Joint Observatory between the European Commission and AIPES
European Observatory for medical radionuclide supply

Working Group 3 (WG3)
Management of conversion from HEU to LEU and Target Production

Overview

Mo-99 is the most important radionuclide in nuclear medicine. It is used to produce Tc-99m generators which are used in more than 30 million diagnostic nuclear medicine procedures around the world each year. Tc-99m is used in more than 100 different types of diagnostic nuclear medicine procedures including evaluation of myocardial function, detection and staging of cancer, brain disorders, infections and many other diseases. Accordingly, a stable and sustained supply of Mo-99 must accompany the conversion process from the use of Highly Enriched Uranium (HEU) to Low-Enriched Uranium (LEU) to manufacture targets for irradiation in the nuclear reactor.

Mission and objectives

The main objective of WG3 is to secure the continuity of supply of Mo-99 throughout the process of conversion of target production from HEU to LEU. It implies a seamless supply of HEU and LEU during this process. The work was completed by examining three major areas including: 1) identify risks that could occur during the HEU/LEU conversion process; 2) define a risk assessment process; and 3) recommend relevant policy options to avoid any discontinuity in the supply chain of Mo-99/Tc-99m caused or induced by the conversion process. In addition to defining the risks and completing a risk assessment matrix, the working group advises to focus primarily on three recommendations which would mitigate several of the significant risk factors in the conversion from HEU to LEU targets for the production of medical radionuclides.

WG3 also received a discussion item from WG4. This item addresses the feasibility of design harmonization of LEU-based targets for use in Europe. Although this may appear to be an infrastructure item, WG3 accepted this item from WG4, due to the specific implications it has on the conversion of targets from HEU to LEU. Target harmonization should also contribute to secure the long-term supply and availability of Mo-99 produced. WG3 appreciates that target harmonization must be implemented by the Mo-99 producers. It was discussed substantially by

WG3 and will be summarized later in this report. The issue of a new LEU target for the production of Mo-99 and other medical isotopes has also been addressed by a working group of the IAEA and in the OECD/NEA High-level Group on the Security of Supply of Medical Radioisotopes.

Meetings

The WG3 had four formal meetings on:
- 15 May 2012, Brussels, Belgium
- 28 June 2012, Brussels, Belgium
- 3 October 2012, Brussels, Belgium
- 1 February 2013, Paris, France

On 9 January 2013 in Petten, Netherlands: MM. Alehno and Hegeman with partial participation of Mr. Brown, held a preparatory meeting before the Plenary meeting of the Observatory.

These meetings included:
- Discussions on the mission statement and action plan.
- Work on the implementation of the action plan.
- Preparation of an evaluation matrix by defining risks, risk factors and advice.
- Preparation of a draft report of the WG3.
- Discussion of the further actions after the finalisation of the report.

Group Members

The working group comprises representatives of the European Supply Agency, AIPES, the fuel and target manufacturers, the reactors and the Mo-99 producers:
- Mr. Ivo Alehno, Euratom Supply Agency, leader of the WG3
- Dr. Jean Bonnet, AIPES
- Mr. Roy Brown, Covidien/Mallinckrodt, representing the Mo-99 processors
- Mr. Hans Hegeman, NRG, representing the reactors
- Mr. Christophe Jarousse, AREVA-CERCA
- Mr. Pavel Peykov, OECD/NEA (since September 2012)

Evaluation of the Risks for Conversion from HEU to LEU

The working group started by writing down a generic description of the production process, then for each process step the risks were identified that arise from the HEU to LEU conversion starting with the risk cause (event), followed by the potential impact. Finally potential mitigating actions were determined including recommendations for the radiopharmaceutical industry (the whole supply chain) and policy-makers.

The Mo-99 production process

The first step that was taken for the risk evaluation for the conversion from HEU to LEU was to identify a common generic description of the production process that envelops both the EU supply chain as well as other supply chains elsewhere in the world. The supply chain has been described extensively in previous reports, such as from the OECD/NEA. However, for the identification of the risk from HEU to LEU conversion these descriptions are either not detailed enough or are missing steps such as waste treatment.

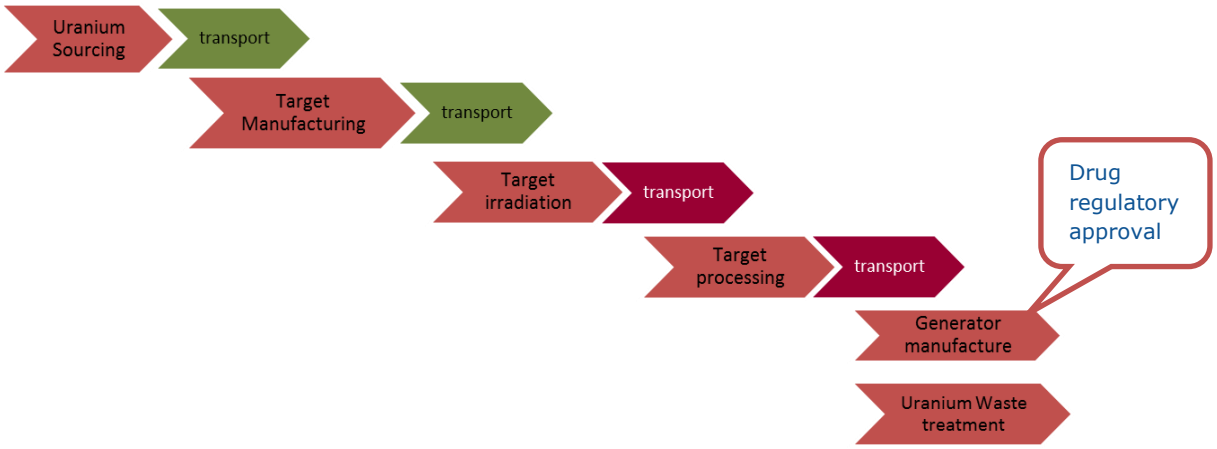

Figure 1. ^{99}Mo production chain

When converting from HEU to LEU in principle all production steps require requalification and most of the time relicensing with authorities. Therefore every single step in. Figure 1 is considered: uranium procurement, target manufacturing, target irradiation, processing, generator manufacture and uranium waste treatment arising from the production process. After every step in the production chain, transportation takes place. In the sections below, a more detailed description of some key parts of the production chain is provided, such as target manufacturing, irradiation and processing, and drug regulatory approval.

Definition of a risk

A risk is an event that may happen during the HEU to LEU conversion process and has a negative influence on the security of supply of medical isotopes, in particular Mo-99 .

Risk analysis

Risks on the security of supply of Mo-99 as a result of the HEU to LEU conversion have been identified at each step of the production chain. Subsequently, potential causes of such risks have been analysed and potential consequences evaluated. Finally, potential mitigating actions have been considered.

Following risk identification and assessment of the risk profile, some key recommendations have been prepared.

The following sections provide a detailed description of three risk areas, related to key parts of the production chain – namely - target manufacturing, target irradiation and processing, drug regulatory agency approval - followed by key recommendations of the working group. Appendix 1 contains a detailed table with the risks identified per process step, made up of four columns: process step, risk consequence, risk factor and cause, and finally potential mitigating actions.

Target manufacturing (including uranium sourcing and transportation)

Prior to introduction into the Research Reactor core, where the fissile uranium contained in the target is transformed into Mo-99, several milestones have to be successfully passed.

This section describes the main milestones which allow a target to be delivered to the reactor - uranium supply, target production and transportation- then identifies potential sources of risk and provides options to avoid and/or limit the associated consequences.

Made of uranium compounds, the construction of a target depends on the supply of uranium. The USA and Russia are the two unique suppliers of such material.

Presently, Europe uses HEU, which raises political issues (Europe is committed to minimising/reducing the use of such material), as well as operational issues in terms of supply security.

Procurement of HEU is strictly regulated by International policy; it is exported under stringent conditions and only through governmental agreements. For the EU Mo-99 producers, USA is the unique source of HEU and this material is currently being delivered in very small quantities, which stresses the global Mo supply chain and reinforces the risk of Mo-99 shortage in the case of any unexpected delay in the LEU Mo-99 conversion program. Since exportation from the USA of HEU material takes more than 2 years, building up a specific HEU safety stock, located in the EU under EURATOM scrutiny, seems to be one interesting option to be investigated by the EU. Nevertheless, the USA has an export policy based on an "as necessary" strategy, taking into account the assessment of the conversion efforts; as a result, the USA promotes delivery on a yearly basis. This contradiction between the US position (nuclear security driven) and the market's need (security of operation supply) deserves to be discussed at EU political level.

The European industry is developing solutions to use LEU, uranium with an enrichment fraction below 20% of U235- instead of HEU. Even though delivery conditions vary according to suppliers, the strategic approach or supply policy (export licence conditions, prices, etc.), the procurement of LEU material is presently not considered as politically and logistically critical. Nevertheless, for a long-term approach, it is strategically important for Europe to investigate different means of securing adequate LEU supply.

In the EU, Mo-99 targets are manufactured in France by AREVA-CERCA, as unique supplier. Historically, HEU targets have always been and continue to be delivered from France, with no breaches in supply having been reported so far for more than 50 years of activity.

Target production is an open and free market. World-wide there exist other suppliers, such as CNEA, who are able to produce LEU targets under proper commercial contracts.

Targets are manufactured on a fuel production line in a nuclear installation. The first set of operational risks is linked to unexpected major events which may cause interruptions of production, e.g. which have a large impact on the installation (fire, flooding and/or the production line destruction). This risk is in fact extremely low, since the production and workshop premises installations are regulated by nuclear authorities, where safety and security are managed through stringent rules which must be and are strictly followed. The first safety and security principle applied is based on "defence in depth" where several barriers of defences are required for each identified risk - global and/or local, e.g. fire, criticality. If occurring, the situation should be brought under control through dedicated means and/or within an acceptable timeframe, with the "effect" confined to a specific space.

The AREVA-CERCA premises are evaluated every 10 years by an independent board of experts under a mandate of the French Nuclear Authority (ASN). The ASN conduct a routine assessment of the premises several times a year and makes recommendations to be strictly followed. Safety investments are made accordingly, whereas licence renewals and plant operation are dependent

on deployment of the necessary safety improvements. In order to ensure the long-term security of target and fuel supply, manufacturers must commit themselves to the business in the long run, preserving their technical ability to upgrade the facility as requested by regulators and therefore ready to invest significantly on a regular basis and for many years. Industrial suppliers need confidence in the market in order to commit themselves financially. As a research reactor fuel and target manufacturer, AREVA-CERCA has its own nuclear licence and is not dependent on other factors. Safety and security are its top priorities.

The second set of operational risks is linked to production quality issues, which may lead to delays in delivery, while waiting for dedicated measures to be implemented. In the case of HEU targets, this risk is extremely low, since the know-how, as stated in the specifications, is wide and has been shared for a long time between the parties involved -manufacturer, reactor and Mo-99 processors.

Beside large scale HEU target production for the European industry, AREVA-CERCA has also been involved for a few years in industrial scale production of LEU targets for Australia and South Africa. These targets are irradiated safely and Mo-99 produced routinely.

The conversion program, defined as the entire action plan to be implemented in order to get the appropriate licence / validation grant for the use of LEU targets (Manufacturing & Irradiation) for Mo-99 production, is carried out through a joint commercial approach between Mo-99 producers, some reactors or operators and target suppliers.

The transition from HEU to LEU targets implies, by definition, some uncertainties are determined and borne by the strategic and technical options selected by the Mo-99 producers and/or the dedicated operator in charge of the conversion program.

Some of those uncertainties, related to the target manufacturing, have been mitigated thanks to AREVA-CERCA's knowledge, obtained through its own R&D investments. The conversion efforts and the timeframe necessary to obtain conversion at an EU level have consequently been reduced.

A remaining risk could impact the conversion schedule through possible unexpected technical concerns on irradiation behaviour and/or Mo-99 processing results. The risk is accentuated by the necessary preservation of dual HEU and LEU Mo-99 supply chain until the full LEU conversion is completed.

Presently, 2015-2016 is considered as the time limit for the HEU/LEU shift.

Keeping a HEU supply chain available until full LEU Mo-99 qualification and implementation have been granted to EU producers is a first priority. This requires continuous exchanges between Europe and the USA, involving yearly assessments of the progress of the conversion programs as well as top level political discussions. At EU level, securing a sustainable production of targets during the transitional phase towards LEU would require an appropriate management of the HEU and LEU targets stock, influenced by a "Just-In-Time" USA HEU delivery strategy, which is putting pressure on the conversion effort.

Risks on target supply during the LEU conversion program stem from two sources:

- Standard risks with regular target supply

    - Uranium not available for the requesting customer. Each customer is responsible for the supply of uranium, and the lead time for supplying uranium may take 18 to 24

months. Any unforeseen increase in a customer's needs or a quality incident should be compensated by a safety stock of HEU raw material.

- Production or delivery concerns: reactors should have enough target inventory to allow for the accommodation of the production of a replacement product or for the rescheduling of a transport operation.

- Reactor incident or program change: other reactors should keep enough target inventories to enable production of Mo-99 in lieu of a reactor being unexpectedly unavailable or to cope with a sharp increase in market demand (transfer of production between European reactors). Mitigation of this risk implies a smart management of the targets technology by the customers.

- Production demand can increase (situation when NRU was stopped) for European producers. In such a situation, target availability may become problematic (24-30 months for a full supply cycle: from Uranium to target).

- Specific risks linked to any qualification program included in the shift towards LEU targets

  - A qualification program may lead to disruptions in the regular production. Since, as a finished product, Mo-99 cannot be stored, the production lines should be able to compensate in the case a problem with a qualification program causes a reduction of Mo-99 availability. The HEU / LEU transition needs to be well managed in order to guarantee the routine secure production of HEU Mo-99 and new LEU Mo-99.

  - A suitable qualification program and associated schedule is required to ensure that the full irradiation capacity of LEU targets can be covered in the EU, this should be defined well in advance and include the transitional period.

  - There must be a careful projection/estimation of target consumption during the period of transition from HEU to LEU targets, as production lead time for HEU targets is long and an unplanned shortage thereof could last up to 24-30 months if uranium is not available. Extra HEU metal could potentially be supplied by DOE to European reactors according to a careful assessment of the transitional period between the first LEU Mo-99 production in Europe and full LEU production.

Transportation is an activity, performed at a number of steps in the chain, it is performed initially for the Uranium to be imported in France, then for the Fresh Targets to be transported to the appointed research reactor, and ultimately for the irradiated targets to be transported to the Mo-99 processing line at Fleurus, Belgium or Petten, Netherlands. Normally, transportation activities concern around three specific things: the container where the product is placed for transport, the transportation itself and administrative authorization encompassing for instance export licence, EURATOM Supply Agency interface, nuclear insurance according to international treaties, etc.

Transportation risk is mainly linked to the timely availability of specifically licensed containers, dedicated to irradiated targets; therefore there is also a big licensing risk. Mitigation of this risk may be evaluated together with the involved regulators, experts on cask licensing activity, as well as Mo-99 producers, which may be the cask owners.

A Unified European Target Design

There are currently two European Mo-99 producers (IRE and Covidien). Both companies are in the process of converting from an HEU target to an LEU target. Both companies are moving to an LEU dispersion plate type of target. There is a possibility of both companies adopting the same target. There are some potential advantages of a unified target design. These advantages include potential cost savings, maximum flexibility for having larger back-up stock of targets, and reducing safety risk (mixing up targets). However, each manufacturer has moved down similar but different paths for a target design. It is not yet clear whether these two manufacturers will be able to agree on an identical target. This decision will be up to the individual companies, and the Working Group does not believe the Observatory should get involved in such commercial matters.

Target irradiation and processing

Target irradiation takes place in various Research Reactors around the world. When a new production facility is being developed in a research reactor, it typically requires multiple approvals from various safety and regulatory bodies (competent authorities). The use of a new target design also requires similar approvals. Such a qualification process often comprises multiple stages e.g. cold testing and subsequent hot testing, depending on the requirements imposed by the individual regulatory body. Only following successful completion of a stage, i.e. demonstrating no damage to the targets, may the next qualification step begin. In some cases, two qualification processes will happen in parallel, especially when a new target design requires the design and build of a new production facility in the reactor.
Since most of the research reactors perform irradiation experiments on a regular basis, being therefore used to the approval processes, the risk on the approval process is considered to be low. A potential risk has been identified in a recent OECD/NEA report on the "market impacts of converting to low-enriched uranium targets for medical isotope production", which has shown that the conversion to LEU might result in a loss of total yield in the shorter term, and have little effect in the long term.

A similar qualification process will take place at the processors and will again include multiple approvals from various bodies. Here, the risk mentioned in the risk analysis relates to potential delays caused by adjustments required by the back-end waste treatment and disposal. Another risk arising from the conversion is linked to the quality and stability of the final product, because the isotopic content of the LEU target is different compared to the HEU target.

The back-end waste treatment stemming from target processing needs to be adjusted, as the waste volumes will change due to the target conversion. Before upscaling to regular production from LEU targets, the waste process needs to be aligned with the new processes and, therefore is a risk of delay in the HEU to LEU target conversion.

As all nuclear transport casks are licensed for a specific content, transport casks need to be relicensed through regulatory bodies in individual countries. Currently, a licence issued by an individual EU country requires acceptance in another country, which makes the whole licensing process for the transport casks of fresh and irradiated targets a very lengthy one. As a consequence, there is a high risk of delay associated with the (re)licensing of the transport casks, which may affect the transportation routes and temporarily change or limit the potential production chains within Europe. Unhindered use of these production chains is currently critical to reduce the effects of reactor outages and issues.

Drug Regulatory Agency Approval

Drug regulatory approvals are controlled by individual governments around the world. The drug regulatory agencies must approve all new sources of Mo-99, and any major modification to an existing process, such as the conversion from HEU to LEU targets. Although different regulatory agencies handle the process and have different names for the various approvals, the process between countries is very similar. For example, the European Medicines Agency (EMA), the Food & Drug Administration (FDA) in the U.S. and Health Canada use a very similar process for raw material, sometimes called Active Pharmaceutical Ingredient (API), review. The API is a major component of a drug product. Molybdenum-99 (Mo-99) is considered an API in Tc-99m generators. A summary of what these processes are named is summarized in Figure 2 below for Europe, the U.S. and Canada.

	Major Drug Component	Document for producing Component	Drug Approval Application
EMA (Europe)	Active Pharmaceutical Ingredient (API)	Drug Master File (DMF)	
FDA (U.S.)	Active Pharmaceutical Ingredient (API)	Drug Master File (DMF)	Supplemental New Drug Application (sNDA)
Health Canada (Canada)	Active Pharmaceutical Ingredient (API)	Drug Master File (DMF)	Notifiable Change (NC)

Figure 2. Regulatory Components

The application for approval to market a drug is sent to those regulatory agencies who are involved in Mo-99/Tc-99m generators or radionuclide-related activities and decision making.

Process for Getting New Supplier Approved

Drug regulatory agencies generally require pre-approval for the use of new Mo-99 sources. Before a new source of LEU-produced Mo-99 can be used to produce Tc-99m generators, it must first be recognized by the drug regulatory agency in the country in which the Mo-99 will be used. For example, if a Mo-99 producer in Belgium or The Netherlands wants to convert their existing process of producing Mo-99 from an HEU target to an LEU target, the LEU-based Mo-99 must be approved by the drug regulatory agency in the countries where those Tc-99m generators will be used. This drug regulatory agency approval is the responsibility of the generator manufacturer, and not the Mo-99 producer. However there are certain things the Mo-99 producer must do before the generator manufacturer can approach the drug regulatory agency for approval to use that new source of Mo-99. There are several recent examples of when a new Mo-99 supplier was added to the approval for a Tc-99m generator manufacturer. In 2010, Covidien in The Netherlands was successful in adding the MARIA reactor in Poland to their drug approval for generators produced at

their facility. Similarly, in 2011 Lantheus in the U.S. successfully added LEU Mo-99 from the SAFARI reactor in South Africa to their NDA in the U.S.

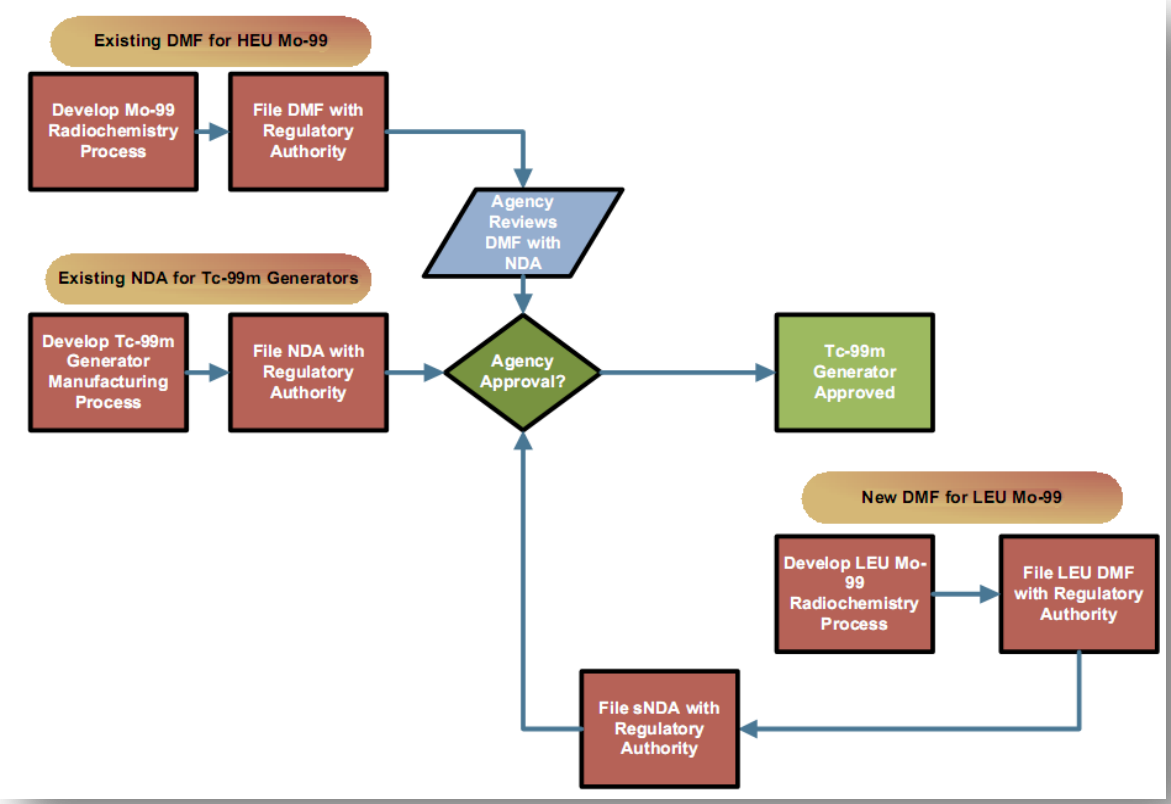

Figure 3. Regulatory Process

Drug Master File

The Drug Master File (DMF) outlines how the Mo-99 is produced. There are existing DMFs for HEU Mo-99. For a Mo-99 producer to start using LEU-produced material, they would need to write a new DMF, or modify the existing DMF to detail the new process used for the different target material. The typical contents of a DMF are as follows:

- **Component Specifications**
- **Master Batch Record**
- **Facility Description [No longer required in the U.S. (Type I DMF)]**
- **Standard Test Methods & specifications for in-process testing**
- **Standard Test Methods & specifications for the release of Mo-99**
- **Stability Protocol**
- **Product release criteria**

The Mo-99 producer files the DMF with the drug regulatory agency for which approval to use that Mo-99 is sought. The holder of the DMF also has to grant the drug regulatory agency access to the DMF. The agency will then review the generator manufacturer's NDA (U.S.) or NC (Canada) submission along with the DMF.

DMFs include a description of the chemistry, manufacturing and controls regarding the production of a drug component such as Mo-99. The DMF should also include data from several batches of

the new Mo-99 produced at the facility using the intended commercial process and qualified equipment.

Before a Tc-99m generator manufacturer can use a new supplier of Mo-99, they must qualify the material and get the appropriate drug regulatory agency to approve it.

Information Needed in a Prior-Approval Submission

The Tc-99m generator manufacturer has to collect information on the new source of LEU-produced Mo-99 for submission in the prior approval supplement in order to qualify the LEU material. Typically three generator qualification runs are made using material from the new supplier.

- The manufacturer produces Tc-99m generators in a range of sizes (Curies).
- Performance data is collected on the Tc-99m eluent from the generator using the new Mo-99
- Performance data is collected on radiopharmaceutical kits reconstituted with the above generator eluent.
- Typically pH, radiochemical purity, radionuclidic purity, stability, sterility are all examined.

These data are compiled and submitted to the drug regulatory agency in a supplement to the Tc-99m generator NDA (sNDA) or as a Notifiable Change (NC). The drug regulatory agency is particularly interested in the quality of the Mo-99 from the new process, the quality of the generators using the new source of Mo-99, and the performance of the radiopharmaceuticals prepared using Tc-99m from the generators using the new source of Mo-99.

Recommendations by the Working Group

Recommendation 1.
In order to prevent risks related to the existence of a unique target manufacturer at EU level and to address all the risks identified in relation to LEU conversion, the WG3 recommends that target stocks be increased at the reactors, especially during the conversion process.

Recommendation 2.

In order to facilitate timely HEU to LEU conversion the working group is recommending that transportation and nuclear competent authorities expedite container approval and transportation licences for LEU.

Recommendation 3.
In order to facilitate timely HEU to LEU conversion the working group is recommending that drug regulatory agencies expedite review of new LEU based Mo-99 sources.

Appendix 1.

"Management of conversion from HEU to LEU and target production for the EU - risk assessment of the radioisotope supply chain - "			
Process step in the value chain	**Risk consequence**	**Risk factor/cause/event**	**Advice**
URANIUM procurement Material procurement, Contract, ... On site assessment, Export licence, …	Timely delivery of HEU Gap between supply from HEU and supply from LEU. Can LEU-20% supply be guaranteed for longer time?	Availability of HEU; small quantities currently shipped of HEU. No path to increase the HEU amount. Conditions/provisions requested for HEU supply and LEU supply. Only two LEU sources outside EU and only one HEU source. Access to HEU stock worldwide limited, even for down-blending to 20% LEU.	Requirement of adapted HEU stock. Put US-DOE HEU stock under EURATOM control as security stock. Plan for contingency time for HEU to LEU conversion. Launching investigation for the need of enrichment to 20%
Transport raw material	Delay of transportation.	High frequency of transports of small amounts. Getting export licence from US DOE. Number of licensed transporters.	Requirement of adapted HEU stock. Put US-DOE HEU stock under EURATOM control as security stock. Less frequent delivery of higher quantities at least sufficient for 2 years.
TARGETS procurement Contract, administrative declaration (EURATOM,) Manufacturing (Production,	Although it has not happened, there is a limited risk of delay of target delivery.	Limited number of fabricators of targets (only one licensed and qualified fabricator in EU)	**Security stock of targets at reactors (licence constraints should be checked of the place of storage).**

inspection,...)			Industry should develop a strategy policy of supply
Unified Target design. Potential opportunity to develop a unified target design during HEU to LEU conversion. Advantages: saving (investment) costs, de-risking Mo supply market, maximum flexibility, possibility for having larger back-up stock of targets, reducing safety risk (mixing up targets)	Delay of the HEU-LEU conversion; unacceptable risk on agreed conversion dates for regular production. Loss of efficiency (yield) Will standard target limit the amount of irradiators?	Extensive negotiations required between reactor operators, processors. Investments already made would need to be recovered. Output yield for a processor may reduce when the developed LEU target from processor A is favored over the LEU target being developed by processor B. A unified target may not fit in all reactors and therefore exclude the particular reactor from production.	Support the effort of the IAEA to organize a workgroup for next generation target designs. Start EU framework programme for next generation target design - proof of principle.
TRANSPORTATION of the fresh targets Delivery management: Export licence, … Transport authorization, ... Cask licensing, …. Contract… Delivery up to the reactor…	Delay in obtaining LEU targets Inflexibility to diverge transport to other destinations	Time needed for cask licensing depends on regulator(s) requests. Need for multiple licences for each individual country. Number of licensed casks is limited.	Industry should develop transport capabilities between reactors; policy makers and competent authorities should ease the export licence issuing between EU countries. EU policy makers should develop a single (export) licence at EU level.
IRRADIATION at the research reactor Order intake and planning Target loading Irradiation Cooling Qualification as needed…	Delay of the HEU-LEU conversion due to additional requirements from safety authorities. Increase sensitivity to reactor	Old state of reactors; additional measures required and will need to be applied during the implementation of chances. Post-Fukushima may result in long-term outages. Increase in logistic actions (more targets due to	Develop plan for LEU introduction, logistic requirements, capacity requirements during introducing LEU

	outages LEU conversion will lead to lower yield (per target).	lower yield) Number of reactors is limited that could recover the loss of yield. Phasing in and out of HEU and LEU while reactors require more maintenance time considering irradiation facilities' age.	
TRANSPORTATION of the irradiated targets Planning Cask licensing as needed Transport	Delay for shipping irradiated LEU targets to processing facilities	Casks currently not licensed for LEU; long licensing periods Only few casks available for irradiated target transports	**Give high priority at Nuclear Safety Authorities for licensing of casks in EU countries to transport irradiated LEU targets.** License other transport casks for back-up solutions.
PROCESSING of Mo-99 Cask unloading Dissolving targets Purification Column preparation & shipment	Delay in Process development and management of modified waste effluent Risk on quality of the final product and stability	Process development and management of modified waste effluent can take a great deal of time. Most Mo-99 producers have already begun LEU process development and waste handling provisions. Optimize processing for yield at the same time as qualifying the LEU process may cause delay in conversion.	Allow adequate time for conversion.
Waste treatment and disposal Separation of waste streams Interim storage Preparation for waste transports Transport to final repository	Waste storage capacity runs out more quickly using LEU targets. Delay for conversion or low yield from the processing	Capacity in final repositories is limited; conversion to LEU will result in more waste per curie Mo; we will reach the capacity limit earlier; extension of repositories required.	Timely build of new repository space is required.

	facility.		
BULK Mo-99 TRANSPORTATION Planning Checking licence requirements Transport to generator manufacturer	No risks are expected from LEU derived Mo-99 since finished product should be identical to HEU derived Mo-99	None	None
GENERATOR production Test according to specs, and accept dilute to appropriate concentration Fill columns Assemble in generator	Not able to use the LEU-Molybdenum in the generator	Incoming raw LEU Mo-99 spec may be different due to introduction of other elements (i.e. Tungsten), which will require revised specs and additional testing prior to vendor qualification. Generator manufacturers have established incoming raw materials spec looking for known impurities which may be contained in LEU Mo-99	Generator manufacturers should be aware of the need to modify any specifications to produce any moly from LEU
Transport to final customer Transport in standard A type cask	LEU derived Tc-99m generator should be identical to HEU derived generators, no risks are anticipated	None	None
Registration process with drug regulators Qualify materials Produce generators and qualification runs Collect data with radiopharmaceutical kits Submit data to drug regulator to get approval	Delays in approval of the dossiers	Concerns raised by regulatory authorities on Mo-99 producers' DMF, or process changes, regulatory agency concerns over potential impurities	**Expedited review by drug regulatory agencies will get LEU Mo-99 into routine use more quickly.** Develop an ad-hoc center of expertise at EU level for this conversion