THE SUPPLY OF MEDICAL ISOTOPES - AN ASSESSMENT OF THE MARKET ECONOMICS, ALTERNATIVE TECHNOLOGIES AND PROPOSED POLICY APPROACH TO ACHIEVING SUSTAINABILITY

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ABSTRACT

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).

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. 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.

As a result of the work undertaken to date, the NEA has released three reports under the new *The Supply of Medical Radioisotopes* series. These reports discuss the uneconomical situation of the supply chain, other vulnerabilities within the supply chain and alternative technologies to produce ^{99}Mo/^{99m}Tc. From this work, the NEA Secretariat and the HLG-MR have started to develop the policy approach and recommendations for governments, industry and other stakeholders that will outline the foundation for ensuring the long-term supply of ^{99}Mo/^{99m}Tc.

1. Introduction

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), which is currently comprised of 22 experts who are representatives from the governments of 13 nations, the European Commission and the International Atomic Energy Agency (IAEA). 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.

Throughout the first year and a half 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. Significant progress has already been achieved on improving the supply situation through increased communication, co-ordination of reactor schedules and a better understanding of demand-management opportunities. Continued action is required on the part of all stakeholders.

As a result of the work undertaken to date, the NEA has released three reports under the new *The Supply of Medical Radioisotopes* series (accessible at www.oecd-nea.org/med-radio). The first, subtitled *An Economic Study of the Molybdenum-99 Supply Chain,* offers a unique analysis of the $^{99}Mo/^{99m}Tc$ supply chain. The second, subtitled *Interim Report of the OECD/NEA High-level Group on the Security of Supply of Medical Radioisotopes,* presents findings related to the main issues affecting security of supply including reactor and processing capacity constraints, transport, demand management, communications and other supply chain problems. The third, subtitled *Review of Potential Molybdenum-99/Technetium-99m Production Technologies,* presents and reviews potential alternatives for the production of ^{99m}Tc and ^{99}Mo.

From this work, the NEA Secretariat and the HLG-MR have started to develop the policy approach and recommendations for governments, industry and other stakeholders that will outline the foundation for ensuring the long-term supply of $^{99}Mo/^{99m}Tc$. This policy approach, as well as the full findings of the HLG-MR, is expected to be published by August 2011.

This paper briefly discusses the findings from these three papers and introduces the policy approach that could address the issues affecting the long-term sustainable supply.

2. Economics of the ^{99}Mo supply chain

2.1 Historical development of the supply chain and its economic implications

Within the current ^{99}Mo supply chain, all the major producers irradiate targets using multipurpose research reactors, which were originally constructed and operated with 100% government funding, mainly for research and materials testing purposes. When ^{99}Mo production started, the reactors' original capital costs had been paid or fully justified for other purposes. As a result, ^{99}Mo was seen as a by-product that provided another mission for the reactor that could generate extra revenue to support research. This resulted in:

- Reactor operators originally only requiring payment of *direct* short-run marginal costs.
- ^{99}Mo prices not covering any significant share of costs of overall reactor operations and maintenance, nor of capital costs or allowances for replacement or refurbishment costs.
- The by-product status remaining with no substantive pricing changes even as the importance of ^{99}Mo production increased within reactor operating activities.

As a result, reactor prices were too low to sustainably support the ^{99}Mo-attributable portion of reactor operations, did not even cover short-run marginal costs in some cases, and did not provide enough financial incentive to support replacing or refurbishing ageing reactors. In addition, even with uncertainty on costs of conversion for a major ^{99}Mo producer, it is clear that the current pricing structure provides insufficient financial incentive for the development and operation of low enriched uranium (LEU) based infrastructure.

The processing component, originally funded by governments, was commercialized in the 1980s and 1990s. Commercialisation was originally thought to be beneficial to all parties; however, contracts were based on historical perceptions of costs and pricing. This resulted in long-term contracts with favourable terms for commercial processing firms, with no substantial change to the prices for irradiation. Once these contracts were established, they set the standard for new processors and reactors that entered the market.

An unintended effect of commercialisation was establishing market power for processors. The contracts, in some cases, created a situation where the reactor had only one avenue for selling its ^{99}Mo irradiation services. Barriers to entry (both natural and created, such as aggressive pricing strategies) sustained the market power balance and contributed to maintaining low prices for irradiation services.

A complicating factor was the historical existence of excess capacity of irradiation services. Some excess capacity is necessary to provide back-up at times when reactors are not operating, or when unexpected or extended shutdowns occur. However, operators were not compensated for maintaining reserve capacity, creating an incentive for reactor operators to use the capacity to gain revenue rather than leaving it idle, driving down the prices of irradiation services further, reducing reliability, and perpetuating processor market power.

Further downstream, pricing strategies of generator manufacturers were focused on encouraging sales of their cold kits. These strategies had a feedback effect upstream, with profits not flowing back up through the ^{99}Mo supply chain and limiting the flexibility to absorb proposed upstream price increases.

However, reactors continued to provide irradiation services even under these uneconomical conditions given the social contract between governments and the medical imaging community. Governments subsidised the development and operation of research reactors and related infrastructure, including radioactive waste management. Using part of this funding, reactor operators irradiated targets to produce ^{99}Mo. In return, citizens would receive an important medical isotope for nuclear medicine diagnostic procedures.

Although reactor operators were aware that government financial support was increasingly used for ^{99}Mo production, this may not have been transparent to governments. In some cases, the magnitude of the change did not become clear until there were requests for specific funding to refurbish a reactor or construct a new reactor. These subsidies were also supporting the production of ^{99}Mo that was exported to other countries.

Recently, governments from almost all current major producing countries have indicated that they are reconsidering or no longer interested in subsidising new or ongoing production of ^{99}Mo at the reactor level at historical levels (or at all), some more formally than others – questioning whether it remains in the public interest. With a changed social contract, the economics have to become sustainable on a full-cost basis or the availability of a long-term reliable supply of ^{99}Mo will be threatened.

2.2 Economically sustainable pricing and impacts

Starting from a representative cost and pricing structure developed by the NEA, based on information from supply chain participants, levelised unit cost of ^{99}Mo (LUCM) calculations determined the magnitude of the price changes needed for economic sustainability. Their impact, based on various capital investment scenarios, was also examined. These scenarios range from using existing reactors to building a fully dedicated isotope reactor and processing facilities. Under all the scenarios, prices must increase; the analysis of the current economic situation found that, for existing reactors, the marginal revenue from production was lower than the marginal costs, with reactors facing a loss on every unit of ^{99}Mo produced.

The LUCM calculations indicated that significant price increases are necessary in the upstream supply chain in order to be economically sustainable (up to a maximum increase of 900%). However, the analysis finds that there is very little effect on the prices per patient dose; at pre-shortage prices, the irradiation price from the reactor is calculated to be only 0.11% of the final reimbursement rate. Even at the most extreme price increase from the reactor, the value of irradiation would increase to only represent 0.97% of the final reimbursement rate.

The analysis indicates that, while prices will increase for the downstream components, these should be able to be absorbed. However, this issue may require further study and possible assessment by hospitals and medical insurance plans, especially in the context of continued downward pressure on reimbursement rates or in cases where the health system provides fixed budgets to hospitals for radioisotope purchases.

The study makes a number of recommendations and investigates options to assist decision-makers to restructure the supply chain. These recommendations have been considered and integrated, where appropriate, in on-going HLG-MR work to develop a comprehensive policy approach to encourage a long-term secure supply of ^{99}Mo/^{99m}Tc. This policy approach is discussed further below.

3. Supply chain vulnerability beyond economics

In addition to the economic issues being faced by the supply chain, there are a number of other related areas of vulnerability that the HLG-MR has been able to identify. These are discussed in-depth within the *Interim report*.

The Canadian and Dutch reactors have come back on line, providing for production of ^{99}Mo to return to levels seen before the 2009-2010 supply shortage. While this is positive news, the current capacity remains fragile and further supply shortages could be expected. A number of the producing reactors within the current ageing fleet are scheduled to be removed from the supply chain over the next decade, with the earliest scheduled for 2015 (OSIRIS) and 2016 (NRU). Coupling these shutdowns with growing demand, there is the possibility that supply would fail to be able to meet demand within the next few years.

Since the shortage, there have been a number of new projects that have been discussed and a few that have started to irradiate targets to produce ^{99}Mo. For example, the MARIA reactor in Poland, the Rez reactor in the Czech Republic, and the Russian reactors have all entered the supply chain. Even with these new additions and a consideration of the other new projects that are under development or discussion, growing demand and the removal from the supply chain of current reactors means that there could still be a supply-insufficient situation as early before the end of the current decade.

This concern on future supplies is partly as a result of regional limitations on processing capacity, which is essential for extracting and purifying the ^{99}Mo from the irradiated targets. These targets are very difficult to transport long distances, requiring processing capacity to be located reasonably close to ^{99}Mo producing reactors. There are some regions where processing capacity is not currently sufficient to support increased production of ^{99}Mo, to meet increasing demand, to deal with possible reactor outages globally or to address the changing supply structure as older reactors are retired. These processing limitations can be a significant barrier to developing new irradiation capacity and can exacerbate regional supply imbalances in shortage situations.

The necessity to transport radioactive material is another area of vulnerability affecting the reliable supply of $^{99}Mo/^{99m}Tc$. At each stage of the supply chain, radioactive material is transported, sometimes across a number of borders or even half-way around the world. In a number of cases, this transportation requires multiple approvals in multiple jurisdictions. There is also the concern that shipments of these vital medical radioisotopes are sometimes denied or delayed by carriers or are refused entry by national authorities. These issues have significant impacts on the economics of the supply chain (delay of one day reduces the amount of ^{99}Mo available by about 23%) as well as affecting the patient that is waiting for their essential medical imaging diagnostic procedure. The IAEA, among other players, continues to undertake important efforts to address these concerns.

4. Alternative Technologies

The importance of nuclear medicine and diagnostics in the world, and also the recent shortage of ^{99}Mo supply, has motivated investigations of alternative technologies. Alternative technologies could be reactor-based (like neutron activation of ^{98}Mo) or accelerator-based (direct cyclotron production of ^{99m}Tc, photofission, etc.) and they are currently at very different development stages.

In order to get a sense of the potential of alternative technologies for producing $^{99}Mo/^{99m}Tc$, the NEA, with the help of its HLG-MR and other experts, developed a common set of criteria that could be used to compare all the technologies. The physical and economic criteria were then applied to the alternative technologies. For convenience, these alternative technologies were classified as short-, medium-, and long-term technologies based on an assessment of their timeframe for potential availability.

The assessment of the various alternative technologies has been done using a three-grade rating system (low, medium and high) derived from the application the common estimation methodology. The set of criteria used within the methodology is:

- Technology maturity
- Production yield
- Available irradiation capacity
- Distribution range and logistics
- Simplicity of processing
- Waste management
- Proliferation resistance
- Other isotope co-production potential
- Normalized capital costs
- Commercial compatibility
- Estimated levelised unit cost
- Ease of nuclear regulatory approval
- Ease of health regulatory approval
- Units required to supply world market

The review defines short-term technologies as those that have already been used for $^{99}Mo/^{99m}Tc$ production, or for which nuclear imaging test have been performed. Today, the list of short-term technologies includes uranium fission route (irradiation of solid targets in research reactors), neutron activation route and direct cyclotron production of ^{99m}Tc. These technologies were considered in detail in the review.

The review highlighted that the use of low enrichment uranium (LEU) targets for ^{99}Mo production has some advantages over HEU, including: proliferation resistance; easier availability of the target material; and easier compliance for target transportation and processing. However, it currently has lower production yield than HEU and may require more targets to be irradiated with correspondingly increased volumes of waste. Increasing the uranium content of the targets (e.g. of the existing high density LEU targets, or using metallic foil targets), to counteract the lower production yield will be a key factor for LEU-based production, but there seems to be no technological or economic reasons not to deploy this technology.

The review also found that neutron activation in a research reactor has advantages in terms of safety, waste management and proliferation resistance, but has low specific activity and, with current technologies, would require the recycling of the highly enriched molybdenum in order to be cost-effective. This is currently not done. Also, more development and experience is needed in (gel) generator technology prior to eventual larger scale deployment.

Direct ^{99m}Tc production using cyclotrons has potential advantages in terms of cost, waste management, proliferation resistance and ease of approval but can only provide local needs (^{99m}Tc is a very-short lived isotope). The technology also requires significant amounts of highly enriched molybdenum (^{100}Mo). As a result, a large number of cyclotrons would be required to meet the world demand and the product would not be able to be shipped far or exported to supply global needs.

5. Policy Approach

The HLG-MR is currently developing a cohesive policy approach to address the issues being faced by the supply chain, in order to move towards a long-term secure supply of ^{99}Mo and ^{99m}Tc. At its last meeting, the HLG-MR agreed on many necessary aspects of this approach.

In order to address the problems being faced by the industry, the HLG-MR agreed that the final policy approach will have to address the following four central pillars of reform:

- Market economics need to be improved.
- Structural changes are necessary.
- The government role has to be clearly defined.
- An effective co-ordinated international approach is necessary.

The HLG-MR agreed that the policy approach most likely to be able to achieve the necessary reforms in a coherent and comprehensive manner is as follows:

- Markets should do what they can, but there are limits to what may be possible.

- Governments have an essential role in supporting market operations by ensuring the proper environment for investment and addressing market failures, while recognising the commercial nature of the supply chain.
- International collaboration is necessary, particularly to avoid policy approaches at the domestic and regional levels that could negatively affect global ^{99}Mo/^{99m}Tc supply security.
- Transparency of market operation is important to ensure that the market continues its evolution to an economically sustainable system.

In order to ensure the consistent fulfilment of responsibilities by the various communities and stakeholders of the supply chain, the HLG-MR is presently working to formulate the policy approach necessary to address the key issues affecting the ability to realise a long-term secure ^{99}Mo/^{99m}Tc supply. This approach will suggest addressing the main issues by:

- Implementing full-cost recovery.
- Sourcing, valuing and paying for reserve capacity.
- Fulfilling the essential government role in setting the proper environment for safe and efficient market operations
- Encouraging the conversion to using LEU targets for ^{99}Mo production.
- Collaborating internationally to ensure a globally consistent approach to addressing security of supply of ^{99}Mo/^{99m}Tc.
- Periodically reviewing progress to implementing an economically sustainable supply chain.

The HLG-MR is currently working to finalise the policy approach, including developing recommendations on how to implement the necessary actions. The policy approach will be finalised in June 2011.

6. Conclusions

The work of the HLG-MR and the associated stakeholders has been important in determining the issues affecting the ability of the supply chain to ensure a long-term secure supply of ^{99}Mo and ^{99m}Tc. It has also undertaken some significant actions already that have made on impact; however, there are still a number of actions that need to be taken to ensure a long-term reliable supply. Even though the current supply situation has stabilised (at the time of writing the article), it is important to stress that the underlying problem – the unsustainable economic structure – has not yet been addressed; supply shortages could become commonplace over the next decade unless longer-term actions are taken to secure supplies.

It is clear that without ongoing financial support from governments, commercial pricing is required for the continued supply of reactor-based ^{99}Mo in the medium to longer term and the conversion to LEU-based production. Changes are necessary to arrive at a ^{99}Mo/^{99m}Tc supply chain that is economically sustainable and reliable.

The policy approach currently being developed by the HLG-MR will set the foundation for consistent and comprehensive steps forward to ensuring the long-term security of supply of the vital medical radioisotopes molybdenum-99 and its decay product technetium-99m.