Major current ^{99}Mo producing reactors

Reactor name	Location	Annual operating days	Normal production per week[a]	Weekly % of world demand	Fuel/targets[b]	Date of first commissioning
BR-2	Belgium	140	5 200	25-65	HEU/HEU	1961
HFR	Netherlands	300	4 680	35-70	LEU/HEU	1961
LVR-15[d]	Czech Republic	–	>600	–	HEU[e]/HEU	1957
MARIA[d]	Poland	–	700-1 500	–	HEU/HEU	1974
NRU	Canada	300	4 680	35-70	LEU/HEU	1957
OPAL	Australia	290	1 000-1 500	–	LEU/LEU	2006
OSIRIS	France	180	1 200	10-20	LEU/HEU	1966
SAFARI-1	South Africa	305	2 500	10-30	LEU/HEU[g]	1965
RA-3	Argentina	230	240	<2	LEU/LEU	1967

a. Six-day curies end of processing (EOP).

b. Fuel elements and targets are classified as either Low Enriched Uranium (LEU), containing less than 20% of ^{235}U, or Highly Enriched Uranium (HEU),which contains greater than 20% ^{235}U (in some cases greater than 95%).

c. Does not account for increase in capacity since April 2010 with the installation of additional irradiation capacity. This increases BR-2 available capacity to approximately 7 800 6-day curies EOP; however it is not yet clear what “normal” production will be at the facility with this new capacity.

d. These reactors started production in 2010 so some data is not yet available.

e. The LVR-15 reactor uses fuel elements that are enriched to 36% ^{235}U.

f. The OPAL reactor started ^{99}Mo production in 2009 for domestic use but has not yet exported significant amounts.

g. SAFARI-1 is in the process of converting to using LEU targets (from targets with 45% ^{235}U) and expects to have completed conversion in 2010.

Not all these reactors have aged at the same pace given specific operating schedules and maintenance programs. Both the SAFARI-1 and BR-2 reactors expect to continue operations to 2020 and possibly beyond; the former partly as a result of its low usage between 1977 and 1993, and the latter as a result of a major refurbishment that occurred between 1995 and 1997. However, the OSIRIS reactor is planning to be retired from service in 2015, the Government of Canada has indicated that it will only seek to extend the NRU reactor license to produce ^{99}Mo to 2016, and the HFR reactor is expected to be shut down around 2018.

The implications of these ageing reactors for reliable ^{99}Mo supply create economic factors that need to be addressed. As will be discussed in Chapter 7 of this report [and in the NEA publication, The *Supply of Medical Radioisotopes: An Economic Study of the Molybdenum-99 Supply Chain* (NEA, 2010a), the current economic return on producing ^{99}Mo at the reactor is not sufficient to support the development of new infrastructure for the production of ^{99}Mo; a new multi-purpose research reactor has been estimated to cost more than EUR 400 million.

An additional challenge that will affect the reactor component of the supply chain is the move to replace targets using HEU with targets using LEU for security and non-proliferation reasons. As is noted Table 1, most of the major research reactors are currently using HEU targets to produce ^{99}Mo. Conversion to LEU targets for the production of ^{99}Mo has been agreed to by a number of governments. In fact one major producer (NTP) expects to have converted their reactor and processing facilities to use LEU targets in 2010 (from targets of approximately 45% ^{235}U). There are also two reactors (the OPAL reactor in Australia and the RA-3 reactor in Argentina) that already use LEU targets, currently producing principally for their local markets.

The main technical issue is the obvious fact that LEU targets contain less ^{235}U compared to the HEU targets currently being used. Since ^{99}Mo is a fission product of the ^{235}U in the targets irradiated in the reactor, there is an impact on the yield of product from a target with less ^{235}U. Two ways to compensate for this are to increase the density of total uranium in the targets or to increase the number of targets irradiated. While LEU targets have higher density that HEU ones, this is still a source of much current research, as is the development of new technologies and targets to increase yields. An increase in the number of targets irradiated may affect other missions within a research reactor or may require more irradiation positions within the reactor.

Without further density augmentations, an increase in costs per curie produced will occur, as there will be a need for some degree of additional irradiation and processing capacity to continue to produce the same quantity of ^{99}Mo globally, depending on the uranium density that can be achieved in the target. There may also be an increase in waste management costs (capital and operational) since, in general, more total uranium waste and liquid wastes will need to be managed. However, until final disposal strategies are implemented, it is difficult to quantify the cost increases. Reduced physical protection costs as a result of dealing with LEU instead of HEU may help to offset any potential cost increases of using LEU targets.

At this time there is not yet an established body of knowledge as to the comparative yield, waste management costs, development costs, capital requirements and the related economic impacts that would be experienced by a major ^{99}Mo producer wishing to undertake conversion. Preliminary experience and estimates have indicated that the impact of conversion on the cost of the final health procedure is expected to be quite small. However, even with the uncertainty on the costs of conversion, it is clear that the conversion to LEU targets is necessary but not currently supported financially by the market (NEA, 2010a).

An additional challenge facing the reactor component of the supply chain is related to the need for reserve capacity. There are two main reasons why this capacity is needed: 1) to account for operational realities of research reactors and the technical characteristics of ^{99}Mo (explained below); and 2) to serve as a back-up in the event of unscheduled outages. However, the need for and existence of reserve capacity raises some interesting economic challenges that will be discussed in Chapter 7 of this report.

With respect to the first reason, the key issues are the operational nature of research reactors, which also perform missions other than isotope production, and the extreme inefficiencies in stockpiling ^{99}Mo with its 66-hour half-life. Research reactors do not operate 100% of the time; they operate on the basis of cycles, with a number of days of operating and then a period where the reactor is shutdown for refueling, changing research project set-ups, regular maintenance, etc. In addition, some reactors do not operate the full year, depending on their research demands and available funding (Table 1 provides the approximate operating days of the main ^{99}Mo producing reactors). Other reactors need to be able to irradiate targets during these shutdown periods, especially for those of longer duration, to ensure a smooth supply of ^{99}Mo to the market.

With respect to the second reason, the key issue is the reliability of producing reactors. When a reactor is unexpectedly shut down as a result of a technical problem or a safety concern that requires an extended repair period, the remaining reactors would need to respond quickly to increase production of ^{99}Mo if the market supply is to be sustained at normal levels. Sustaining these levels is desired by the medical community so that patients can continue to have access to this medical nuclear imaging technique. This reliability issue has become the main reason or rationale for reserve capacity, particularly as the reactors age and the occurrence of unexpected or extended repair shutdowns increases. In parallel, the market demand for ^{99m}Tc has continued to increase.

As a result of the two issues above, if one were to merely add up the irradiation capacity at the producing reactors it should significantly exceed 100% of demand. However, at any one moment in time the producing capacity should, in a preferred scenario, be just sufficient to meet global distribution and demand.

If one were to ignore the 2009-2010 reactor outages for extended maintenance periods, the current producing capacity of reactors would exceed the current demand for ^{99}Mo. However, the recent supply shortage has drawn attention to the capacity of the ^{99}Mo/^{99m}Tc supply chain and the fact that there is a long-term supply issue looming. Figure 1 shows the supply situation out to 2025 based on the annual production of the current fleet of reactors and their expected final shutdown dates, compared to two demand scenarios (2 and 5% annual growth), based on historical growth patterns. (Chapter 5 discusses demand in more detail.) The figure shows that if the current suite of reactors were producing at normal levels, demand would exceed the normal supply of ^{99}Mo by 2013 in a situation of 5% growth and by 2017 in a situation of 2% growth. In addition, reactors can produce above their normal levels for limited time periods, when required. Assuming that reactors were able to produce at their maximum capacity[1] during all of their production periods and processing facilities were unconstrained, this supply shortage would be postponed until around 2019 for both the 5% and 2% growth scenarios. However, this latter scenario is not entirely realistic as the maximum production at the most reactors would require the forgoing of other activities in the reactor, such as important research projects, and assumes reactor and processor operating schedules that allows for full use of the available capacity.

Another consideration when looking at future supply and demand is whether there are limitations to processing irradiated targets from the reactors. Figure 2 builds on the last figure by adding in data related to limitations in regional processing capacity. This regional limitation can impact the ability of reactors to utilise their full ^{99}Mo production capacity, under normal and maximum operating conditions (this issue will be discussed in more depth in Chapter 3). With these regional processing limitations the dates when demand will exceed supply are advanced, occurring as early as 2012.

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[1] Based on information from reactors on past maximum production levels or potential maximum production.

Figure 1: Current supply *vs.* demand

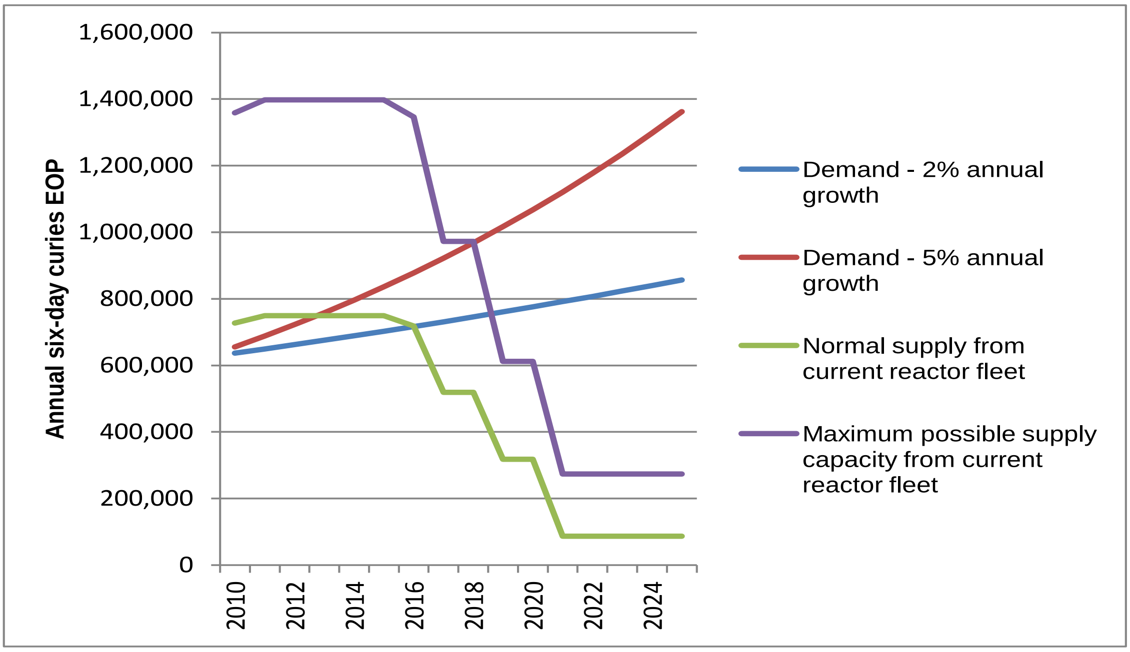
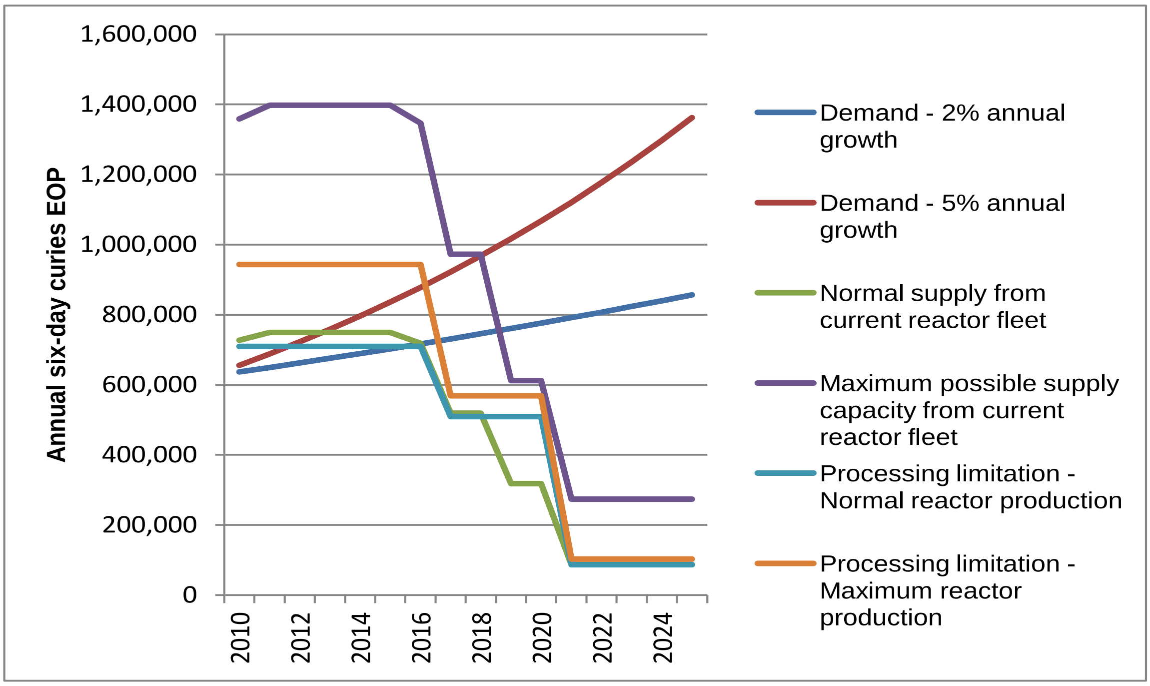


Figure 2: Current supply *vs.* demand with processing limitations



The 2009-2010 supply shortages highlighted reliability concerns of the current reactor fleet, but the looming reactor and processing capacity limitations create significant challenges for continued supply in the short, medium and long term. The ^{99}Mo supply chain requires new production infrastructure but there are some significant barriers to its development, as will be discussed in Chapter 7.

2.2 Reactor scheduling co-ordination

In order to ensure the best use of the suite of available reactors during the 2009-2010 shortage period, the HLG-MR sought to better understand the available capacity and the production schedules, with a goal to encourage co-ordination among reactor operators. Without co-ordination, each reactor operator would be determining their production schedule without the knowledge of the other capacity expected to be used. It was recognised that co-ordination would help to eliminate this uncertainty and ensure that the most beneficial production decisions are taken.

Following its first meeting, the HLG-MR asked the Association of Imaging Producers and Equipment Suppliers (AIPES) to work with its members to better co-ordinate reactor schedules in order to minimise the effects of the on-going and expected reactor outages. The goal was to be able to provide a schedule for the following 12 month period that would attempt to smooth out supply shortages and, where not possible, would provide advance notice to stakeholders to allow for better planning on their use of ^{99}Mo and ^{99m}Tc.

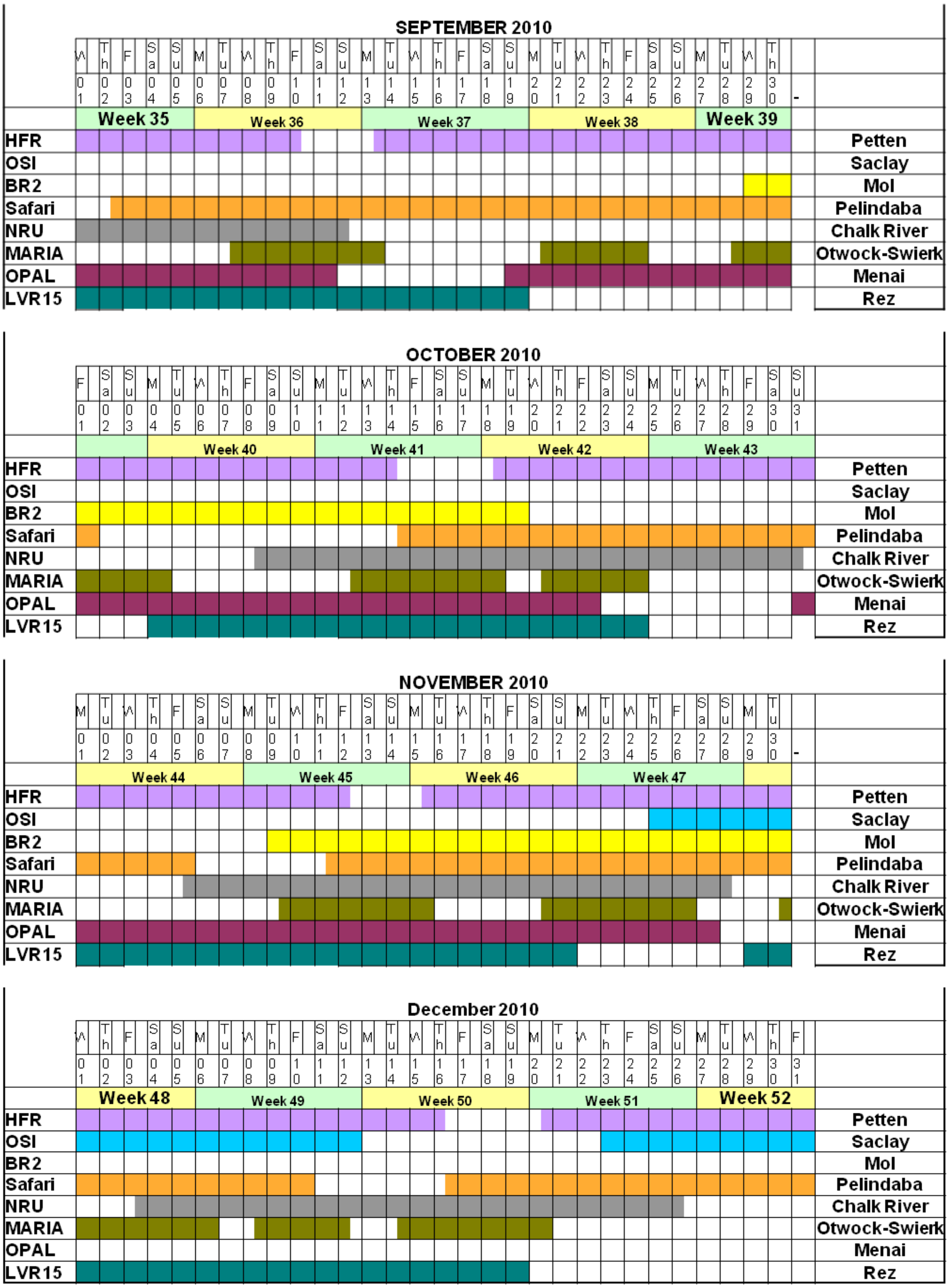
AIPES undertook intensive communication between all its members and relevant non-members on capacity, timing, output, maintenance schedules and incidents and worked on an on-going basis with members to co-ordinate operating periods of reactors on a global scale. AIPES members, who now include all of the major reactors operators and processors, participated in these co-ordination discussions on a voluntary basis.

The co-ordination efforts were not straightforward, given the difficulties in defining the exact periods and timing of certain repairs. During the co-ordination process, it was necessary for AIPES and its members to consider the number of production days of each reactor, the planned or contracted research activities at the reactors, other priority contractual industrial activities, commercial agreements, the financing capacity and the number of trained and certified staff at the reactors and processing facilities. In addition, co-ordination efforts recognised the priority of safety and the role of national safety authorities. Of course, reactors and processors required approval for any significant changes to operations and schedules by national nuclear regulatory authorities and at times related ministers.

Under these constraints, reactors, processors and AIPES were able to arrive at a schedule that recognised the necessary repair work and maintenance periods, but that was able to minimise the periods of time with very little supply coverage. Through these efforts, schedules were altered and changed to increase supply availability in 2010; BR-2 added an additional cycle and the OSIRIS altered the timing of their extended shutdown period. In addition, all operating reactors and processors increased their level of production. However, even with these efforts there were periods of significant shortages given that the NRU, one of the major reactor suppliers, was out of service from May 2009 until August 2010, and that the HFR, the other major reactor, was out of service from February to September 2010. These shortages would have been significantly worse if it wasn't for these co-ordination efforts. Figure 3 presents the results of these co-ordination efforts (as presented in June 2010).

Moving forward, these co-ordination efforts will continue to be required to minimise shortages during unexpected events. In addition, as more capacity is added in the future, co-ordination efforts will be important for the proper management of reserve capacity to avoid the potential for price depression. This depression would negatively affect the ability of reactors to support ^{99}Mo production. Co-ordination efforts will need to ensure that this reserve capacity is not used to service the market when it is not required (NEA, 2010a).

Figure 3: Reactor schedule



Source: Cabocel, 2010.

2.3 Potential new reactor-based ^{99}Mo production capacity

With the backdrop of the 2009-2010 shortage, ageing reactors and the impending longer-term shortage, a number of stakeholders are suggesting new projects to produce ^{99}Mo/^{99m}Tc. Many of these projects are reactor-based using existing research reactors that are currently not producing ^{99}Mo or new reactors that are at various stages of development. There are also proposed projects that are based on alternative technologies, such as irradiation in power reactors or using cyclotrons. Chapter 8 discusses work that the NEA Secretariat is undertaking to review these various technologies, including developing criteria that can be used to evaluate specific project proposals.

Some of the potential projects discussed in late 2009 have already become a reality. For example, in February 2010 Covidien and POLATOM announced that they were irradiating HEU targets at the MARIA reactor (Poland) for processing at Covidien's processing facility. In May 2010, IRE and Nuclear Research Institute of Rez announced that they were irradiating HEU targets at the LVR-15 reactor (Czech Republic) for processing at IRE's processing facility.

With these announced potential reactor projects, it appears that there are many opportunities for production that are under consideration or development. Table 2 presents the various projects with their potential annual production and estimated production starting dates. Plotting these projects independently and with current reactor capacity gives Figure 4 (including the shutdown of the various reactors of current fleet over the next decade, as presented in Figure 1). If all the capacities in Figure 4 were achieved, it would appear that there will be no concerns on supply as the potential projects will apparently be able to produce enough ^{99}Mo to meet growing demand.

Table 2: Potential reactor-based projects for ^{99}Mo production

REACTOR	Six-day ci EOP/yr	Six-day ci EOP/wk	Weeks/yr	Potential first year
PROJECTS WITH PROCESSING FACILITIES AS PART OF PROJECT				
ROSATOM*/**	52 000	1 000	52.0	2011
ROSATOM*/** – TOTAL	130 000	2 500	52.0	2012
Babcock and Wilcox	144 000	3 000	48.0	2014
China advanced RR***	25 710	1 000	25.7	2015
SAFARI-2	108 930	2 500	43.5	2018
PROJECTS REQUIRING ADDITIONAL PROCESSING FACILITIES****				
MURR**	156 000	3 000	52.0	2012
FRM-II**	102 860	3 000	34.25	2014
GE-Hitachi	144 000	3 000	48.0	2014
US – LEU target technology	144 000	3 000	48.0	2014
US – Accelerator technology	144 000	3 000	48.0	2014
Jules Horowitz***	108 000	3 000	36.0	2015
INR, Pitesti**	120 000	3 000	40.0	2015
PALLAS	266 390	6 215	42.85	2017
MYRRHA	178 290	5 200	34.25	2022

* Project includes three reactors, two of which would be used to produce ^{99}Mo in a continuous fashion, with the third being a back up.

** Research reactor already exists, but is not yet irradiating targets for ^{99}Mo production.

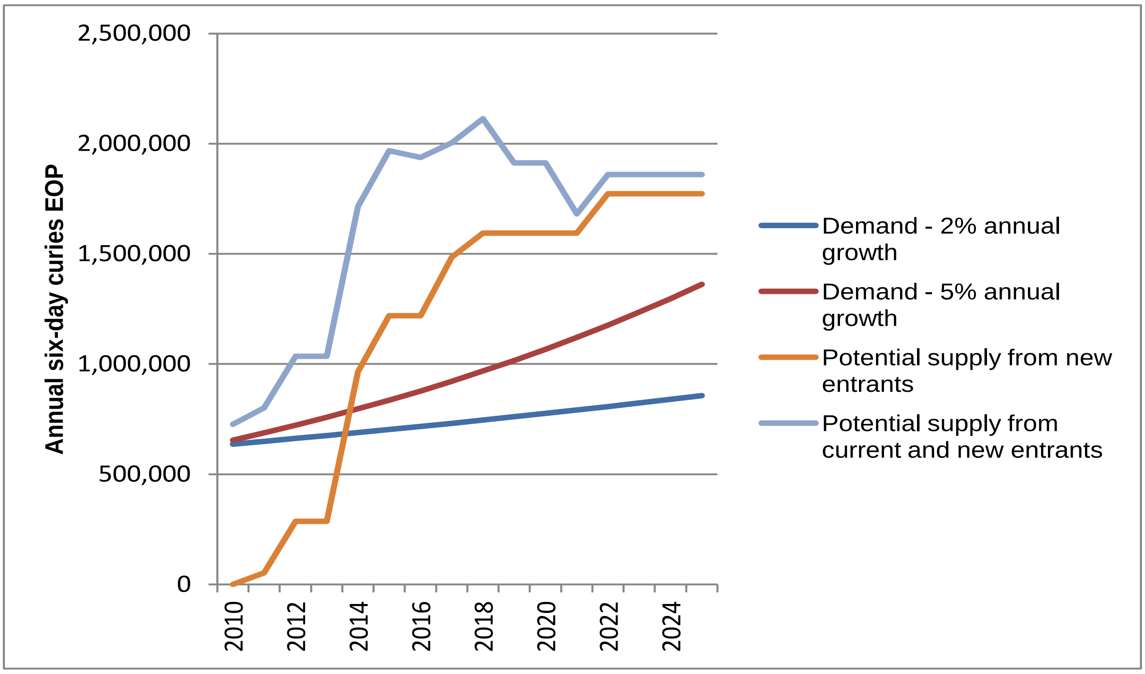
*** Under active construction.

**** Projects in Europe would face a processing capacity limitation, explained in more detail in Chapter 3.

However, this possible outlook assumes that all the projects go forward and that there are no other limiting factors that could affect the ability to get the product to market. For example, the values presented do not account for any regional processing constraints. These processing constraints are not included in the figure, as some of the projects include processing capacity and there is less information available on possible new processing capacity. However, as will be made clear in the next chapter, if there is no processing capacity in place, the new reactor capacity is not useful for increasing available ^{99}Mo supply. In addition, a number of the proposed projects rely on HEU targets; the planned conversion to LEU targets will have an impact on multiple aspects of the production and supply chain.

Another possible limitation in terms of the timing of these projects supplying ^{99}Mo/^{99m}Tc to the market is related to transportation and health regulatory approval. The transportation of the isotopes has to be approved by all relevant jurisdictions (discussed more in Chapter 6) and all new sources of ^{99}Mo have to be separately approved by health authorities in various markets. These regulatory approvals take a certain period of time and could result in supply reaching the market at a later time period than presented in Figures 4 and 5. However, it is clear that these regulatory review processes are important and necessary.

Figure 4: Potential supply *vs.* demand



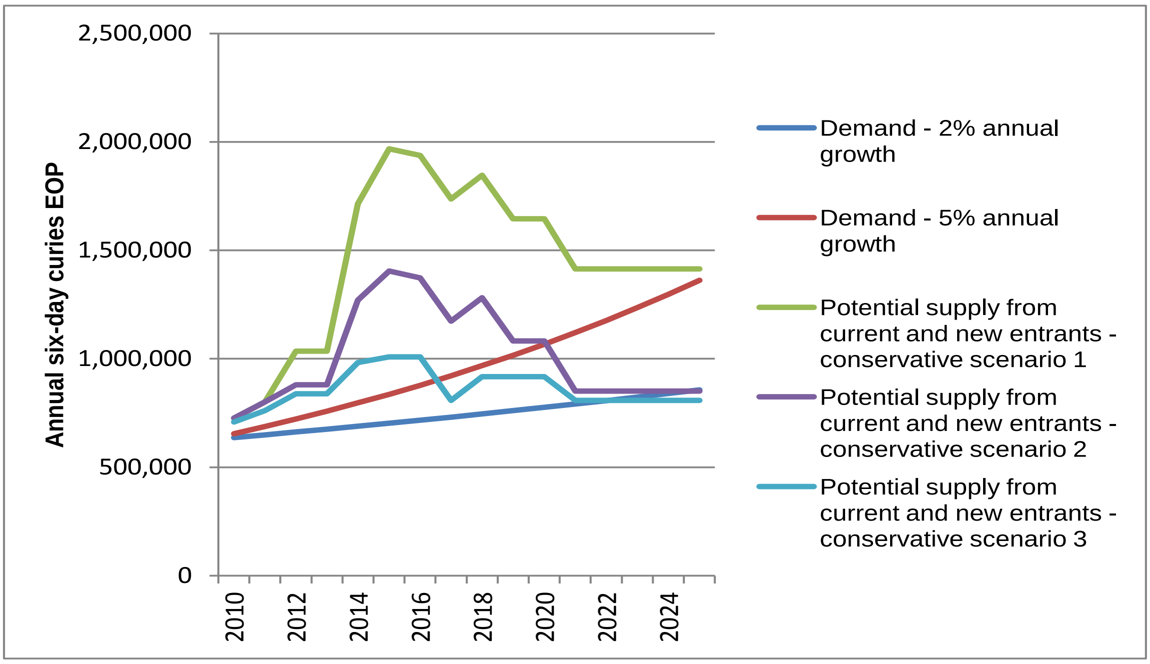
There are still economic and technical hurdles related to the production of ^{99}Mo via these alternative projects to overcome. If these projects materialise without any changes to the fundamental economic structure of the supply chain, these projects could have a negative effect on the current supply chain economics being faced by reactor operators. Depending on the remuneration provided to reactor operators and the related agreement with the host government, new projects could potentially be detrimental to the long-term economic sustainability of LEU-based ^{99}Mo provision. If any new project follows the historical remuneration model, paying only for the direct costs of irradiation with no or partial payment for the reactor investment costs directly related to ^{99}Mo production, it will be the responsibility of the host government to cover those costs not included. As a result, the continued production of ^{99}Mo under this situation will depend on the agreement with the host government (NEA, 2010a).

Overall, while these projects could help the supply situation if they proceed (and the processing capacity is available), the economic impacts on the market of the mix of commercial-based and government-supported projects could be detrimental to longer-term supply availability. If the pricing structure perpetuates the current economic situation whereby there are not sufficient financial incentives for new ^{99}Mo production infrastructure without government assistance, the commercial-based projects may not be able to come to fruition.

Recognising the challenges in ensuring a project moves forward, Figure 5 presents three scenarios where some of the projects identified in Table 2 and included in Figure 4 do not proceed and therefore do not produce ^{99}Mo for the global market. These three scenarios should not be construed as a prediction, forecast or expectation of which projects will proceed; they are entirely meant as illustrative of situations where some of projects do not proceed. The "conservative scenario 1" includes all the current producers and the potential projects listed in Table 2 with the exception of the PALLAS and MYRRHA projects. This scenario was created to show the impact if the two largest potential projects do not proceed as planned. The "conservative scenario 2" is more restrictive, only including the current producers and the following potential projects: ROSATOM, FRM-II, 2 of the United States projects (at 144 000 annual six-day curies EOP), Jules Horowitz, China Advanced RR and the SAFARI-2.

The "conservative scenario 3" is even further restrictive, eliminating any projects that do not have processing facilities available. For the scenario all the current producers are included; however, there is an annual processing capacity limitation in Europe (explained further in Chapter 3) meaning that for the European projects, the amount that can be processed in any given year is included as the capacity. In terms of the potential projects identified in Table 2, the projects that currently are included in this scenario are: ROSATOM, Babcock and Wilcox, China Advanced RR and SAFARI-2, as well as any production from the potential European project for which there is processing capacity available.

Figure 5: Potential supply *vs.* demand based on conservative scenarios



It is clear that the very positive medium-term outlook that was presented in Figure 4 becomes less optimistic when the potential that some projects do not proceed or do not produce ^{99}Mo is taken into consideration. Even if some of the projects proceed, there could be a shortage in the coming decades as the current fleet stops producing ^{99}Mo and demand continues to increase. When the limitations on processing capacity are included in these possible future scenarios, the outlook becomes even less secure, with possible supply shortages starting as early as 2017 under the 5% growth scenario.

These potential projects provide the future source of reactor-based ^{99}Mo production and are currently seen to be necessary to ensure the reliable supply of ^{99}Mo/^{99m}Tc in the medium to long term. The fact that the projects are being discussed should not be a reason for decision-makers to assume that they will proceed. Even with projects where the research reactor is currently under construction or already in existence, decision-makers should not be lulled into a situation of complacency to the infrastructure needs for medium- to long-term supply reliability. In all these cases, on-going concentrated efforts on the part of governments and industry players are required to ensure that the projects do, in fact, come into existence and have the infrastructure to irradiate targets for the production of ^{99}Mo.

Chapter 3

PROCESSING CAPACITIES AND CONSTRAINTS

3.1 Introduction

During the 2009-2010 shortage of medical radioisotopes, there has been much attention focused on the current and future capacity of reactors to produce these isotopes. What is often missed in the examination of the situation is whether there are limitations to processing facilities that either create or perpetuate unreliability in the supply chain.

The processing component of the supply chain generally involves the transportation of the irradiated targets from the reactor to the processing facility, the extraction of ^{99}Mo from the target and the purification of the ^{99}Mo. At these facilities the irradiated targets are dissolved through chemical processes and the ^{99}Mo is separated and then purified through additional chemical processes to produce raw ^{99}Mo. This very complex and demanding process is required to obtain the bulk ^{99}Mo and to ensure that it meets or exceeds the minimum levels of impurities that are required for its medical application. Once purified, the bulk ^{99}Mo is transported around the world from the processing facility to generator manufacturing facilities, predominately on roads and commercial airlines, to be prepared for application in medical procedures.

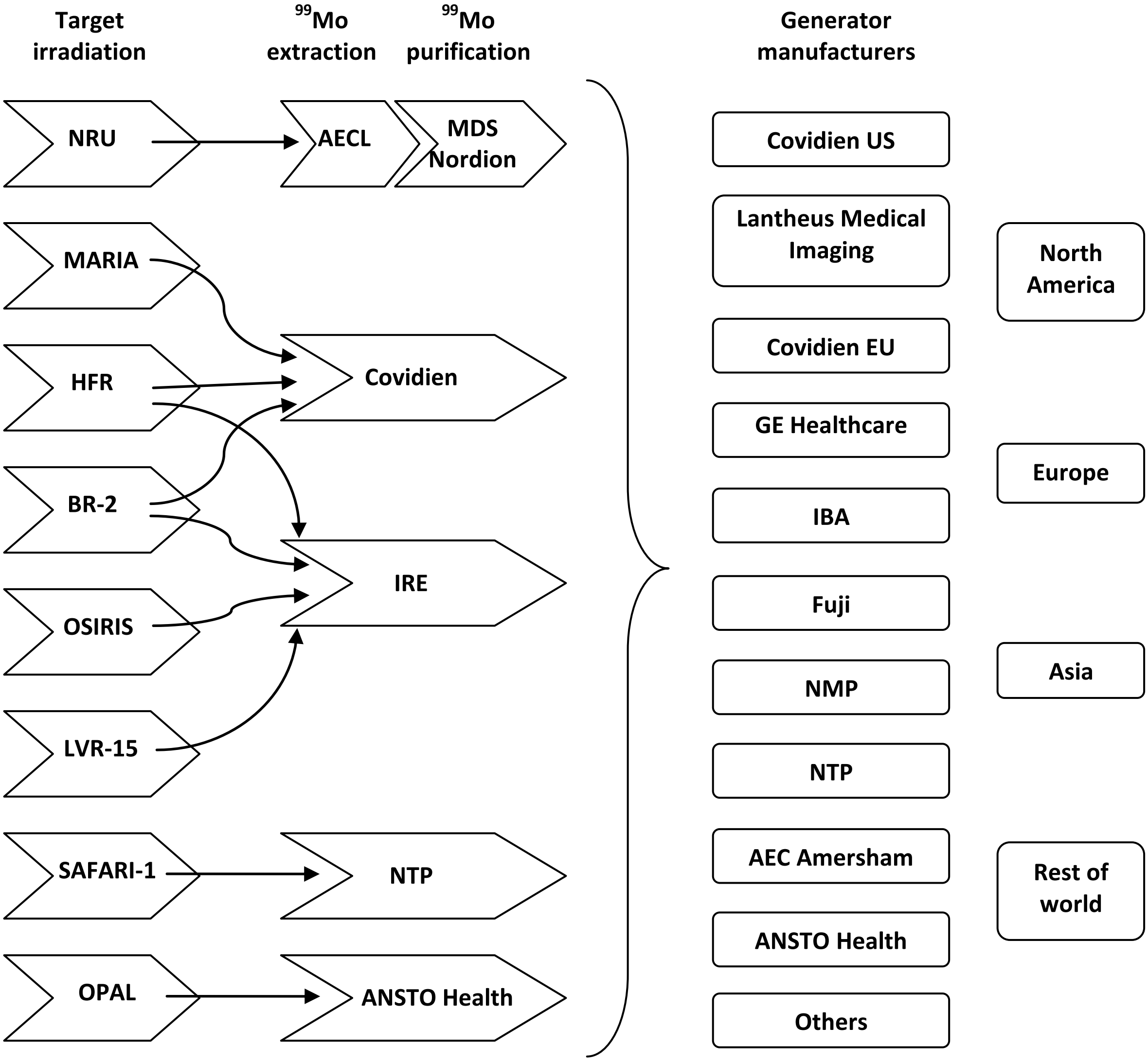
The important question is: are the processing facilities capable of meeting the world’s demand or are there constraints that could reduce the reliability of the supply of ^{99}Mo even if there is sufficient reactor capacity?

3.2 Current situation

There are four main processors that supply the global market: MDS Nordion (Canada); Covidien (The Netherlands); The Institute for RadioElements (IRE, Belgium); and NTP Radioisotopes (South Africa). In addition, ANSTO (Australia) and CNEA (Argentina) currently produce bulk ^{99}Mo for their domestic markets and expect to be or are exporting smaller amounts. The unique situation in Canada must be pointed out here; AECL irradiates the targets and also does the initial extraction of the ^{99}Mo from the irradiated target. This extracted ^{99}Mo is then shipped to MDS Nordion for purification. Figure 6 provides an overview of the full supply chain.

Prior to the NRU shutdown, MDS Nordion supplied approximately 40% of the world market; Covidien, 29%; NTP, 18%; IRE, 12%; and ANSTO about 1% (Vanderhofstadt, 2009). After the shutdown of the NRU, MDS Nordion’s supply was not available and the other processors stepped in to partially fill the gap. Although estimates vary on actual percentages, it is safe to say that Covidien, NTP and IRE have all increased their market share, albeit of a smaller total supply.

Figure 6: ^{99}Mo supply chain major participants and distribution channels
(as of June 2010)



This supply chain is becoming much more complicated as generator manufacturers are diversifying their sources of bulk ^{99}Mo and therefore most processors are supplying multiple generator manufacturers. The "other" box in Figure 6 is to indicate that most of the producers sell bulk ^{99}Mo to other smaller generator manufacturers that supply their local markets (such as in Brazil, China, Israel, Poland, Turkey, etc.).

If one were to only look globally at the available capacity of the processing facilities, it would appear that there were no concerns related to the processing capacity. Table 3 provides the available processing capacity and one project that is currently under development. Table 4 provides two demand scenarios in line with historical growth (based on 2 and 5% global growth in demand). From these two tables, it is clear that the available *global* capacity greatly exceeds current world demand for ^{99}Mo and will continue to exceed capacity for more than a decade even with a continuous increase in demand. However, based on the 5% growth scenario, processing capacity will not be sufficient by 2021.

Table 3: Processing capacity

Processing facility	Location	Processing capacity six-day curies EOP/wk[1]
ANSTO	Australia	> 1 000
Covidien	Netherlands	> 3 500
CNEA Ezeiza Atomic Centre	Argentina	>600
IRE	Belgium	> 3 000
MDS Nordion	Canada	> 7 200[a]
NTP	South Africa	> 3 000
NTP – In development	South Africa	2 625[b]
Total		>21 425[a]

1. A common unit measure used in the industry is the six-day curie, defined as the radioactivity of ^{99}Mo six days after the end of processing component of the supply chain (EOP).

Source: Based on information from Vanderhofstadt, 2010, with modifications:

a. adjusted from Vanderhofstadt, 2010, based on MDS Nordion's ability to process AECL production, that can reach a maximum of 60% of global demand or 7 200 six-day curies EOP per week;

b. the capacity is currently meant to serve as back-up and not to be used immediately for production. Capacity value is estimated by NEA and represents a modification from Vanderhofstadt, 2010.

Table 4: Demand scenarios for ^{99}Mo

Demand growth (%)	2010	2013	2015	2017	2020	2025
2	12 240	12 990	13 515	14 060	14 920	16 475
5	12 600	14 585	16 080	17 730	20 525	26 195

However, this global capacity overview does not recognise the complexities of the ^{99}Mo supply chain and the implications of these complexities creating capacity limitations at the regional level, affecting the ability to supply the global market. There are a number of factors that reduce the effective processing capacity, including regional limitations, differences between target designs in use, potential processing failures and the potential impacts of the conversion to LEU targets. These issues can exacerbate global shortages and are discussed in the remainder of this chapter.

3.3 Concerns on processing

3.3.1 Location requirements

One of the key limitations to processing capacity is the location requirements of processing facilities – they should be located close to the reactor. Irradiated targets have to be shipped to the processing facility in secure containers that weigh approximately four tonnes. These containers can only be transported at reasonable costs and under current regulations via road transportation. In order to minimise the decay of the ^{99}Mo that would occur during transportation, the processor should be located as close to the reactor as possible. Recognising the time required for transportation, 1 000 km (on land) was considered to be the maximum acceptable distance for transporting irradiated targets from the reactor to the processing facility (with much shorter distances being preferred).

Transportation via roads is required, as air transportation would not be cost effective and would require dedicated cargo airplanes. In addition, there are no containers that are widely licensed for transporting irradiated targets via air and it is expected that it would be a challenge to license such containers. Currently there is no air transportation of irradiated targets for the production of ^{99}Mo.

In terms of limitations, if the processing facility was further away than 1 000 km, the decay of the ^{99}Mo during transportation time would create a meaningful loss of product. This would result in an overproduction of material, resulting in an increase in radioactive waste volumes and increased waste management costs, increased use of valuable reactor fuel and an increase in safety risks as more radioactive material is required to be handled and transported than would otherwise be necessary.

In addition, the further away that processing facilities are located from reactors, the more complicated the transportation logistics and regulatory requirements. For example, crossing multiple jurisdictions requires approval from all the jurisdictions that are transited. There is also an increased risk of delays (regulatory delays, etc.).

However, the benefits of a processing facility being located close to the reactor must be balanced with the benefits of locating further away but being better positioned to obtain irradiation services from multiple reactors. This latter situation would allow the supply chain to minimise impacts of a failure at one reactor and increase supply reliability.

As a result of these issues, transportation is a significant barrier to flexibility, limiting possibilities for locating processors and for using reactors that could produce ^{99}Mo.

3.3.2 Current regional limitations

As noted in Section 3.2, *globally* there is sufficient processing capacity. However, there are limitations when one compares the reactor capacity and the corresponding processing capacity that can be used to process irradiated targets from those reactors. For example, the total peak reactor ^{99}Mo production capacity in Europe is greater than 18 000 six-day curies EOP per week, while the processing capacity is around 6 500 six-day curies EOP per week. In addition, when either the BR-2 or HFR reactor is operating alone and irradiating their full capacity of targets, each reactor alone will more than occupy the full processing capacity of Europe.

Of course, not all the reactors operate at the same time, nor do they all operate all year round. Theoretically, Europe’s reactors could produce up to 583 000 six-day curies EOP annually. However, processing capacity in Europe is only sufficient to manage about 338 000 six-day curies EOP annually. It is clear from these numbers that processing, more than reactor capacity, is a limiting factor in Europe.

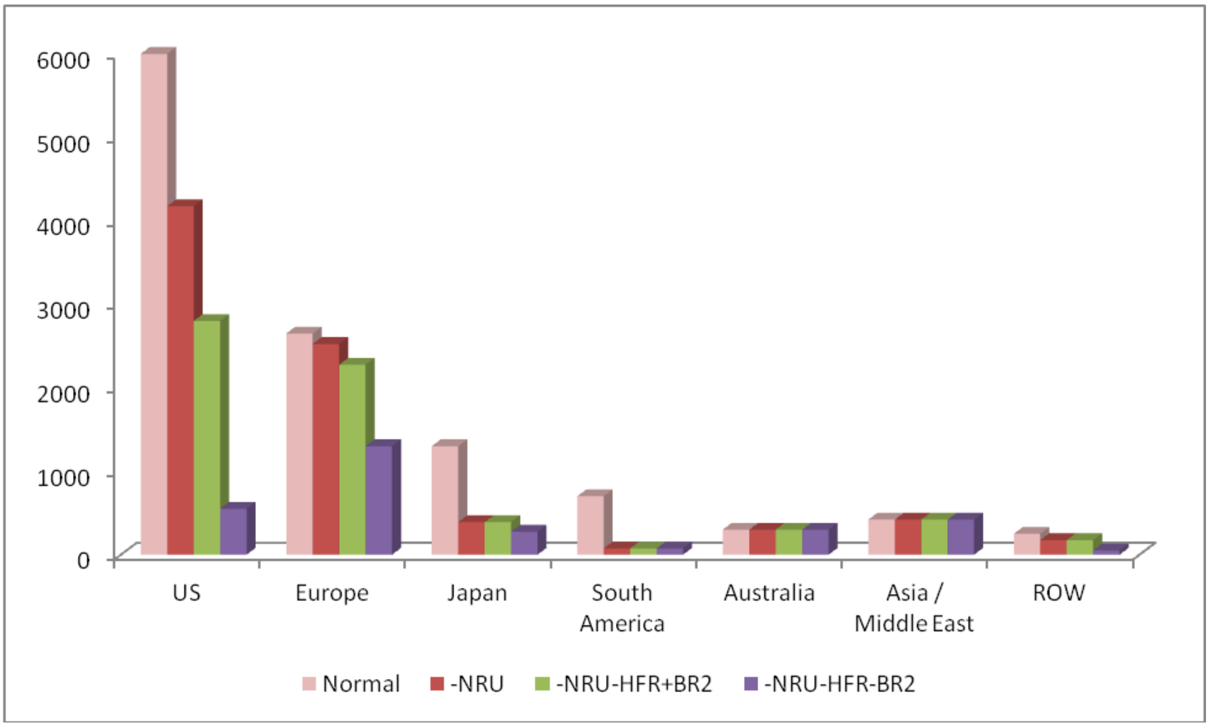
This situation is the same in Australia, where ANSTO’s OPAL reactor could theoretically produce half of the world’s demand of ^{99}Mo when operating (about 6 000 six-day curies EOP per week) but the limiting factor is its processing facility, which has the capacity to handle a maximum of 1 500 six-day curies EOP per week. In addition, there are some regions where there are no processing facilities for ^{99}Mo, such as in Japan, the United States and in some parts of South America.

The current processing capacity in those regions where processing exists is sufficient to supply demand *in those regions*. For example, European processing capacity is around 6 500 six-day curies EOP per week and demand in Europe is about 2 600 six-day curies EOP per week. However, these processing facilities are also important for supplying the broader global market.

This regional processing capacity limitation is important to consider when discussing possible new reactor supply; it is not useful to have reactors that can supply ^{99}Mo if there is not sufficient capacity to process it. This limitation is especially important when there are problems with reactor availability. The ideal situation when one reactor is down for extended maintenance (either planned or unplanned) is for another reactor or reactors to step in and irradiate additional targets to fill in the supply gap. However, regional processing capacity limitations reduce the ability of reactors to increase production to fill in the supply gap. For example, during the ^{99}Mo supply shortages of the later part of 2009 and early 2010 European reactors were not operating at full capacity because there was not enough processing capacity to handle the full reactor potential. Some European reactor operators indicated that during some of the shortage period, they were only running at 50 to 60% of theoretical capacity because their customers (the processors) were not able to process any additional irradiation services. This restricted level of production meant that the global market remained 20 to 30% under supplied.

For those regions with no processers, this regional capacity limitation can translate to a larger impact during a disruption of the supply chain (e.g. when a reactor is down for extended repair). Figure 7 shows the expected impact on various world regions when one or more of the major irradiating reactors are not able to contribute to the global supply chain. As can be seen, those regions without their own reactor and processing capacity are the hardest hit during a reactor outage.

Figure 7: Supply availability impacts of reactor unavailability



Source: Vanderhofstadt, 2009

Another concern is that the lack of processing capacity in some regions can limit the possibility to produce ^{99}Mo from regional reactors. This has been a limiting factor for some short-term ^{99}Mo production proposals in the United States, where there was a reactor that could potentially produce ^{99}Mo but no processing facility. This means that supply for these regions must continue to be transported from other regions, with the corresponding safety and security risks faced by long-distance transportation, as well as greater decay of the product.

This lack of regional processing capacity and the possible impacts is becoming a larger issue as the growth in nuclear medicine imaging techniques is expected to be most significant in those countries where the techniques are currently not widely used and ^{99}Mo is not currently produced (e.g. Brazil, China and India).

3.3.3 Risk of processing capacity failure

Processing plants are less susceptible to long downtime. However, there is the possibility that the processor can face an unexpected shutdown, as occurred with the incident from August to November 2008 at the IRE facility. In such a case, processing capacity to fill the gap would have to come from another processor as the entire facility would be closed. Alternatively, there could be a situation where one production line of hot cells becomes unavailable due to some mechanical failure. In this case, if there is redundant capacity within the facility (a second line of hot cells) this capacity could continue to be used.

In a situation where there is a single reactor serving a single processor or where the regional reactor supply is greater than the remaining processing capacity, an outage at the processing facility would create a significant disturbance in the ability to supply ^{99}Mo. If the regional network is supported by processors that use different target designs, an outage at one of the processors may not be able to be compensated for by the other processor. This results in a supply chain with weak supply reliability.

3.3.4 Impact of LEU conversion on processing capacity

As discussed in the chapter on reactor capacity, conversion to LEU targets for the production of ^{99}Mo has been agreed to by most governments for security and non-proliferation reasons. As noted in that section, in order to produce the same amount of ^{99}Mo with LEU there may need to be a significant increase in the ^{235}U density in the targets or an increase in the number of targets irradiated.

In the cases where the density cannot be increased sufficiently to offset the lower ^{235}U content, there will be impacts resulting from increased target irradiation and processing to maintain the same amount of final production in a given period of time. For the processor, this will mean some degree of:

- Increase in processing facility capacity (such as additional hot cells) and staff and processing activity.

- Regulatory approval to process additional targets.

- Increase in waste volumes and possibly additional waste management infrastructure.

Where the density can be increased to levels that do not result in the need for increasing the number of targets irradiated, there will not be a need for additional production infrastructure. The industry is working towards this outcome. However, even with denser plate targets there will be an increase in waste volumes. If, however, the proposed new foil targets were developed to a stage where they could be used commercially, this could lead to lower liquid waste volumes.

If these issues cannot be resolved, there could be an effective reduction in processing capacity in some regions until additional capacity can be developed and regulatory approvals received to process additional targets. Any required increase in processing capacity or activity to produce the same amount of ^{99}Mo would result in an increase in cost per six-day curie produced. However, reduced physical protection costs as a result of dealing with LEU instead of HEU may help to offset any potential cost increases of using LEU targets.

The industry is currently working to increase the density of the targets, including determining any possible changes required to the process and the processing facility. The barrier to be overcome is that the use of LEU targets has been demonstrated for smaller scale production (i.e. at the OPAL, RA-3, and BATAN (Indonesia) reactors) but not yet for large scale production. Some industry participants have indicated this as a significant challenge, indicating that scaling up production is not a straightforward process and may require a reconfiguration of the current process; however, this view is not universally shared, with other participants being more positive on the possibility to scale up production. Current major reactors and processors have indicated that they are dedicated to working through the issues.

One dilemma will be how to set up LEU irradiation in tandem with HEU production to ensure a continuous, reliable supply of ^{99}Mo to the global supply chain and to ensure continued revenue for processors and reactor operators. This may require additional investment in capacity. NTP has been able to undertake the LEU conversion process without stopping production given that they had sufficient hot cells available.

The NTP experience has revealed interesting information on the impacts on yield from their conversion from HEU (45% of ^{235}U) to LEU targets. They used LEU targets with a density 85% greater than the HEU targets and therefore only saw a decrease in yield per target in the range of 10 to 15% (Ball, 2010).

As noted in Chapter 2, at this time there is not yet an established body of knowledge as to the comparative yield, waste management costs, development costs, capital requirements and the related economic impacts that would be observed for a major ^{99}Mo producer using targets of higher enrichment (greater than 95% ^{235}U) wishing to undertake conversion. However, even with the uncertainty on the costs of conversion, it is clear that the conversion to LEU targets is necessary but not currently financially supported by the market (NEA, 2010a).

3.4 Barriers to the development of processing facilities

3.4.1 Costs

The market is characterised by significant barriers to entry. Extracting and processing the ^{99}Mo is a very capital intensive process, with a new large processing facility anticipated to cost about USD 200 million (NEA, 2010a). This is a significant investment to be made for an industry where there is uncertainty around reliability of irradiation services and a revenue stream that does not currently support the economic sustainability of the industry.

Historical prices have not been sufficient to support the development of significant new investment in some cases (NEA, 2010a). For example, one reason why larger processing facilities in Australia have not been developed is because the historical prices for bulk ^{99}Mo have not been high enough to justify the construction of a larger facility.

This cost barrier is exacerbated by the uncertainty in the current supply chain, which can greatly affect the expected return on investment. For example, if the major supplying reactor to the processing facility gets shut down for an extended period, the processing facility is making no revenue unless they find an alternative source for target irradiation or bulk ^{99}Mo from another supplier to continue to support their clients.

In addition, the necessary conversion to using LEU targets creates uncertainty on the final cost of production (and hence profits) that is expected for a major ^{99}Mo producer. Conversion will likely have some effect on the payback of investments in the processing capacity, possibly creating higher costs per unit of production.

3.4.2 Complex process

In addition to cost barriers, there are knowledge barriers to the development and use of additional processing capacity. Processing of ^{99}Mo is a knowledge-intensive procedure, with each processor having their method for extracting and purifying the ^{99}Mo and managing the waste developed through the process. Given its complexity, it has sometimes been described as an art, not a science.

The knowledge capacity is even more important as regulations and consumer expectations on the quality of the bulk ^{99}Mo are becoming more demanding in some countries. In some cases, radiochemicals are being tested for impurities at radiopharmacy levels even though the product is bulk ^{99}Mo and not the final radiopharmaceutical product. These increased demands on purity levels increase the value of the knowledge and skill of the processing company and its employees.

As well, given that bulk ^{99}Mo is transported around the globe and has a short half-life, there is important logistics knowledge that can make a difference between a successful processor and an unsuccessful one. A key addition of value at the processor component of the supply chain is the handling of the complicated logistics to get the bulk ^{99}Mo to generator manufacturers in as short a time as possible; for every hour of shipment approximately 1% of the remaining ^{99}Mo is lost due to decay.

The knowledge required to extract, process and then deliver bulk ^{99}Mo is therefore essential to being able to reliably participate in the supply chain. However, this knowledge is well protected as it provides a competitive advantage.

3.4.3 Waste issues

As with the operation of reactors, there is a concern among national governments and citizens that processing facilities in their country are producing waste that must be dealt with domestically, while the ^{99}Mo produced is being exported at prices that do not necessarily cover the long-term waste management costs. The developers of new processing capacity first have to be able to convince regulators and the public that ^{99}Mo processing is important and the waste can be managed in a responsible and economic manner. In addition, some current processing facilities are being faced with limitations to their current waste management facilities. These current limitations are also relevant when discussing LEU conversion as there may be additional waste volume to manage.

3.5 Conclusions

Global processing capacity is sufficient for at least the next decade but regionally there are immediate and longer-term concerns. The challenges related to regional processing capacity raise issues for the long-term reliability of the supply chain, having an impact on the ability of the industry to respond to such events as unplanned outages and meeting future demand growth. Reserve reactor capacity cannot effectively be used if the product cannot be processed and delivered to the global market. The location of reserve reactor capacity also imposes limits upon where additional processing capacity is located and vice versa.

Given the issues presented here, the ^{99}Mo supply chain could consider:

- Taking into account regional processing capacity limitations when examining possibilities for investments to ensure a correlation between reactor and processing capacity. A better geographical spread of reactor and/or processing capacity over different continents, including for emerging markets, would strengthen reliability in those countries currently greatly affected.

- Working toward a pricing structure that would ensure sustainability in processing capacity, including new investment, where required.

- Collaborating on LEU conversion efforts, including on target design and processing, with a goal of developing a common target design (or at least a common approach to new target approval) that can be used and processed by all supply chain participants. Realising this goal would increase the availability of reliable reserve capacity. This may raise some commercial confidentiality issues that would have to be recognised and worked through.

These issues need to be addressed with a goal of finding a path forward to ensure reliable and sufficient processing capacity.

Chapter 4

COMMUNICATION PROTOCOLS

Following the first HLG-MR meeting, the HLG-MR asked the AIPES to work with the industry to encourage the adoption of best practices related to communicating supply concerns to the health community. The AIPES agreed to undertake this task and developed communication protocols for the industry to follow in the event of unexpected shutdowns. These protocols have been adopted by the industry and integrated into individual company procedures as of January 2010.

For an event that does not affect the supply of ^{99}Mo and only has a local effect, the reactor operator would communicate with regulatory authorities and undertake internal communication as required. This protocol is demonstrated in Figure 8.

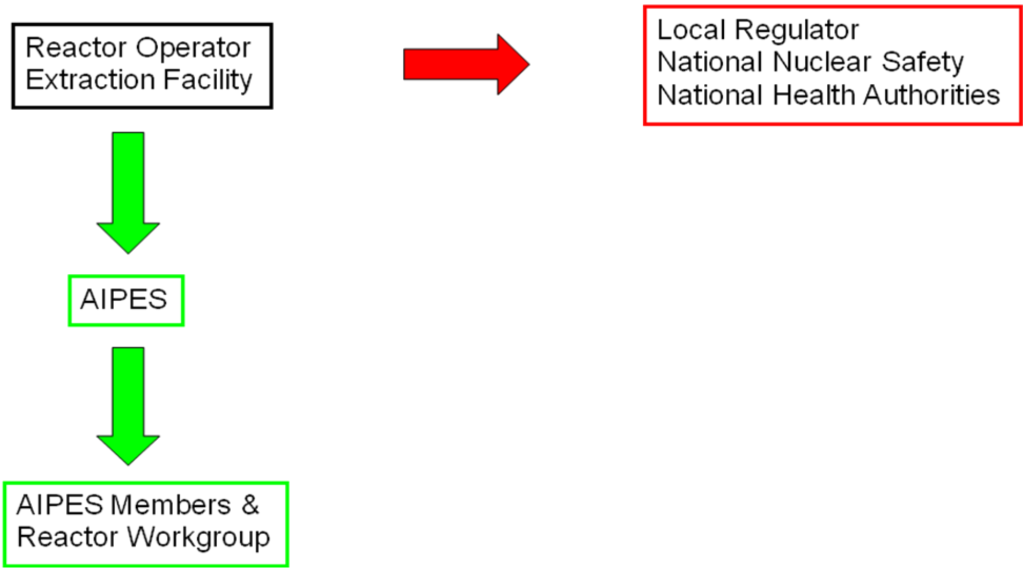
Figure 8: Event requiring local communication

Source: Gheeraert, 2010.

In the case of an event that affects the maintenance schedule of the reactor, but does not have an immediate impact on the supply of ^{99}Mo, the reactor operator would communicate with regulatory authorities, utilise internal communication and work with AIPES. This last step would involve working with the AIPES members and the Reactor Workgroup to share information about the event and its impact and to update the maintenance schedule. This protocol is demonstrated in Figure 9.

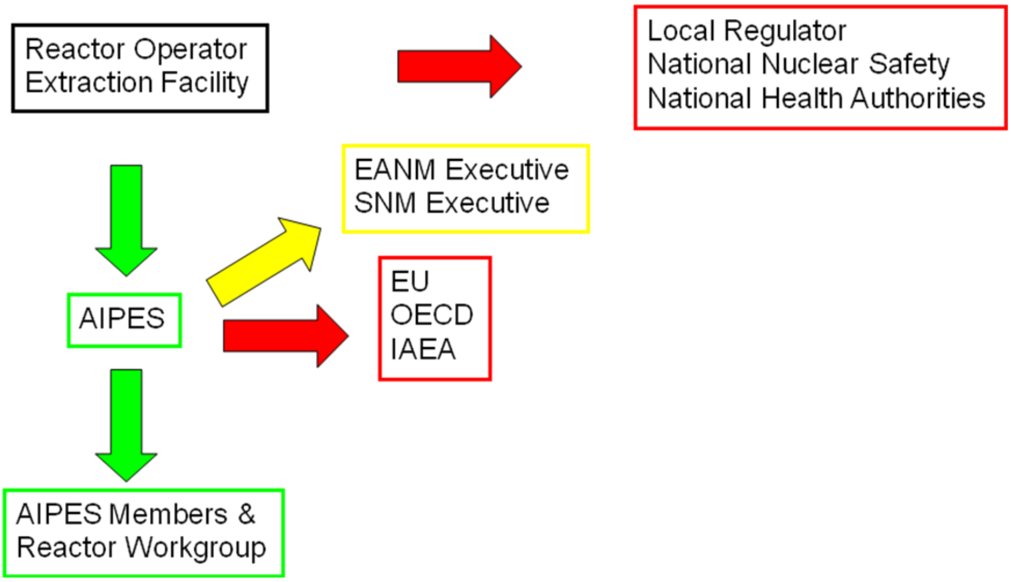
In the case of a more serious event, where attention and/or support is required from local and/or international authorities, the reactor operator would follow the steps outlined in the last protocol and AIPES would work with the nuclear medicine community and international organisations to address the impact of the event. Specifically, the AIPES would contact the executives of the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine (SNM), as well as officials from the European Union, the OECD/NEA and the International Atomic Energy Agency (IAEA). The AIPES would provide a warning to these bodies of any possible future difficulties in ^{99}Mo supply arising from the event and any support required by these bodies. It would also share on-going information with these international bodies to ensure proper communication about the event and its impacts. This protocol is demonstrated by Figure 10 below.

Figure 9: Event requiring reactor workgroup communication



Source: Gheeraert, 2010.

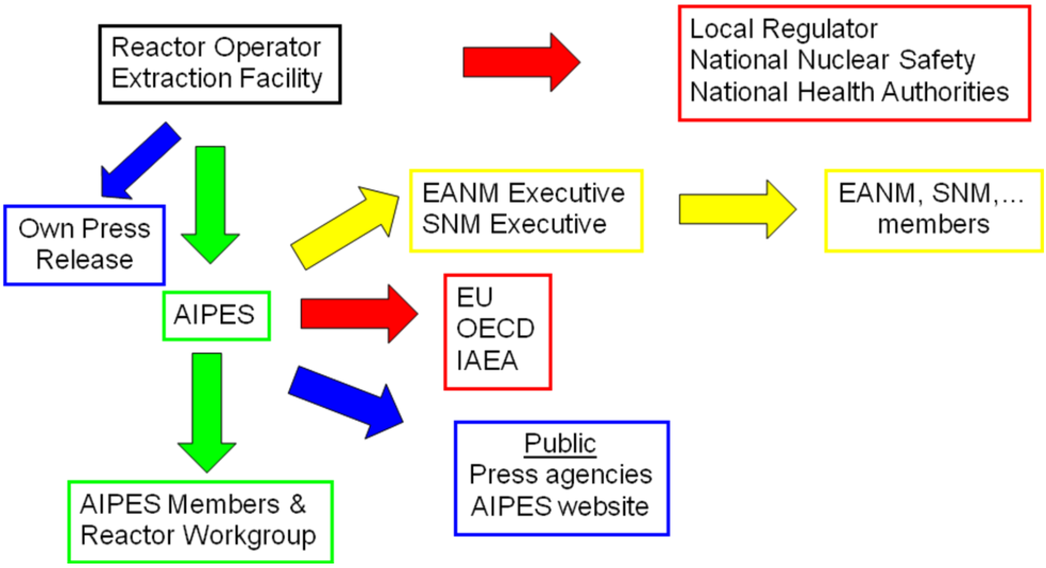
Figure 10: Event requiring stakeholder communication



Source: Gheeraert, 2010.

If a more serious incident occurs, one that would affect the supply of ^{99}Mo/^{99m}Tc in the near future, the reactor operator and AIPES would follow the steps outlined for less serious incidents, as well as also communicating with the broader nuclear medicine community and the general public. This broader communication would take the form of reactor operators and AIPES releasing their own press releases and the executives of the EANM and the SNM informing their members. This information would provide details on the event, a warning to the public on the expected impacts of the event, and ongoing information on the evolution of the incident and its ramifications. This protocol is demonstrated in Figure 11 below.

Figure 11: Event requiring general public communication



Source: Gheeraert, 2010.

These protocols have been tested since June 2009 by AIPES members and experience has indicated that they have worked well.

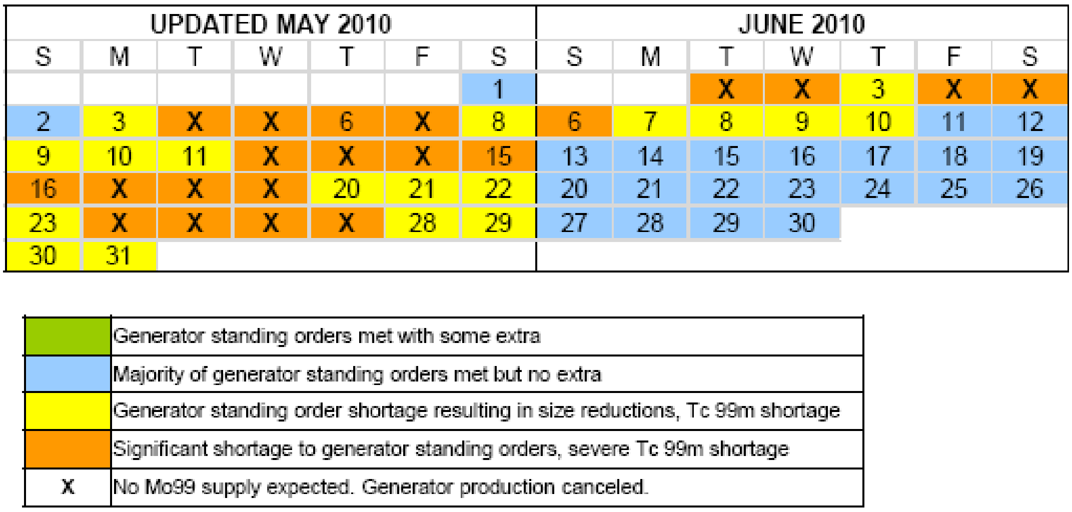
In addition to communication protocols for unexpected outage events, the HLG-MR requested that the industry provide better communication to the health community on expected available ^{99}Mo/^{99m}Tc supply. The industry associations indicated that the global nature of the supply chain and its related product decay made it difficult to provide a definitive prediction on available supply to the end customer. As a result, they concluded that it was the role of the individual generator manufacturers and distributors to inform their customers of their supply situation and any possible shortages.

The HLG-MR called on generator manufacturers to provide clients in the health community with projected supply levels for extended future periods (such as 90 days out) in its second rolling action plan. Being aware that supply availability can change on short notice, it was understood that these supply projections could be updated and refined through regular, ongoing dialogue with clients.

At the second meeting of the HLG-MR, the efforts by the industry to increase communication during the 2009-2010 shortage period were recognised by the nuclear medicine community, although it was also acknowledged that information was not consistent among suppliers or between regions. The HLG-MR also recognised that the industry had made efforts to improve communication with end users and was looking to the industry to voluntarily “standardise” its communication.

Figure 12 below provides an example of a future projection, provided by Covidien on their website (taken on 1 June 2010) and distributed to end users via a letter. Other generator manufacturers provide similar types of projections and communications to their customers. This example provides a colour-coded projection on available Covidien generator supply, indicating those days where no generators are expected to be delivered. This communication projection model was replicated further down the supply chain by Cardinal Health, a major radiopharmacy in the United States (http://nps.cardinal.com/nps/supplychaininfo/index.asp).

Figure 12: Example of available ^{99}Mo supply communication



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						🟦 1			🟧 X	🟧 X	🟨 3	🟧 X	🟧 X
🟦 2	🟨 3	🟧 X	🟧 X	🟧 6	🟧 X	🟨 8	🟧 6	🟨 7	🟨 8	🟨 9	🟨 10	🟦 11	🟦 12
🟨 9	🟨 10	🟨 11	🟧 X	🟧 X	🟧 X	🟧 15	🟦 13	🟦 14	🟦 15	🟦 16	🟦 17	🟦 18	🟦 19
🟧 16	🟧 X	🟧 X	🟧 X	🟨 20	🟨 21	🟨 22	🟦 20	🟦 21	🟦 22	🟦 23	🟦 24	🟦 25	🟦 26
🟨 23	🟧 X	🟧 X	🟧 X	🟧 X	🟨 28	🟨 29	🟦 27	🟦 28	🟦 29	🟦 30			
🟨 30	🟨 31												

🟩	Generator standing orders met with some extra
🟦	Majority of generator standing orders met but no extra
🟨	Generator standing order shortage resulting in size reductions, Tc 99m shortage
🟧	Significant shortage to generator standing orders, severe Tc 99m shortage
X	No Mo99 supply expected. Generator production canceled.

Source: Covidien, 2010.

Communication efforts across the entire supply chain have improved drastically during the 2009-2010 shortage period. Co-ordination efforts and the related communication on the part of AIPES, reactor operators and processors (as discussed in Chapter 2), communication protocols for unexpected outages and ongoing supply updates to end users have resulted in a more transparent supply chain. These efforts have provided for a greater understanding within the full supply chain (including end users) of the available supply and allowed for all members of the supply chain to make efforts to reduce the impact of the supply shortages. This information has, for example, enabled medical practitioners to take steps to manage their demand for ^{99m}Tc procedures, maximising the use of the available supply. Without these communication efforts, the 2009-2010 shortage would have had a much larger negative impact on the health system.

Chapter 5

DEMAND FOR MOLYBDENUM-99/TECHNETIUM-99M

5.1 Value of understanding demand

In Chapter 2, demand growth for ^{99}Mo was presented as 2% to 5%, based on past growth. These scenarios were used for illustrative purposes and were based on general historic trends. However, there are many uncertainties as to what the demand forecast should actually be, given the 2009-2010 shortage and the substantial changes throughout the entire supply chain that occurred. There are also other external factors that are at play that could affect demand.

The HLG-MR recognises that understanding the future demand is essential when discussing the need for new ^{99}Mo production infrastructure, especially given the required level of investment. Decision makers need to have information to allow them to assess whether or not the investment will be used in the future, at least for a period long enough to make the investment worthwhile.

Most recent studies on the future demand for ^{99}Mo and the related nuclear medical testing are based on information and views from before the 2009-2010 shortage. With the shortage, there have been a number of factors in play that could serve to reduce the future demand, such as increased demand management practices, using improved software in order to reduce the amount of ^{99m}Tc in procedures, better logistic and product management in order to reduce product-decay losses and growth of alternative imaging techniques, among other issues. Many of these have occurred without a decrease in clinical availability of tests and are, therefore, not likely to be reversed. At the same time, there are historical growth patterns, ageing populations and the potential for increased use in emerging economies that could serve to drive the demand upward. As a result of these factors, there is currently a degree of uncertainty in the industry as to the future of ^{99}Mo/^{99m}Tc, with some supply chain participants expecting continued or increasing growth, while others predict growth to a saturation point then levelling off, and others predict a decrease in demand.

As a result of this uncertainty, the HLG-MR has set a goal to better understand future demand for ^{99}Mo/^{99m}Tc and/or related nuclear medicine procedures that take into account the recent changes, where relevant. It should be noted that this is different than understanding the future demand for *reactor-produced* ^{99}Mo, which would ask questions related to alternative technologies for producing ^{99}Mo. Although the HLG-MR is not specifically asking about this demand, it is considering the other possible technologies to produce ^{99}Mo. This issue is discussed further in Chapter 8.

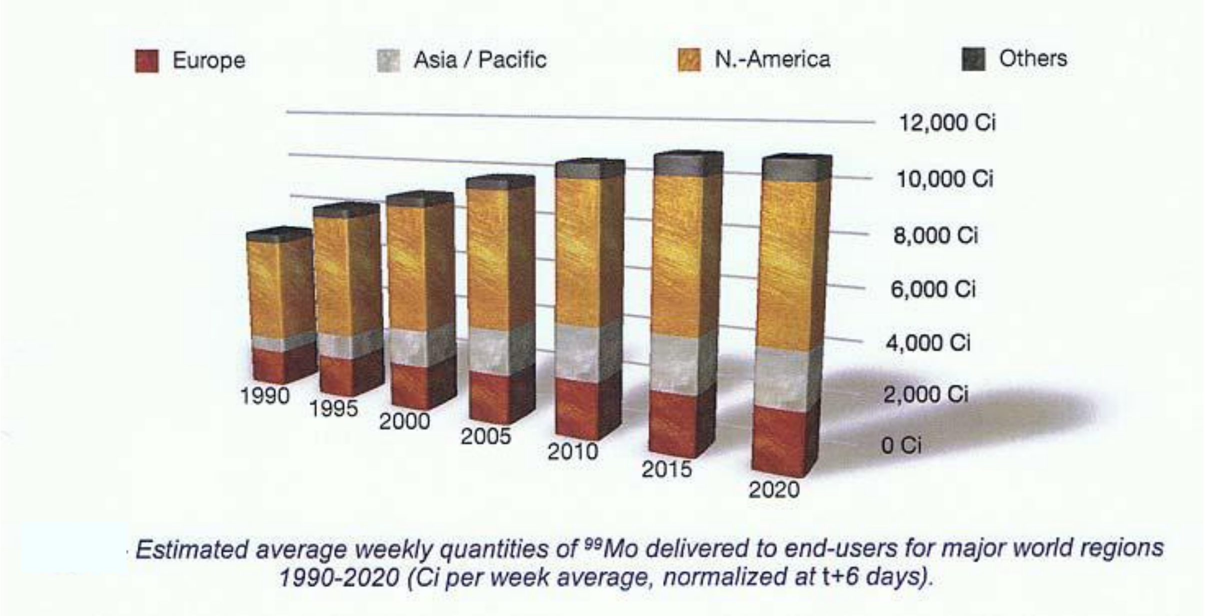
5.2 Current demand estimates

There have been a few studies in the recent years that include a discussion on the global future demand for ^{99}Mo/^{99m}Tc; however these outlooks rarely went out to 2020 or beyond. This time frame is relevant when discussing new investments, as the development of a new reactor can take longer than eight years. This section will discuss the findings of two studies that look out to this time period (these studies can be accessed through the NEA medical radioisotope website, www.nea.fr/med-radio).

In November 2008, the AIPES released its *Report on Molybdenum 99 Production for Nuclear Medicine 2010-2020.* The Report provided forecasts of future demand for ^{99}Mo and acknowledged that these forecasts could be overestimated given the supply shortages that were being seen in the industry. These estimates were based upon expert opinion of interviewees and not the result of detailed surveys. The Report indicated that:

- ^{99m}Tc will remain a major radionuclide for nuclear medicine at least for the next 20 years.
- The strong growth experienced since the early 1970s is not expected to continue from 2010 onward. A forecasted annual growth rate of 1%-2% indicates that the previous period of fast development will be now followed by consolidation (see Figure 13).
- This growth rate could become higher in case of fast growth of SPECT/CT systems or lower if a substitution in favour of PET radionuclides or other imaging technologies takes place on a large scale.

Figure 13: AIPES 2008 forecast



Source: AIPES, 2008.

The Report indicated that there was the potential for technology substitution, stemming from an unreliable supply and some negative public attitudes towards nuclear reactors resulting in a shift towards *non-reactor* radionuclides for both imaging and therapy purposes. The report noted that previously the common view among practitioners was that the growth of alternative modalities (such as PET, magnetic resonance imaging, ultrasonic echography and others) would add a layer of diagnostic, therapeutic or pain palliation technologies but would not *replace* "conventional" nuclear medicine procedures. However, it pointed out that supply shortages could change perspectives, resulting in the medical community seeing these modalities as *substitutes* for the conventional nuclear medicine procedures.

The study indicated that such issues warranted more detailed investigation, as they could significantly adjust the current forecasts.

In December 2008, a study was released on behalf of the Ministry of VROM (Dutch Ministry of Housing, Spatial Planning and the Environment) by the Technopolis Group, entitled *Radioisotopes in Medicine: Foresight of the use of reactor isotopes until 2025* (Technopolis Group, 2008). This study, based on a survey of Dutch experts, indicated that:

- The total number of nuclear medicine scans will show a significant increase in the future.
- It is unlikely that technetium-based imaging will be replaced by other technologies in the medium term (till 2015), with the use of ^{99m}Tc remaining constant until it may slightly decrease (<10%) in the period from 2015-2025.
- The current accelerated development of PET is anticipated to continue, causing a relative decline in the use of reactor isotopes. However, due to the low costs and relative simplicity of SPECT and planar nuclear imaging, these technologies will continue to exist and, in absolute terms, will be used just as much.
- The relative share of SPECT modalities probably remains unchanged in the future, but the single SPECT will be replaced in time by SPECT/CT and later on by SPECT/MRI (not available yet).
- A number of experts also indicate that to date, no imaging modality has ever been replaced.
- The demand for radiopharmaceuticals that are produced in nuclear reactors will continue to exist till 2025.

These studies recognise that the expectation is that there will be a long-term demand for ^{99m}Tc, but the degree of growth is up for discussion. In addition, in discussions with ^{99}Mo/^{99m}Tc supply chain participants there was a great deal of uncertainty expressed as to the general direction and magnitude of the future demand, with some stakeholders questioning whether there will be a demand for ^{99}Mo by 2020.

5.3 Uncertainty on future demand

There are a number of factors that continue to support assessments of increasing growth in the market. For example, ageing populations and increasing obesity levels and the increase in related ailments in some developed countries could result in increased demand for nuclear medicine imaging, including ^{99m}Tc procedures. In addition, there is significant potential for growth in emerging economies as additional wealth leads to better health care supported by increased nuclear medical imaging.

However, the 2009-2010 shortage has led to a number of changes in the delivery and use of ^{99}Mo and ^{99m}Tc that may have a lasting impact on the demand for these medical radioisotopes. In addition, there have been discussions of other potential changes that could further impact the future demand, such as new software that reduce ^{99m}Tc dose requirements. On top of the changes from the shortage, there are other external factors in play that could impact demand, such as reimbursement rate levels.

In the past there have been some practices that have led to the potential overproduction of ^{99}Mo, given an economic structure that resulted in underpricing of ^{99}Mo (NEA, 2010a). In some cases, this has resulted in a supply chain that has not used the produced ^{99}Mo in the most efficient manner, allowing for significant product decay to occur in the supply chain. With the 2009-2010 shortage, many supply chain participants have worked to improve their processes and logistical arrangements to minimise product loss. For example, generator manufacturers have been altering production schedules to prepare and ship product as soon as possible once the bulk ^{99}Mo has been received.

In terms of radiopharmacy preparation practices, there have been some preparation and delivery practices that may be suboptimal because of the historical economic structure. For example, hospitals may receive a generator and not elute in a manner that maximises the use of the ^{99m}Tc produced. In some cases, patient doses were prepared a number of hours in advance, requiring additional ^{99m}Tc to be eluted to account for the decay of the product, instead of eluting the ^{99m}Tc closer to the time of the actual procedure. These practices were normal and accepted as the time as they sought to minimise other input costs (e.g. labour) and provide regular scheduling to medical practitioners and patients. With proper pricing (see NEA, 2010a), the optimality of these practices could be established. Regardless of the assessment, it is clear that some of these practices have evolved during the recent shortages.

These potentially suboptimal practices along the full supply chain have resulted in the need to irradiate more targets, produce more bulk ^{99}Mo and transport more radioactive material than necessary. This overproduction also resulted in related radioactive waste management requirements. In addition, the need to handle more radioactive material than necessary could be contrary to the ALARA (as low as reasonably achievable) principle. Under this principle, radiation exposure must be as low as reasonably achievable, economic and social factors being taken into account.

Radiopharmacies, hospitals and physicians have been changing these historic practices during the recent shortage period to deal with a reduced supply. For example, Covidien has created its “Tc-99m Conservation Program” that encourages more thoughtful unit dose ordering practices by its customers to maximise the availability of ^{99m}Tc. According to Covidien, this Program has freed up enough ^{99m}Tc to serve about 10% more patients each day (Haynes, 2009).

In addition, some hospitals have reduced their ^{99m}Tc orders during the shortage and have instituted practices to use the available supply more efficiently. For example, many hospitals have altered the scheduling of their scans to periods when ^{99}Mo is available and to maximise the use of that available ^{99}Mo, including on weekends and evenings. In addition, some are finding ways to reduce ^{99m}Tc doses when possible. Some hospitals do not expect to return to their full previous order quantities even when more supply becomes available (Urbain, 2010).

To support these efforts, a number of medical organisations and governments have developed guidelines for the health community on efficient use of available ^{99}Mo/^{99m}Tc supplies during a substantial or extended medical isotope shortage. For example, the SNM and the Government of Canada have separately published guidelines, which are available on the NEA medical radioisotopes website (www.nea.fr/med-radio). The communication efforts undertaken by the supply chain discussed earlier in this report have contributed to the effectiveness of these demand management actions as practitioners are able to plan around expected future available supply.

It must be recognised that some of the demand management actions have been reported to have a detrimental effect on staff morale in some cases, as work schedules are irregular and there is added stress. These negative effects will likely affect the acceptability of adopting some of the demand management actions on a permanent basis during times of normal supply availability.

In addition to demand management actions, there are a number of advances in studies, software and technology that indicate possible significant reductions in the use of ^{99m}Tc from current practices. For example, a study was undertaken that found that for SPECT myocardial perfusion imaging study of a patient, the at-rest component is unnecessary if the results of the patient’s stress SPECT are normal; the impact is a reduction of the ^{99m}Tc required by as much as 61% for those patients (Miller, 2010). In addition, there are a number of software applications and technologies that are being developed and promoted by the industry that reportedly would reduce the amount of ^{99m}Tc needed per patient scan (Ultraspect, 2009; Spectrum Dynamics, 2010). As well, computer algorithms have been developed and piloted to help determine the appropriateness of using SPECT procedures for patients, based on Appropriate Use Criteria. In the pilot, SPECT testing was deemed to be inappropriate on about 15% of the sample body, who had all received SPECT testing (Dalton, 2009). These advances, if widely adopted, could result in reduced demand for ^{99}Mo and reduce radiation exposure to patients and medical practitioners, respecting the ALARA principle discussed above.

As well, there are some external factors at play that could impact the future growth of ^{99}Mo. One of these factors is the development and growth of alternative imaging modalities and isotopes that could potentially serve to replace or reduce the demand for ^{99m}Tc, especially given the recent supply concerns. There are also activities going on related to changing reimbursement rates and government concern on overuse that could have an impact on future demand for ^{99}Mo/^{99m}Tc.

In terms of alternative modalities and isotopes, as indicated in the previous section, there are other modalities (such as PET, magnetic resonance imaging, ultrasonic echography and others) that in some cases could replace SPECT testing based on ^{99m}Tc. For example, there are cases where hospitals are replacing ^{99m}Tc testing with Thallium-201 for cardiac studies or looking to use PET scans for bone imaging (such as using 18-F Sodium Fluoride) and using myocardial perfusion PET imaging agents. The interest in other modalities is increasing, with PET growing at 20% per year (World Nuclear News, 2010) and many hospitals and companies setting up cyclotrons to increase access to PET isotopes. Of course, there are many cases where there are currently not any clear substitutes for ^{99m}Tc based SPECT imaging tests and any substitution possibilities that do exist would depend on if the technicians were trained on the new modalities.

As well, there are a growing number of activities that are examining alternatives to ^{99m}Tc procedures. For example, the European Medicines Association held a workshop in February 2010, "Current Use and Future Needs of Radiopharmaceuticals Labelled with Radionuclides Produced in Reactors and Possible Alternatives" (the workshop report can be accessed through the NEA medical radioisotope website, www.nea.fr/med-radio).

In some cases, these studies and activities are finding that there are no alternatives for some ^{99m}Tc-based procedures. However, where possible, alternatives are being used to deal with supply shortages. The question is whether these are short-term shifts to alternative technologies or long-term shifts given concerns on supply reliability. There is also a question of whether emerging economies will jump directly to alternative technologies (such as PET) given supply reliability concerns.

However, when looking at the long-term impacts, there is recognition that changing technologies takes time, with switching costs to new technologies often been quite high. In addition, SPECT has significant advantages over other technologies, with high resolution, low radiation doses and transportation logistics of isotopes that allow a wide distribution, which will support its continued use (Plan Clear, 2009).

Another concern that could impact the future demand for ^{99m}Tc and ^{99}Mo are falling reimbursement rates for ^{99m}Tc based procedures. In the United States, SPECT scan reimbursement rates were cut 36% as of 1 January 2010. These rates were adjusted upwards by approximately 16% in May 2010, but still represent an overall reduction from the previous year (SNM, 2010). As an additional example, the United Kingdom's National Health Service (NHS) budget has been cut as part of government cost reduction strategy, impacting individual departmental budgets. These cuts could have a direct impact on nuclear medicine procedures as there is less funding to pay for these procedures.

There have been additional pressures in relation to reduced reimbursement rates, with potential increasing costs for the other components that need to be paid through these declining reimbursement rates, including for imaging devices, salaries, etc. For example, in the United States there have been changes to the assessed utilisation rates for imaging devices, meaning that cost reimbursements per procedure are reduced since the devices are assumed to be used more often and thus the capital cost is spread out over more procedures that previously calculated.

At the same time as there have been reduced reimbursement for SPECT procedures in some jurisdictions, there have been increases for PET reimbursement rates in some jurisdictions. Further, some health insurance systems are expanding the types of alternative procedures to SPECT that are reimbursable, such as PET imaging agents for bone metastasis. These changes could result in the rise of PET scans at the expense of SPECT scans.

Another external factor that could have an impact on future demand for ^{99}Mo/^{99m}Tc is increased government attention to and concern about the potential overuse of nuclear medical imaging. For example, the United States Congress has initiated a study on physician self-referral of advanced medical imaging and radiation therapy treatments (including MRI, CT and PET procedures, not just SPECT) based on the concern that many self-referral procedures are unnecessary (American College of Radiology, 2010). Depending on the results of the study, this could lead to pressure to reduce the amount of these imaging procedures.

In addition, some governments are concerned about radiation doses from nuclear medicine sources (both diagnostic and therapeutic). In February 2010, for example, the United States House of Representatives' Committee on Energy and Commerce, Subcommittee on Health, held a hearing entitled *Medical Radiation: An Overview of the Issues*. This hearing examined the potential benefits and risks of the use of radiation in medicine. In addition, the California Senate passed a law requiring medical facilities to record radiation doses in patients' medical files (Associated Press, 2010). Although concern is mostly directed towards higher radiation-dose techniques (such as x-rays and CT scans), SPECT procedures could also be affected. With this increased scrutiny, there could be a push towards an overall reduction of nuclear medicine procedures or it could lead to an increase in SPECT procedures given the value of the procedures and that radiation doses from SPECT are lower than doses from some other alternative modalities.

How all the changes discussed above will play out in the future is currently uncertain. There is a question about whether the changes will remain if and when there is a reliable supply of ^{99}Mo/^{99m}Tc or if the supply chain, including hospitals, will return to their past practices. There is also the question about how the external factors at play will affect the long-term demand (Health Imaging, 2010a). Overall, it is expected that the medical imaging market will grow in the long term given the increasing incidence of some diseases and the benefits of medical imaging for drug development and clinical studies. However, how this increase impacts the demand for ^{99}Mo/^{99m}Tc, given the other factors at play has not yet been answered.

5.4 HLG-MR demand assessment action plan

As a result of this uncertainty in future demand and the lack of a long-term comprehensive demand overview that includes recent changes in the supply chain, the HLG-MR has set a goal to better understand future demand for ^{99}Mo/^{99m}Tc and/or related nuclear medicine procedures. At its second meeting, the HLG-MR identified this as one of its action plan items:

> The HLG-MR will convene an expert advisory group to provide guidance to the HLG-MR on future demand scenarios for ^{99m}Tc, recognising differences in developed

and developing countries and building on available studies, which will be incorporated into the final report.

To move forward with this action item, the NEA Secretariat will collect and assess data on expected future demand for ^{99m}Tc. The process will be taken in three phases:

- Phase 1: Creation of an expert advisory group, development of on-line questionnaire.
- Phase 2: Communication of on-line survey, collection of on-line data.
- Phase 3: Assessment, verification, and communication of collected data.

Recognising that there have been other demand surveys that have occurred in the past, the expert advisory group will first be asked their opinion on the degree of the long-term impact of the recent changes in the supply chain. If they are unanimously of the opinion that the recent charges are only short-term and will not impact long-term demand, the HLG-MR will consider whether it is worth proceeding with this work.

The advisory group is expected to consist of a small number of experts with an understanding of medical imaging and should be able to represent the views of health authorities, referring physicians, radiopharmacists and the nuclear medicine community. The experts will be aware of differences in geographical needs/uses of medical imaging.

The goal of the survey is to obtain a comprehensive informed view of the future demand of ^{99}Mo/^{99m}Tc and related nuclear medicine procedures from independent observers of the market and the main users. The survey respondents would ideally be from a variety of related fields, mainly from referring physicians and nuclear medicine specialists. This would ensure a balanced perspective of the future of nuclear medicine diagnostic testing.

The survey questions would not be focused on determining what actions are/were being used by supply chain participants during the supply crisis to minimise the impacts. Questions would focus on obtaining stakeholder expectations on the future demand for ^{99m}Tc in order to determine the potential long-term impact of those issues that could affect the industry, including (among others):

- Continuation of demand management actions when the 2009-2010 short-term supply shortage has been resolved.
- Growth of new software and technologies that reduce required ^{99m}Tc procedure doses.
- Preference for other imaging modalities (PET, PET/CT, MRI, etc.) resulting in modal shifting.
- Development of new tracers that could support modality growth.
- Growth in regions where currently not widely used.

The results of the survey and the expert advisory group’s future demand scenarios will be communicated in a final document.

Chapter 6

TRANSPORTATION ISSUES

This section considers the transport issues for the supply chain from the purchase of uranium through to generator delivery to hospitals or radiopharmacies. At each stage, there are issues to do with approvals for transport routes and containers. In most cases, these are covered by existing transport regulations, based on the *Regulations for the Safe Transport of Radioactive Material – 2009 Edition*, IAEA Safety Standards Series (TS-R-1) (IAEA, 2009), but other regulations relating to handling nuclear materials are also invoked in various stages of this process (including security and safeguards). The 2009-2010 shortages have put pressure on these processes and revealed some areas where additional processes may be needed to minimise delays. This is especially true for operators wishing to open up new routes.

6.1 Procurement and transport of enriched uranium

Purchase of special nuclear material for civilian use will usually require that a bilateral safeguards agreement between the supplier and purchasing country (or equivalent) be in place beforehand. The export of HEU or LEU from the United States requires a licence issued by the US Nuclear Regulatory Commission. The licence application requires that a contract with Y12 for the supply of the enriched material be in place. The approval is a multi-agency process involving the National Nuclear Security Administration and the Department of State.

In addition to required approvals to purchase enriched uranium, approvals are required in order to export the material. NRC Regulations 10CFR Section 110.42 permit export of HEU to be used as a fuel or target in a nuclear research or test reactor, provided:

- There is no alternative LEU nuclear reactor fuel or target that can be used in that reactor.
- The proposed recipient of the uranium has provided assurances that whenever an alternative LEU nuclear reactor fuel or target can be used in that reactor, it will be used in lieu of HEU.
- The United States Government is actively developing an alternative nuclear reactor fuel or target than can be used in that reactor.

Other requirements for export approvals include provision of a letter of assurance from the recipient country. The export licence also identifies intermediate and ultimate consignees (person, organisation or government which prepares a consignment for transport) and any other parties involved.

Section 134 of the Atomic Energy Act of 1954 (42 U.S.C. 2160d) was amended by Section 630 of the Energy Policy Act of 2005 (Pub. L. 109-58, 8 August 2005, 119 Stat.594) allowing for the United States to continue exporting HEU to Belgium, Canada, France, Germany and the Netherlands solely for the production of medical isotopes on certain conditions, including that the countries supply an end-use assurance, and that the HEU will be irradiated in a reactor that uses LEU fuel or commits to convert to LEU fuel when it is available.

However, a proposal was recently passed in the House (HR3276) that seeks to set a time limit on continued export of HEU for the purposes of ^{99}Mo production, provided the United States domestic supply can be ensured within that timeframe. DOE funding for the establishment of United States commercial LEU ^{99}Mo production is a provision in this bill. As of August 2010, this bill had not yet been approved by the United States Senate.

The other main source of HEU and LEU is Russia. No information was obtained on what the arrangements are for approvals.

Issues

The key issues related to procurement and transportation of enriched uranium are the potentially long process involving multiple United States agencies and the need for separate approvals to purchase and to export enriched uranium. These processes relate primarily to controls to prevent proliferation of nuclear material.

Recommendation

This is not the highest priority issue, since the purchases are infrequent but, nevertheless, there are opportunities for streamlining the process. The use of longer-term contracts with appropriate approvals would have advantages in shortening the transport and procurement process.

6.2 Transport of uranium and target plates (to and from manufacturer)

To transport uranium and un-irradiated target plates requires compliance with safety, safeguards and security regulations, recognising the nature of the material as both a radioactive substance and nuclear material subject to security and non-proliferation requirements. Most organisations use a transport agent experienced in the export process, given the need for an export licence from the supplier country, an import licence from the importing country and transport route approvals, including in any countries where the uranium will be processed (e.g. made into targets, etc.). This expertise is also required for the similar process required for sending manufactured target plates to the reactor operator.

In addition to the safety transport regulations, security requirements, usually based on INFCIRC/225/Rev4 (currently being updated to Rev5) are recommended for IAEA Member States. An understanding of each “transit” country’s regulatory framework and degree to which INFCIRC/225 and TS-R-1 have been adopted is necessary.

Depending on the level of enrichment of the uranium, there are different security categorisations of shipments, requiring different measures to be followed by the transporter. Categorisation of shipments is described in Table 5 and determines physical protection requirements during transport and storage. Fuller details are found in the relevant regulations.

The range of measures required for multi-country transits for shipment of Category 1 material are complex. This complexity is compounded if regulations applying to safety, transport modes and physical protection during transport of radioactive materials are not aligned between countries.

Table 5: Categorisation of uranium for shipments

Unirradiated ^{235}U	Cat I	Cat II	Cat III
Uranium enriched to 20% or more	5 kg or more	Less than 5 kg More than 1 kg	1 kg or less but more than 15 g
Uranium enriched to 10% but less than 20%	n/a	10 kg or more	Less than 10kg but more than 1 kg
Uranium enriched above natural but less than 10%	n/a	n/a	10 kg or more

For multi-country transits, the consignor must notify the competent authority in the *country of origin* of the shipment and the competent authorities of *each country through or into* which the consignment is to be transported. Transport may be by road, sea or air but there are different requirements for transport containers:

- Competent authority country of origin certification is required for the transport cask.
- Competent authority validation of country of origin certification required for all transit or overflight countries.

Issues

There are a number of issues that make the transportation of uranium and target plates difficult:

- Multiple approval processes (for storage, security and safety purposes) from multiple regulators in each country concerned by the shipment are needed; the concerned countries are the ones through or into which the transport is taking place, and sometimes the ones over-flown. For example, the notification of shipments (for safety) and the certification of routes and means of transport (for security) are required from different regulators in the same country.
- Approved package designs (from safety regulators) may not always be available for one of more country on the itinerary.
- The transport of fissile material requires a multilateral approval which potentially can lead to longer approval processes.
- There can be a potential misalignment between countries in regards to the applicable transport regulations, with the implementation of different editions of TS-R-1 and in regards to its application. This would result in a more stringent review of the package design safety case performed by one of the countries concerned by the shipment.
- The recent shortages required countries to seek alternative supply routes and therefore required package designs and new routes to be approved by the competent authorities concerned by the transport.

Recommendation

This is a medium priority issue, since there are other reactors entering the supply chain and there will be a need for fabrication and transport of targets. Common adoption of best practices by regulators on package design approval could shorten and harmonise the authorisation/approval process and make more routes available to alleviate worldwide shortages.

6.3 Transport of irradiated targets

To be transported, irradiated material requires either a type B(U) or B(M), B(U)F or B(M)F package design, depending on the maximum mass of transported fissile material. A type B(U) package design does not require validation in every country concerned by the shipment (i.e. those through or into, and sometimes the ones over, which the transport is taking place) if already validated in one concerned country. A type B(M) package design requires a multilateral approval, meaning that the package design approval must be validated by all the countries concerned. A package design with a content of more than 15g of ^{235}U (fissile material) is required to comply with type F requirements. The type F package, like the type B(M), requires multilateral approval. Given the lower content of ^{235}U in LEU targets, greater quantities of LEU targets than HEU ones can be transported in one package.

Transport of irradiated targets using B(U)F packages by road is now done in Europe. Most recent additions to the transportation routes has been for the transport of targets from the MARIA reactor in Poland to Covidien's plant in the Netherlands and for the transport of targets from the LVR-15 reactor in Czech Republic to IRE in Belgium. These packages are generally able to be docked into the hot cell at the receiving area. Due to the significant decay that takes place and the potential requirements for multiple drivers and vehicles, a maximum distance of 1 000 km is considered the limit for transporting irradiated targets.

For transport of irradiated targets through multiple countries, approvals are required from multiple national regulators, based on similar but not identical requirements for safety cases and package design approval. Again, some form of standardisation of approval processes, including de facto mutual recognition, would seem to offer the potential for shortening the approval time. Such moves are already underway in Europe and North America but not elsewhere in the world.

Transport by air requires adapted packages and related approvals, but this mode of transport for irradiated targets is unlikely because of concerns by the various air carriers and transit countries and the costs of transporting large packages by air. However we note that Russia has transported spent fuel from Romania by air and that the detailed safety case was approved by the regulator. A dedicated plane was used for the shipment.

It has been proposed by the transport community to increase the fissile excepted threshold of ^{235}U to 45g. This change is unlikely to come into force before 2013, since this kind of content requires multilateral approval.

Recommendation

This is a medium priority issue as it is linked to increasing the number of reactor sources. Mutual agreements between regulators in shipment countries could shorten the approval and validation process and make more routes available to alleviate any possible future worldwide shortages. However, this would need to involve both safety and security regulators. The development of common targets may also streamline the safety approval process, since it would increase experience and sharing of information among regulators.

6.4 Transport of bulk ^{99}Mo and generators overseas

Transport of ^{99}Mo either in bulk or in generators involves the same issues faced by the transport of the enriched uranium and the irradiated targets:

- Approval of package designs or validation for shipment is required by the countries concerned by the shipment (i.e. those through or into, and sometimes the ones over, which the transport is taking place).
- Certification of transport routes is required, meaning that a package design approved for transport on one route may not be approved on a different route.
- Package design approval or route certification processes are often different in different countries.
- In many countries several agencies are involved in the approval process and there may not be adequate coordination internally or a single process available to the licensee.
- Between countries, there may be no acceptance of another country's approval and therefore often requires additional approvals that can have quite lengthy timeframes.

An additional concern related specifically to the transport of bulk ^{99}Mo and generators is the denial of shipment for ^{99}Mo transport that occurs in all parts of the world, with the greatest problems appearing to be in Canada, Japan and the United States. These denials may be exacerbated by the labelling of ^{99}Mo as radioactive material – a class which covers a full range from medical isotopes to large activity sources – without any distinction of its medical nature.

There was some discussion during the last five years regarding a new classification for medical isotopes currently under the Class 7 designation. It received very mixed reviews from regulators, the International Air Transit Association (IATA), the International Civil Aviation Organization (ICAO) and the International Steering Committee (ISC) members and has not been taken forward. Nevertheless, some groups involved in medical isotope transport are raising this possibility again. Although it sounds reasonable and may help to differentiate medical isotopes from other radioactive material, there are both practical considerations (i.e. definition, labelling, etc.) and timeframe (i.e. could take years to move it through the necessary process) issues. Another possible approach is to work with IATA to address the wording on the aircraft manifest; this could be taken up by the IAEA.

From a denial perspective, the ISC is aware of, and working to mitigate, issues in Europe where airlines such as KLM and BA have restrictions that create challenges for ^{99}Mo movement into and from the region. There are also ongoing issues where medical isotopes get off-loaded regularly from scheduled flights due to misinformation, lack of education of pilots or airlines, misinterpretation of the regulations, etc. The ISC has seen medical isotope shipments off-loaded when live animals, biological samples or human remains are on board the aircraft, when the pilot deems this other cargo to be a higher priority. The latter may be resolvable through education and awareness.

Of all the tools the industry and ISC have available, education and awareness of the products' uses, time criticality, patient impact, safety in packaging and shipment, and safety and security track record is the most effective and most needed. There is an IATA/CORAR video which was widely distributed to air carriers, pilot associations etc. to be used for education purposes. This had a positive effect and it is this type of effort that needs to be continued throughout the rest of the world.

Issues

In addition to the issues shared with the transportation of enriched uranium and targets, the issues specifically related to the transport of bulk ^{99}Mo and generators are:

- The time taken to do dangerous goods checking (between four and six hours when a dangerous goods qualified person is available) makes it difficult and expensive to ship the short half-life products. This time requirement remains even when the same products are shipped very regularly.
- Some countries or territories require import permits five days in advance even though the product is only transiting.
- Transport companies have concerns related to the transportation of radioactive materials leading to the denial of shipments. For example, there have been problems with return of spent generators because some shippers do not understand the difference between an "excepted package of radioactive material" and a radioactive package.

Recommendations

This is a high priority issue, since it relates directly to the transport of ^{99}Mo and generators that are designed to provide doses for patient treatments.

As with the shipment of enriched uranium and targets, harmonisation by regulators on package design approval could shorten the approval and validation process and make more routes available to alleviate any potential future worldwide shortages. This is occurring currently in Europe and could be extended to other countries. The IAEA could provide a helpful role in assisting regulatory authorities to either utilise the competency of another regulator or encourage development of codified design standards that can be easily checked to establish the ability of a package design to meet its purpose.

In order to facilitate the dangerous goods checking process, especially in the case of regular shipments, a standard licence for carriers of radioactive material should be pursued, similar to that expected to be proposed by the European Commission in 2011. This accreditation of shippers could allow for the process to move more quickly.

To deal with the issue of denial of shipments, more work on producing educational materials may alleviate concerns by transport companies. An updated education and awareness programme addressing the shortages and the priority need to expedite shipments should be considered by the shippers of ^{99}Mo.

For both of these last two issues, further examination of the use of different labelling may help reduce the incidence of denial of shipments and speed up the dangerous goods checking process. In addition, changing the wording of some of the descriptions used for the radioactive material could facilitate these processes.

6.5 Summary

The key issues in transport are the need to streamline and gain greater harmonisation in approval processes, and to tackle denials of shipment. The IAEA would be the appropriate organisation to work with international bodies and national regulators on common approaches to package design approval and route certification and the HLG-MR encourages the IAEA to take forward this issue as a matter of priority.

Chapter 7

MOLYBDENUM-99/TECHNETIUM-99M SUPPLY CHAIN ECONOMICS

Introduction

Consistent with early realisation that appropriate economic information and signals were critical to the pursuit of the security of supply of medical radioisotopes for the medium to long term, the HLG-MR commissioned the NEA Secretariat to undertake an economic analysis of the supply chain, from the irradiation of targets in research reactors to the delivery of the radiopharmaceutical to patients. Such an economic analysis had never before been conducted.

The HLG-MR discussed the results of this analysis at its June 2010 meeting, jointly with representatives of industry and nuclear medicine societies, and endorsed the publication of a report by the NEA Secretariat presenting this analysis as an important contribution to the future work of the HLG-MR and to policy discussions in this and other fora. The report (NEA, 2010a) provides a good overview of economic factors affecting the supply chain historically and sets out a range of approaches to promote conditions for medium- to long-term security of supply. The report can be accessed through the NEA medical radioisotope website, www.nea.fr/med-radio.

Recognising that it is difficult to derive fully representative quantitative estimates of costs or prices in the supply chain inasmuch as circumstances differ for individual operators and markets geographically and over time, the HLG-MR draws the following observations and conclusions from the economic analysis and its own discussions to-date.

The historical economic model or "social contract"

- The production of ^{99}Mo delivers a significant health benefit through the use of ^{99m}Tc in medical imaging for diagnosis and treatment, as evidenced by a growing, complex and sophisticated industry globally.

- The price structure for this industry – the allocation of revenue to various stages of the supply chain – reflects private contracts or arrangements negotiated over time between reactor operators and ^{99}Mo processors, between processors and ^{99m}Tc generator manufacturers, and finally between generator manufacturers and radiopharmacies and hospitals.

- Reactor operators are publicly-owned entities. Processors, originally publicly owned, now include a mix of public and private (profit-motivated) entities. The major generator manufacturers are privately owned. End users are, directly or indirectly, supported by governments given the public benefit of health care.

- Publicly-funded authorities therefore are found at both the beginning and end of the supply chain. They are the original producers of ^{99}Mo in the irradiated targets and the ultimate buyers of ^{99m}Tc-based imaging services. Private entities operate in the middle of the supply chain.

- Historically, the production of ^{99}Mo in research reactors represented an activity secondary to the primary mission of the reactor, which is to support nuclear-based research. This secondary activity was seen to be attractive so long as marginal revenue exceeded the marginal cost of production. The "profit" generated from this secondary activity was then set against the costs of other, public-good missions of the reactor (research activities intended to have broad or long-term societal benefit) that were funded through annual budgets, which were under pressure.

- This situation of government funding for the provision of ^{99}Mo is characterised in the report as a "social contract" that emerged over time with the formal, tacit or unknowing endorsement of governments as owners of the reactor operators.

The (unintended) consequences of the social contract

- The social contract described above conditioned behaviour. Importantly, it fostered a price for the irradiated product that, together with other significant barriers to entry, discouraged investment in new sources of supply.

- Costs of reactor operators rose over time given heightened regulatory obligations for safety and security, accumulating radioactive waste and the need to repair or replace a capital infrastructure used increasingly for ^{99}Mo production. However, the terms of the social and private contracts resulted in significant and growing financial losses for reactor operators undertaking this production.

- The cost and price estimates drawn from information collected by the market participants and presented in the NEA Secretariat report, while approximate and illustrative, show two basic results that the HLG-MR considers to be representative:

  - The price earned historically by reactor operators is insufficient to compensate appropriately for the full costs, and in some cases even the marginal costs, of ^{99}Mo production.

  - The payment made to reactor operators for the ^{99}Mo represents a very small proportion of the value at the end of the supply chain – less than 1% of the reimbursement of the ^{99m}Tc-based imaging procedure.

- The HLG-MR has no reason to conclude that excess profits are earned downstream in the supply chain, as costs are significant and reimbursement rates have been falling. However, the analysis shows further that:

  - Compensation to reactor operators would have to increase by a significant factor (e.g. by three to five, recognising a wide range of individual circumstances) to cover marginal costs and a reasonable proportion of reactor operating and capital costs.

  - Such adjustment could occur without a significant impact on the cost of the final imaging procedure (less than one per cent in all the cases examined) and therefore on costs incurred by public health care systems or private insurers.

- The historical situation is unsustainable. It has contributed to inadequate investment in replacement infrastructure and fragility and shortage in the supply chain. It has meant that some governments are subsidising health care services delivered in other jurisdictions. It has also discouraged investment in the conversion from HEU-based reactor fuel and targets to LEU-based alternatives.

- As these factors have become more evident amid the recent period of supply shortage, the "social contract" is drawn into question, private contracts are being re-assessed or re-negotiated and attention is focused on means to establish the economic conditions for more secure, sustainable long-term supply of ^{99}Mo produced without HEU. Governments have a critical role to play in this process, given their presence at both ends of the ^{99}Mo/^{99m}Tc supply chain.

Looking forward – the need for a new model

- The HLG-MR is mindful that there are differences nationally and regionally on how governments may wish to fund nuclear research infrastructure, assign ownership and management responsibility and fund obligations for radioactive waste management.

- It is also mindful of the fact that there are commercial contracts between suppliers and recognises that the activities of market participants must be consistent with all applicable competition and anti-trust laws.

- As a general proposition, it would hold that the full costs of ^{99}Mo and ^{99m}Tc production should most appropriately flow through the supply chain and be reflected in the costs of the final medical procedure, to be reimbursed appropriately by health insurance systems.

- This would send the right economic signals through the supply chain and encourage sound decision-making in both the supply and demand of ^{99}Mo/^{99m}Tc. For example, it would create the conditions whereby new sources of ^{99}Mo and new processing capacity could be better supported and alternatives to ^{99m}Tc imaging procedures could also emerge where economically and technically viable. It would also remedy the problem of cross-subsidisation from one jurisdiction to another.

- Conceptually, the right price structure would remunerate in comparable fashion older infrastructure, to reflect costs of capital maintenance, refurbishment and replacement, and new LEU-based infrastructure to fund the necessary conversion or Greenfield investments. It would also apply in comparable fashion across all markets to establish a level playing field.

- With this, the HLG-MR recognises the further, critical challenge of ensuring that the pricing structure and the operation of the market accommodate a reserve capacity that can be deployed if and as necessary, for both planned and unplanned reactor outages and other supply chain breakdowns.

- Indeed, for supply to be fully reliable for the patient, production capacity will have to be held back at all stages of the supply chain and released only if and as needed. Moreover, when excess capacity is available, product must not be "dumped" into the marketplace because this will again depress prices, distort signals and create future vulnerability. The right economic behaviour may be induced, at least in part, by buyers through the supply chain diversifying their sources of supply and by some arrangement to pay more for a commitment of reserve capacity for security of supply.

- Indeed, a situation of excess supply may occur temporarily starting in fall 2010 when both the NRU and the HFR return to normal operation. It must not create a false sense of comfort, as the infrastructure remains fragile and as some capacity will be retired over the coming years.

- Without question, the HLG-MR concludes that the market model must evolve from its historical form to establish a framework that will be conducive to sustainable, secure, non-HEU-based supply that operates efficiently and effectively.

- The HLG-MR has not resolved how this may best be realised in practice. What can be the contribution of a well functioning, well informed market? What is the role of governments as owners or funders of supply infrastructure and health care systems, as promoters of the use of LEU, or as regulators? What is the contribution of regional arrangements among public authorities and/or market participants?

Next steps

- Correspondingly, the HLG-MR asks that, building on its economic analysis, the NEA Secretariat define and assess alternative market models and approaches that may support sufficient supply capacity, including reserve capacity, globally and across regions.

- This work will help the HLG-MR formulate recommendations for governments and market participants in its final report. In the interim, the HLG-MR encourages governments and market participants to draw lessons from the economic analysis appropriate to their circumstances, keeping in mind shared global, long-term objectives and goals.

Chapter 8

TECHNOLOGIES FOR PRODUCING MOLYBDENUM-99/TECHNETIUM-99M

One of the actions requested by the HLG-MR was a review of other technologies for producing ^{99}Mo. For this review, the HLG-MR asked the NEA Secretariat to develop a set of criteria for assessing the existing and proposed technologies, as well as an analysis of those technologies based on the criteria.

This report (NEA, 2010b) will provide a set of criteria and an initial assessment of the situation at the present time for a variety of technologies, based mainly on published sources of information and on information provided by industry representatives. The work is not regarded as comprehensive; however it does provide a technological and economic review of the various technologies, which should be helpful for decision makers in deciding further investment. Clearly more in-depth work will be needed to examine the technologies and the IAEA is currently compiling a more comprehensive report on the promised technologies (see www.iaea.org/OurWork/ST/NE/NEFW/rrg_Mo99.html for more information), which will add to the information presented here.

The review examines two broad groups of technologies: reactor-based and accelerator-based. It should be recognised that the technologies being assessed are at very different states of maturity and as a result the knowledge around the technologies range from well established to uncertain. The report will recognise these differences but will not make any examination of the path to development of the lesser developed technologies.

The technologies that are examined in the report are:

Short-term technologies[2] (could be available in 2010-2017 timeframe)

- HEU fission in research reactor (as the reference case);
- LEU fission in research reactors;
- LEU fission in solution reactor;
- neutron activation of ^{98}Mo in a research reactor;
- neutron activation of ^{98}Mo in a power reactor;
- direct cyclotron production of ^{99m}Tc via ^{100}Mo(p,2n)^{99m}Tc reaction.

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[2] Depending on national policy, research on each isotope production technology could be accelerated; the classification of short-, mid- and long-term technology is therefore only indicative and essentially based on the amount of information available today.

Mid-term technologies (could be available in 2015-2025 timeframe)

- Photofission based on the $^{238}U(\gamma,f)^{99}Mo$ reaction using an electron accelerator;
- $^{100}Mo(\gamma,n)^{99}Mo$ reaction using an electron accelerator.

Long-term technologies (could be available in 2020-2035 timeframe)

- $^{235}U(n,f)^{99}Mo$ reaction using spallation neutron sources in a high-energy proton accelerator;
- $^{100}Mo(n,2n)^{99}Mo$ reaction using a deuteron accelerator.

These technologies will be assessed based on the criteria developed and described in the report. The review may not examine all the criteria if the information is not available. This was found to be the case for some of the less mature technologies. The non-ordered list of criteria includes:

- technology maturity;
- production yield;
- available irradiation capacity;
- distribution range and logistics;
- processing safety;
- waste management;
- proliferation resistance;
- potential for other isotope production;
- normalised capital costs;
- commercial interest;
- levelised unit cost;
- ease of nuclear regulatory approval;
- ease of health regulatory approval;
- units required to supply world market.

No weighting for the assessment criteria has been proposed. Such weighting could not be universal because it strongly depends on national political and economical factors.

The NEA Secretariat is currently developing the review and it is expected to be published on-line in the second half of 2010.

Chapter 9

IODINE-131 SUPPLY SITUATION

Following its second meeting, the HLG-MR asked representatives from Covidien, CORAR (Council on Radionuclides and Radiopharmaceuticals) and DRAXIMAGE to identify the bottlenecks in the supply chain for Iodine-131 (^{131}I). The issue of a shortage of ^{131}I in North America was raised during discussions at the meeting. These representatives agreed to this work and presented their findings at the third meeting of the HLG-MR. This chapter is based on that presentation (Brown, 2010).

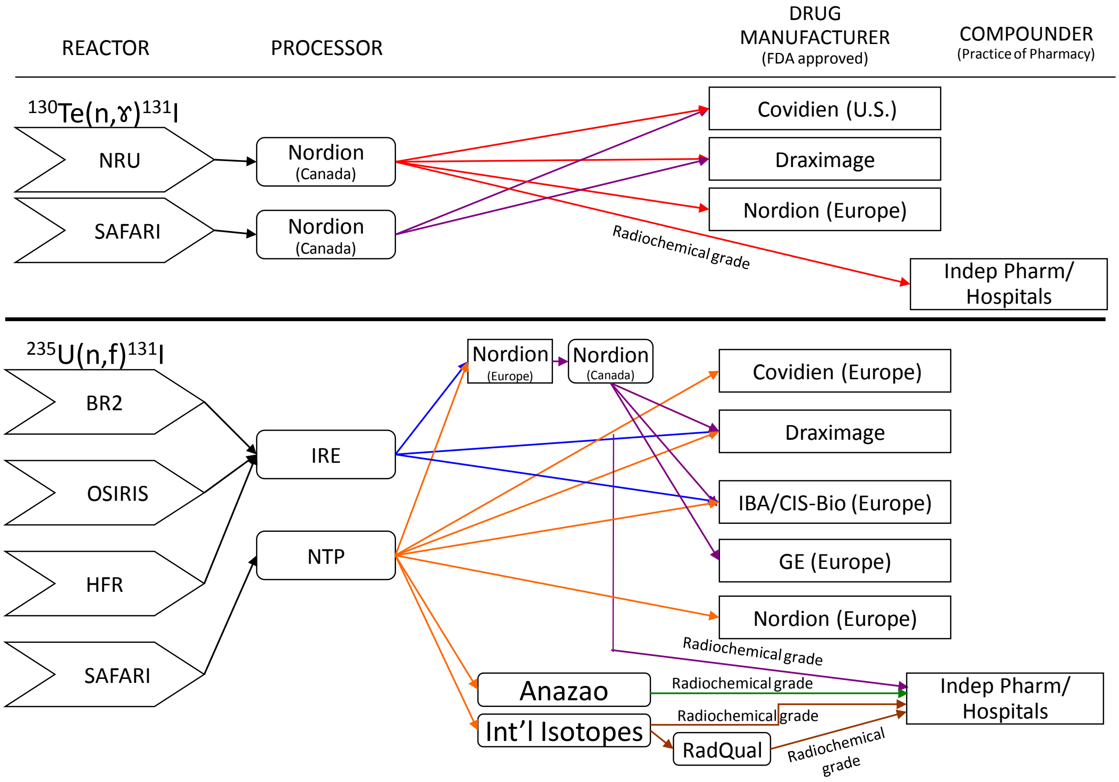
There are two methods that are used for producing ^{131}I for the global market: irradiation of Tellerium-130 (^{130}Te) in a nuclear reactor and as a by-product of the irradiation of ^{235}U for ^{99}Mo production. Both of these methods are used by the major suppliers to the United States market. In 2009, the United States market was served by DRAXIMAGE (66%), Covidien (26%) and MDS Nordion (8%). Figure 14 shows the supply chain for the United States and European markets for each of these processes.

The identified shortfall of ^{131}I in the North American market came from the shutdown of the Canadian NRU reactor that was producing ^{131}I from ^{130}Te; Covidien was only able to obtain 70% of their needs from their supplier as they were only using ^{130}Te-derived ^{131}I. At the same time, there was an excess global supply of ^{131}I based on the ^{235}U fission process. Given the use of ^{235}U-derived ^{131}I in Europe, there were no supply shortages experienced.

In order to use alternative suppliers of ^{131}I and alternative methods for deriving ^{131}I, it is required to obtain approval from the relevant health authorities. Since the North American shortage began, Covidien has been working to qualify ^{235}U-derived ^{131}I, coming from alternative suppliers. In addition, during the shortage, NTP increased their supply of ^{130}Te-derived ^{131}I to compensate for the disruption in North American supply. With the NRU back on line and Covidien seeking regulatory approval to use alternative sources, the supply situation should be stabilised.

The shortage of ^{131}I highlights that the ageing reactor fleet has an impact beyond the supply of ^{99}Mo. Although ^{99}Mo supply is the key concern given its short half-life, the limited number of reactors that have the neutron flux required to produce it and its importance in medical diagnosis, these research reactors produce many other isotopes for medical and industrial needs and are essential for important research.

Figure14: North American and European ^{131}I supply chain



Source: Brown, 2010.

Chapter 10

CONCLUSION AND NEXT STEPS

Throughout the first year of its mandate, the HLG-MR has been able to examine the major issues that affect the short-, medium- and long-term reliability of ^{99}Mo/^{99m}Tc supply. The collective efforts of HLG-MR members and nuclear medicine stakeholders have allowed for a comprehensive assessment of the key areas of vulnerability in the supply chain and an identification of the issues that need to be addressed. This report, along with the two studies undertaken by the NEA Secretariat at the request of the HLG-MR on the supply chain economics and alternative technologies for producing ^{99}Mo/^{99m}Tc, identify these issues and provide some initial discussion on the mechanisms that could be used to address them.

The reports and the meetings of the HLG-MR demonstrate the increased understanding among all stakeholders of the complexities of the supply chain; significant information sharing has provided the various stakeholder perspectives and requirements that the supply chain needs to accommodate. They also show that significant progress has already been achieved on improving the supply situation through such actions as increasing communication, improving reactor co-ordination and increasing demand-side opportunities. The work also points to the need for continued action on the part of all stakeholders to address the issues.

The second year of the HLG-MR mandate will be mostly dedicated to identifying and assessing the mechanisms that could be used to address the issues affecting the reliability of ^{99}Mo/^{99m}Tc supply. This work should result in concrete options and recommendations to increase long-term supply reliability. Work on examining some key remaining questions, such as the state of future demand, will continue.

For the coming year, the HLG-MR, the NEA Secretariat and nuclear medicine stakeholders have a significant amount of work to undertake. The third instalment of the HLG-MR rolling action plan arising from the last meeting sets the work for the first half of the coming year (provided below). The next meeting will occur in January 2011 and will focus on policy options for ensuring a long-term reliable supply of ^{99}Mo and ^{99m}Tc.

At the end of its two year mandate, the HLG-MR will produce a final report with recommendations for governments and market participants. The work to date and the work to be completed over the coming year will form the foundation of the final report.

Third instalment of the rolling action plan

From the 3rd Meeting of the HLG-MR, 24-25 June 2010, Paris, France:

Enhancing supply

1. AIPES and its members will continue efforts to co-ordinate reactor scheduling, even once the short-term shortage situation has been passed. Following its meeting in September,

AIPES will disseminate the 2011 schedule. As part of their on-going co-ordination role, efforts will be made by AIPES and its members to determine how best to address co-ordination in a situation of surplus supply to ensure the availability of reserve capacity, and how best to communicate levels of available reserve capacity as an indicator of supply reliability.

2. The IAEA through countries involved in its activities will continue the work to examine opportunities for production of ^{99}Mo from additional non-HEU sources, including non-fission methods, and how and when these additional opportunities could be brought to market. This work will culminate in final reports in 2011, serving as a basis for further action by countries.

3. Governments and supply chain participants will continue efforts to foster the development of long-term non-HEU supply options, taking into account technological, economic, regulatory, and other relevant factors, including funding models and timelines for potential deployment.

Improving regulation

4. The IAEA, in conjunction with the NEA, AIPES, and CORAR will develop a guidance document for regulators on approval processes for containers for intermediate products, supporting on-going work with regulators to address regulatory issues affecting the supply chain.

5. CORAR, with the support of the NEA and AIPES, will continue discussions with the IAEA on how to improve communication to the shipper of the medical nature of the shipment of ^{99}Mo, both in bulk and in generators. Possible options to be pursued include developing a new UN shipping classification for the medical isotope shipment, more information on the aircraft manifest, or adding a new label on the container to provide additional information.

6. Operators and industry participants will continue to supply information to the IAEA on different transport-related issues as they arise, including denial of shipments. Systematic reporting of these issues should be done via the process laid out in IAEA’s Denial Network Handbook, which can be found at http://ns-files.iaea.org/fileshare/rit/default.asp?fd=774.

Improving communications

7. Drawing on communication protocols developed by AIPES and its members, ^{99}Mo supply chain participants will continue to provide clients in the health care community projected supply levels for extended periods (such as 90 days), to be updated and refined through regular, ongoing dialogue with clients and contingency planning for unexpected shortages.

Optimising use

8. Nuclear medicine associations will continue efforts toward efficient use of ^{99}Mo and ^{99m}Tc through implementation of guidelines for product-use optimisation and continued promotion of such guidelines even once the short-term shortage situation has passed.

9. Any documentation of efforts or experience will be provided to the NEA Secretariat for posting on its website to encourage sharing and the on-going integration of demand management practices even when the short-term situation returns to normal. This documentation will include, but is not limited to, surveys done on the effects of the medical

isotope supply disruption on health system practitioners by the Canadian Institute for Health Information (the CIHI study) and the Society for Nuclear Medicine, as well as upcoming studies being done in France and the United Kingdom.

10. The EANM will consider undertaking a study to determine the effects of the shortage on medical practitioners in Europe. If this study is undertaken, its results will be posted on the NEA website with a goal of sharing lessons learned.

Supporting nuclear non-proliferation

11. Governments, reactor operators and processors should continue to collaborate on LEU conversion efforts, including on target design and processing, with a goal of developing standardised approaches to conversion that can be used by all supply chain participants in order to increase reliable and available reserve capacity.

Supporting sustainable future economic conditions

12. The NEA Secretariat will draft an executive summary and appropriate disclaimer and finalise the economic study based on comments received and publish results by September 2010. HLG-MR members will provide any additional comments on the draft economic study by 15 July.

13. The NEA Secretariat will develop a series of background papers to support the discussions of policy options at the next HLG-MR meeting in January 2011. These papers will follow up on the findings of the economic study and will look at different market models and approaches to ensure sufficient capacity, including reserve capacity.

Additional specific HLG-MR actions

14. The NEA Secretariat will redraft the state of the art report on technologies for producing ^{99}Mo/^{99m}Tc and provide to HLG-MR members for review before the end of July. Comments from the HLG-MR will be provided to the Secretariat by 20 August to enable publication of the study (via pdf on web) by September 2010. This report will include a discussion of criteria to be used when assessing promising reactor and non-reactor opportunities for securing ^{99}Mo production in the short, medium, and long term, providing information to decision makers in order to accelerate appropriate decisions.

15. HLG-MR members will provide comments on the existing draft of the Mid-Term Diagnostic Report to the NEA Secretariat by 29 July. The Secretariat will provide a final draft by mid-August for HLG-MR approval and publishing (via pdf on web) by September 2010.

16. The HLG-MR will convene an expert advisory group to provide guidance to the HLG-MR on future demand scenarios for ^{99m}Tc, recognising differences in developed and developing countries, which will be incorporated into the final report.

17. To support the demand scenario work, HLG-MR members will provide suggestions of experts for the advisory group by 20 August. The experts should provide for regional and professional diversity, including referring physicians (e.g. cardiologist, oncologist), nuclear

medicine specialists and medical imaging technology experts (e.g. on software, camera advances).

18. The NEA will ensure governments of member countries are kept abreast of developments by disseminating reports and papers to the members of the NEA Steering Committee and by posting them on its website.

Annex 1

HLG-MR MEMBERS

(as of June 2010)

Argentina	Pablo CRISTINI Manager of Radioisotope Production Ezeiza Atomic Center National Commission of Atomic Energy
Australia	Adrian (Adi) PATERSON CEO Australian Nuclear Science and Technology Organisation (ANSTO)
Belgium	Leo SANNEN Director of the Institute of Nuclear Materials Science SCK•CEN
	Mr. Jean-Michel VANDERHOFSTADT CEO – General Manager, Institut des Radio-Eléments (IRE) The National Institute for Radioelements
Canada	Meena BALLANTYNE Assistant Deputy Minister, Health Products and Food Branch Health Canada
	Serge DUPONT (Chair) Deputy Minister Privy Council Office, Intergovernmental Affairs
European Commission	Remigiusz BARANCZYK European Commission, Directorate-General for Energy Directorate D – Radiation protection
France	M. Daniel IRACANE Adjoint des Relations Internationales du Commissariat à l'Énergie Atomique (CEA), Saclay
Germany	Winfried PETRY Scientific Director FRM II Technical University Munich
	Jochen SÜSSENBERGER Bundesministerium für Wirtschaft und Technologie

Italy	Sandro SANDRI ENEA – CR Frascati
Japan	Tatsuo IDO Executive Director of Japan Radioisotope Association
	Hiroki TAKAYA Director, Office for Quantum Radiation Research, Basic and Generic Research Division, Ministry of Education, Culture, Sports, Science and Technology (MEXT)
Korea, Republic of	SunJu CHOI Director, Radioisotope Research Division Reactor Utilization & Development Center Korea Atomic Energy Research Institute
Netherlands	Harrie SEEVERENS (Vice-chair) Ministry of Health, Welfare and Sport (VWS) Department of Pharmaceutical Affairs and Medical Technology
	Rob J. STOL Managing Director Nuclear Research & consultancy Group (NRG)
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	Svyatoslav MAKAROVSKY Director, Department of Foreign Economic Relations Joint Stock Company “V/O IZOTOPE”
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United States	Mary Lisa MADELL Director of the Office of Europe and Eurasia, Office of Global Health Affairs, Department of Health and Human Services
	Parrish STAPLES Director of European and African Threat Reduction Office of Global Threat Reduction, U.S. Department of Energy
OBSERVERS	
IAEA	Natesan RAMAMOORTHY Director, Division of Physical and Chemical Sciences International Atomic Energy Agency (IAEA)

Annex 2

TERMS OF REFERENCE AND OUTLINE WORK PROGRAMME

High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR)
Under the Auspices of the OECD Nuclear Energy Agency

Background

On 29-30 January 2009, the OECD Nuclear Energy Agency hosted a workshop *Security of Supply of Medical Radio-isotopes.* The purpose of the workshop was to discuss the challenges facing the reliable supply of technetium-99m (^{99m}Tc), a key medical isotope derived from molybdenum-99 (^{99}Mo), and to identify measures that should be taken to ensure reliability of supply.

Workshop participants placed priority on challenges relating to the management of existing capacities and maximisation of these capacities in times of shortages, on the economic validity of the current model, on flexibility and efficiency of the supply chain, on regulatory impediments and demand side management. They identified the need to develop, deepen and share, as appropriate, contingency plans for future supply disruptions. They also focused on the longer term and on the need to engage the health authorities to reduce uncertainties regarding long term demand and the means by which to encourage more investment in production and greater redundancy in the system.

Participants identified the following measures to enhance short-term supply security:

- reactor owners and operators should continue to share information and to enhance co-ordination of reactor maintenance schedules, with a view to ensuring an uninterrupted global supply of isotopes;
- options for increasing production from existing reactors in times of global shortage should be further explored and encouraged;
- current economic conditions for irradiation services should be reviewed to provide better incentives to reactor operators, including where the main mission is research in support of national nuclear energy or scientific programmes;
- unnecessary impediments to the distribution of medical isotopes, such as restrictions in transport capabilities and denial of shipment by airline companies, should be removed;
- anticipative actions to avoid the dilemma between meeting nuclear safety requirements or meeting health care needs should be encouraged; in this regard, participants were pleased to be informed of the outcome of the nuclear regulators meeting held in Paris three weeks earlier;
- radiopharmacies, hospitals, health product regulators and the medical community should explore options for more efficient patient scheduling and utilisation of ^{99}Mo/^{99m}Tc generators to make best use of currently available supplies of ^{99}Mo and/or other potential alternatives.

There was unanimous support for the establishment of a working group to carry forward the agenda of the workshop, also involving the International Atomic Energy Agency (IAEA).

Establishment of the High-level Group

(A) Mandate from the Meeting of the NEA Steering Committee, 28-29 April 2009

On 29 April 2009, the NEA Steering Committee held a policy debate on the isotopes issue, during which they reviewed the outcome of the workshop, heard presentations from four invited speakers and discussed the way forward. The Steering Committee endorsed the proposal for a high-level group on the Security of Supply of Medical Isotopes under the auspices of the NEA to carry forward the agenda of the workshop and to identify the practical measures that should be taken.

The Steering Committee discussion covered the following points:

- in order to cover the supply side and demand side of the issue, a high level group consisting of 8 to 12 members would be established and that will consist of senior representatives nominated by interested member governments; several countries indicated at the Steering Committee meeting that they would nominate a representative to sit on the group;

- countries represented on this high level group should be ready to consider, subject to their agreement to the work programme, to share the burden of providing resources in order that the work can proceed.

The group will approve its terms of reference and action plan at its first meeting and to facilitate an early meeting, the NEA will send out letters to all member countries asking if they have a senior representative whom they wish to nominate to the group.

It is anticipated that the group will sustain engagement on this issue; it will ensure co-ordination of the above efforts and foster transparency and accountability; it will give due recognition to the fact that governments have the responsibility for establishing an environment conducive to the private and/or public sector investments that may be required; that the conversion to low enriched uranium is a common goal and the feasibility and timing of implementation should be weighed against impact on the vulnerability of the supply chain.

(B) Terms of Reference

To review the total ^{99}Mo supply chain from uranium procurement for targets through to patient delivery, indicating the areas of vulnerability and identifying issues to be addressed, and mechanisms to address them, to strengthen the reliability of supply. The group should consider the immediate issues, the medium term issues (2-5 years) and the longer term issues (greater than 5 years) in arriving at their conclusions and recommendations.

- The High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) will report to the Steering Committee of the OECD Nuclear Energy Agency.
- The NEA will provide the Secretariat to the HLG-MR.
- The NEA may also undertake specific studies within its area of expertise, as requested.

- HLG-MR members will identify necessary resources to enable this work to proceed.
- The HLG-MR will have a two year mandate. This will only be extendable by consent of the members and endorsement by the Steering Committee.
- The HLG-MR will establish an action plan at its first meeting, compatible with the available resources, to be approved by the Steering Committee. The action plan will contain specific deliverables, allocation of responsibilities and timing of deliverables.
- The NEA Steering Committee will be invited to approve the terms of reference and the action plan prior to its next meeting in October 2009.
- The action plan will be developed in close co-operation with the IAEA and key international organisations and institutions that are well positioned to propose and implement the necessary changes.
- Specific HLG-MR members will be responsible for obtaining early and clear commitments from key international organisations and institutions to provide support in the development and implementation of the action plan and will report on progress at each subsequent HLG-MR meeting.

Roles and responsibilities

The following provides a breakdown of roles and responsibilities to be further refined in consultation with key international organisations. As such, the roles and responsibilities listed below must be considered as indicative only. The HLG-MR will refine them as required.

Lead organisation	***Roles and responsibilities***
OECD/NEA	Review the value chain for ^{99m}Tc with emphasis on the economics of the upstream segment of the market. Explore and advise on the role of government in the commercial market. Asses options to fund back up capacity to ensure security of supply; assessment of market or other mechanisms to fund back-up capacity. Assess and identify solutions to supply chain inadequacies; development of a mathematical model system reliability.
AIPES/isotope industry	Co-ordinate existing reactor schedules used to produce medical radioisotopes to enhance supply response. Establish a mechanism to assess the production of ^{99}Mo over the coming short, medium and long term and the ability to meet demand. Establish an arrangement whereby additional production capacity can be brought into action as needed in times of emergency. Establish communications protocols for early warning for unanticipated events.
Reactor owners/ operators	Assess and implement options for increasing production in times of shortages. Define their maximum output capacity and the time it would take to ramp up capacity.

	Assess the viability of existing reactors used to produce medical radioisotopes. Assess the options for expanding/introducing production in existing reactors used to produce medical radioisotopes.
IAEA	Assess the possibilities of utilising existing reactors, not currently being used to produce medical radioisotopes, for ^{99}Mo production, the timescale and the measures that would be needed to enable this to happen. Assess transport impediments and identify measures to remove impediments. Assess capability and requirements of smaller countries and the option of regional centres for irradiation and production. Assess the stage-wise needs, timelines and economics of large scale ^{99}Mo production using LEU and final waste management aspects. Assess the capabilities of alternative (non-reactor) technologies for the production of ^{99}Mo and the likely impact as well as the need for new reactor production capacity.
INRA/ASN	Facilitate standardisation/licensing of transport packages and other regulatory issues. Streamline inter-country agreements on approval processes for transport and certification of packages.
Health community (SNM, HC)	Develop options for efficient patient scheduling and utilisation of available supplies Assess potential alternatives to procedures using ^{99}Mo, for employment in shortage situations Assess long term demand for ^{99m}Tc including the impact of alternative procedures and new technologies Enhance contingency plans and information sharing on contingency plans; establish communication protocols for early warning for unanticipated events.

NEA Secretariat

The NEA will form a small Secretariat, supported by voluntary contributions, to support the work of the HLG-MR; the Secretariat will arrange and host meetings/workshops, co-ordinate efforts with the organisations noted above, prepare necessary documentation (agendas, reports of meetings).

In addition, as noted above, the NEA may undertake specific studies as requested by the HLG-MR, subject to the resources being made available.

Annex 3

FIRST INSTALMENT OF ROLLING ACTION PLAN

From the 1st Meeting of the HLG-MR, 17-18 June 2009, Toronto, Canada.

1. The NEA will undertake analysis of the economic considerations of the upstream isotope supply and provide preliminary findings for the next face to face meeting.

2. The chair of the HLG will write a letter to the AIPES asking them to confirm actions related to upstream and downstream communication on supply availability, including reactor schedules and information by members to the health care system.

3. The chair of the HLG will write a letter to the SNM requesting an assessment of the demand for ^{99m}Tc and the impact of alternative procedures and new technologies in the long-term. The letter will also confirm that they will undertake analysis of the current supply shortage and ways to optimise use of supply.

4. The IAEA will advise on the scope for increasing production from new producing countries over the medium term, constraints such countries are facing, and actions that might be taken by the IAEA or member countries to overcome such barriers.

5. The IAEA will advise on the current regulatory requirements governing the transportation of irradiated products and how such requirements would best be met.

Annex 4

SECOND INSTALMENT OF ROLLING ACTION PLAN

From the 2nd Meeting of the HLG-MR, 14-15 December 2009, Issy-les-Moulineaux, France.

Action plan from the open session

SNM, EANM and Health Canada will provide guidelines for the health community on the most efficient use of available ^{99}Mo/^{99m}Tc to the NEA for public availability by end of January.

6. AIPES and its members will continue efforts to co-ordinate reactor scheduling and to implement the agreed communications protocol, including an early warning protocol for unexpected supply disruptions. Correspondingly, generator manufacturers will provide clients in the health care community projected supply levels for periods of 90 days, to be updated and refined through regular, ongoing dialogue with clients and contingency planning for unexpected shortages.

7. The IAEA through countries involved in its activities will continue the work to examine opportunities for production of ^{99}Mo from additional sources, including non-fission methods, and how and when these additional opportunities could be brought to market. This work will culminate in final reports in 2011, serving as a basis for further action by countries.

8. Processors will continue efforts to diversify their sources of supply by crystallising opportunities for irradiation of materials in other research reactors, subject to resolution of funding and regulatory issues.

9. The HLG-MR will detail the regulatory impacts on the supply chain, in particular related to transportation and target supply, and provide guidance on how harmonisation and greater co-operation can be encouraged and accelerated.

10. The IAEA, in conjunction with the NEA, AIPES, and CORAR will support the work with regulators to address regulatory issues affecting the supply chain, with priority to be given to standardisation of containers for intermediate products and their approvals. Operators and industry participants will continue to supply information to the IAEA on different transport-related issues as they arise. The HLG-MR will facilitate the agreement on responsibilities and time lines for these issues.

11. The HLG-MR will produce a mid-term diagnostic report in mid-2010, as well as the economic study on the supply chain, and will discuss next steps related to the key issues and challenges facing the medical radioisotope supply chain.

12. To contribute to the economic study, nuclear medicine societies will provide information on the scope and level of reimbursements by health authorities or insurance plans and how these

may affect demand and the ability to absorb increases in ^{99m}Tc prices, which in turn will influence the capacity for adjusting the price of ^{99}Mo.

13. AIPES will work to define the units of measurement of ^{99}Mo in order to ensure effective communication among stakeholders.

14. Covidien and CORAR will work to identify the bottlenecks in supply for ^{131}I.

Additional specific HLG-MR actions

1. NEA Secretariat, with ongoing input from other HLG-MR members and stakeholders, will complete the economic study and publish results mid-2010. If deemed necessary from the economic study, the HLG-MR will examine options for infrastructure funding models and international financing mechanisms.

2. The HLG-MR, working closely with the IAEA, will articulate criteria and details of the most promising reactor opportunities for securing ^{99}Mo production in the short, medium, and long term to provide information to decision-makers in order to accelerate appropriate decisions.

3. NEA Secretariat, in co-ordination with the IAEA and with input from other HLG-MR members and stakeholders, will produce a state of the art report on alternative technologies (non-fission and non-reactor methods) for producing ^{99}Mo.

4. The transportation sub-group will complete its work on transportation issues, this work will be incorporated into the mid-term and final reports.

5. The HLG-MR will examine issues related to processing capacity for incorporation into the mid-term and final reports.

6. The HLG-MR will convene a group to provide guidance to the HLG-MR on future demand scenarios for ^{99m}Tc, recognising differences in developed and developing countries, which will be incorporated into the mid-term and final reports.

Annex 5

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Annex 6

FURTHER READING

The NEA maintains a list of non-NEA documents on its medical radioisotope webpage www.nea.fr/med-radio. This "external documents" list was developed in order to provide a central repository of the most recent, relevant studies, position papers and guidance documents related to ^{99}Mo and ^{99m}Tc. Links to the following documents can be found at the website.

External documents

Background information/non-NEA position papers

- IAEA Coordinated Research Project on Production of Mo-99 from LEU or Neutron Activation.
- Annex to IAEA Nuclear Technology Review 2010 (September 2010) *Production and Supply of Molybdenum-99.*
- COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL on medical applications of ionizing radiation and security of supply of radioisotopes for nuclear medicine (6 August 2010).
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