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COMMISSION STAFF WORKING DOCUMENT

**Report to the European Commission on activities following up the Council Conclusions
of 15 December 2009
on the Security of Supply of Radioisotopes for Medical Use and the Council Conclusions
of 6 December 2010 and 7 December 2012 ‘Towards the Secure Supply of Radioisotopes
for Medical Use in the European Union’**

REPORT TO THE EUROPEAN COMMISSION
on activities following up the Council Conclusions of 15 December 2009
on the Security of Supply of Radioisotopes for Medical Use and
the Council Conclusions of 6 December 2010 and 7 December 2012
‘Towards the Secure Supply of Radioisotopes for Medical Use in the European Union’.

Euratom Supply Agency, June 2015

This report was reviewed at working level by the European Commission services involved in the European Observatory on the supply of medical radioisotopes as well as by the European Medicines Agency and was endorsed by the Euratom Supply Agency's Advisory Committee at its meeting held on 28 April 2015 in Luxembourg.

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1. INTRODUCTION

The subject of medical radioisotope production came into focus for the European Union (EU) a few years ago, in 2008, when the EU Health Ministers raised the issue of a supply shortage of the most vital medical radioisotope — Technetium-99m.

In parallel, OECD's Nuclear Energy Agency (NEA) decided in 2009 to establish the High-Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR).

The EU addressed this issue through a series of Council Conclusions calling upon the European Commission to take action:

1.1. Council Conclusions on the Security of Supply of Radioisotopes for Medical Use, 15 December 2009

- The Council invited the Commission to investigate with relevant stakeholders different possibilities for short-, medium- and long-term solutions to secure the supply of radioisotopes for medical use in the EU, taking due account of production facility projects in Member States, technical developments and predictions of future demand for radioisotopes in medical applications.
- The Commission was also invited to collaborate with other fora (i.e. OECD/NEA, HLG-MR and IAEA) dealing with this issue and to regularly report on the progress of the work to the Council and the European Parliament.

1.2. Council Conclusions 'Towards the Secure Supply of Radioisotopes for Medical Use in the European Union', 6 December 2010

- The Council urged the Commission to define, on the basis of a refined 'Reference Scenario' and after having specified the objectives to be met, a European solution, for instance a Joint Undertaking, for ensuring medium and long-term security of supply of radioisotopes within the European Union, without prejudice to Member States' national research budgets.
- It invited the Commission to report regularly on the progress of the work to the Council and the European Parliament.

1.3. Council Conclusions ‘Towards the Secure Supply of Radioisotopes for Medical Use in the European Union’, 7 December 2012

- The Council invited the Commission to present a proposal for a relevant instrument providing EU support to the conversion from highly enriched uranium (HEU) to low enriched uranium (LEU) targets, bearing in mind that any financial assistance by the EU through this instrument should be dedicated to supporting the installation's use for medical purposes, contributing to the secure supply of medical radioisotopes in the European Union and identifying the necessary research needs regarding the supply of medical radioisotopes that might be supported by the Euratom Framework Programme.
- The Council also invited the Commission to present a report on activities following up the Council Conclusions of 15 December 2009 on the Security of Supply of Radioisotopes for Medical Use and the Council Conclusions of 6 December 2010 ‘Towards the Secure Supply of Radioisotopes for Medical Use in the European Union’.

This report describes the current situation in terms of responses by the EU institutions and looks at further short- and medium-term actions to be undertaken.

The report was consulted with the Euratom Supply Agency Advisory Committee, which endorsed it at its meeting held on 28 April 2015 in Luxembourg.

2. BACKGROUND INFORMATION ON NUCLEAR MEDICINE

Nuclear medicine is a branch of medicine that uses radioisotopes (radionuclides) for the diagnosis and treatment of various diseases, including some of the most severe and frequent ones, like cancers and cardiovascular diseases. Radioisotopes are combined with pharmaceuticals to form radiopharmaceuticals. These radiopharmaceuticals, after administration to the patient by injection, inhalation or orally, reach and accumulate in specific organs or tissues, and can thus provide a non-invasive and highly sensitive method of detection. This unique ability distinguishes nuclear medicine from most other imaging modalities, by being primarily a functional and molecular imaging technique, studying and visualising molecular, cellular and physiological processes and functions, as opposed to traditional anatomical imaging such as computed tomography or most forms of magnetic resonance imaging. Therefore, nuclear medicine imaging procedures often identify

abnormalities in the early stage of a disease — long before many medical problems become apparent with other diagnostic tests.

There are about 100 different nuclear medicine imaging procedures available today, including for the diagnosis of hyperthyroidism, cardiac stress tests to analyse heart function, bone scans for orthopaedic injuries or cancers, lung scans for embolism, and liver, gall bladder and kidney procedures to diagnose dysfunctions. Over 10000 hospitals worldwide use radioisotopes in medicine and the vast majority of the procedures (about 90%) are for diagnosis.

2.1. Molybdenum-99/Technetium-99m

Technetium-99m (Tc-99m) is the most widely used isotope in nuclear medicine diagnostic applications, accounting for around 90% of all radioisotopes used, which corresponds to around 30 million examinations yearly worldwide, about 7 million of them in Europe. Tc-99m's main use is for cardiac imaging and for bone scans to detect cancer, where early and reliable diagnosis is critical. Europe is the second largest consumer of Tc-99m.

Tc-99m is a gamma emitter with a half-life of only 6 hours, thus allowing scanning procedures which collect data rapidly and keep total patient radiation exposure low. However, the short half-life presents a problem in terms of a reliable supply chain since Tc-99m cannot be stockpiled. A more practical arrangement is for the supply of Tc-99m to be provided by producing Molybdenum-99 (Mo-99), which decays into Tc-99m with a half-life of 66 hours.

The parent isotope Mo-99 is produced in a limited number of nuclear research reactors by irradiation of uranium targets. Once irradiated, the targets are shipped to specialised processing facilities where the Mo-99 is extracted from the irradiated targets by dissolving the targets and purifying the solution into a pharmaceutical-grade substance. Finally, the processed Mo-99 is shipped for production of Technetium generators, from which Tc-99m can be eluted. The Technetium generators are delivered to nuclear medicine facilities and hospitals weekly for administration to patients. Any supply disruption can have negative and sometimes life-threatening consequences for patients.

2.2. Mo-99 global supply chain

Only eight nuclear research reactors provide about 95% of the world's Mo-99 production: the NRU reactor in Canada, the HFR reactor in the Netherlands, the BR-2 reactor in Belgium, the OSIRIS reactor in France, the SAFARI reactor in South Africa,

the OPAL reactor in Australia, since March 2010 the MARIA reactor in Poland and since May 2010 the LVR-15 reactor in Czech Republic. Several other smaller reactors provide local and regional supplies with no major influence on the global market.

Almost all the above-mentioned reactors are over 40 years old and are approaching the end of their lifespan. Because of this they have an increasing need for planned maintenance cycles and a growing frequency of unplanned production interruptions. As a result, the global supply of radioisotopes has become more fragile in recent years. In August 2008, the HFR reactor in the Netherlands, one of Europe's main research reactors producing Mo-99, was shut down due to gas bubbles detected in the main cooling system. It remained shut down until February 2009. In addition, routine maintenance shutdowns of the HFR reactor were undertaken in July and September 2009, and another major 6-month shutdown was started on 19 February 2010 to repair the reactor's cooling water pipework. In May 2009, the detection of a heavy water leak at the NRU reactor in Canada — also a major global supplier of Mo-99 — led to an extended shutdown until August 2010.

The European Association of Nuclear Medicine (EANM) conducted a survey amongst its members which showed that the supply shortage that occurred in autumn 2008 seriously affected 14 European countries (Belgium, Croatia, Czech Republic, France, Germany, Greece, Hungary, Iceland, Ireland, Lithuania, the Netherlands, Slovakia, Switzerland and the United Kingdom). Further but less severe shortages occurred between November 2012 and June 2013 (HFR outage) and between October 2013 and April 2014 (HFR and Petten Mo-99 production facility outage).

2.3. Economics of the Mo-99/Tc-99m supply chain

The supply chain of radioisotopes for medical use is characterised by the interaction of public and private actors and relies on global cooperation and partnership between a number of government and private stakeholders. The nuclear research reactors in which radioisotopes are produced are owned by governments all over the world. Private companies manufacture radiopharmaceuticals and distribute them to hospitals and other healthcare providers (including private practices); some of the hospitals in which most of the nuclear medicine procedures are carried out are publicly owned, while some are operated by the private sector. Finally, public social security schemes, which provide reimbursements for a large number of nuclear medicine procedures, decide on the amounts they reimburse for such procedures.

The government-funded reactors where radioisotopes are produced were constructed in the 1950s and 1960s for a variety of research-related purposes (nuclear research and material science). When Mo-99 production from those reactors was developed, it was considered as a 'sideline' activity, so that reactor operators only required reimbursement of direct short-run marginal costs. The historical neglect of the broader direct and indirect costs led to prices for target irradiation that were too low to be of interest to industrial and commercial investors, at least at the level of production of raw Mo-99. A resulting, indirect, consequence of this is that some governments (those with medical radioisotope-producing reactors) subsidise the Tc-99m radiopharmaceuticals for their health services or those of other European and non-European countries.

A study on the economics of the upstream and downstream Mo-99 and Tc-99m supply chain was part of the work plan of the OECD/NEA High-Level Group on Medical Radioisotopes (HLG-MR) established in April 2009 to oversee international efforts to address the challenges of medical radioisotope supply reliability. The study found that the problem is linked to insufficient capital investment and insufficient remuneration in the Mo-99 production and processing sector, and confirmed that unless the market, policy and technology failures are addressed, a secure supply of Mo-99/Tc-99m will not be achieved¹.

3. COUNCIL CONCLUSIONS AND COMMISSION RESPONSES

3.1. 2009 Council Conclusions and the Commission's response

3.1.1. Council Conclusions on the Security of Supply of Radioisotopes

Following deliberations and discussions at political and technical level on the fragility of the supply of medical radioisotopes, the European Commission established an ad hoc inter-service group at the beginning of 2009, which produced a Preliminary Report on Supply of Radioisotopes for Medical Use and Current Developments in Nuclear Medicine². The report describes current uses of radioisotopes, the supply situation and available production capacities, as well as possible future initiatives regarding nuclear reactor capacities,

¹ The Supply of Medical Radioisotopes -An Economic Study of the Molybdenum-99 Supply Chain, OECD 2010, NEA No 6967 (<http://www.oecd-nea.org/med-radio/reports/MO-99.pdf>)

² Preliminary Report on Supply of Radioisotopes For Medical Use And Current Developments In Nuclear Medicine, SANCO/C/3/HW D(2009) Rev. 8, 30 October 2009 (http://ec.europa.eu/euratom/docs/2009_radioisotopes_report_en.pdf)

radiopharmaceuticals and nuclear medicine, at both EU and international level. In November 2009 the European Commission presented its Report to the Council.

The Council saw this as an appropriate time to give guidance on future work aimed at addressing the continuing tight situation in the market for supply of radioisotopes. Under the Swedish Presidency it prepared Council Conclusions on the Security of Supply of Radioisotopes for Medical Use, which were adopted in December 2009³.

In these Council Conclusions, the Commission was invited to investigate with relevant stakeholders different possibilities for short-, medium- and long-term solutions to secure the supply of radioisotopes for medical use in the EU, taking account of production facility projects in Member States, technical developments and predictions of future demand for radioisotopes in medical applications.

3.1.2. The Commission's response:

Communication to the European Parliament and to the Council on medical applications of ionizing radiation and security of supply of radioisotopes for nuclear medicine

In response to this invitation of the Council, the Directorate-General for Energy (DG ENER) hosted a meeting on the Security of Supply of Medical Radioisotopes in EU Member States in Luxembourg in May 2010, aimed at providing a forum to exchange information on possible medium-term solutions and on the most promising reactor opportunities for securing Mo-99 production in the long term.

About 50 participants from 20 Member States attended the meeting, including the main stakeholders (reactor operators, Mo-99 processors and Mo-99/Tc-99m generator producers), representatives of international organisations and professional associations.

Based on the input provided by the stakeholders the European Commission prepared and adopted in August 2010 a Communication to the European Parliament and to the Council on medical applications of ionizing radiation and

³ Council Conclusions on the Security of Supply of Radioisotopes for Medical Use, 2986th Agriculture and Fisheries Council meeting, Brussels, 15 December 2009 (http://ec.europa.eu/euratom/docs/2009_radioisotopes_council_ccl_en.pdf)

security of supply of radioisotopes for nuclear medicine⁴ accompanied by a Commission Staff Working Document⁵. The Communication proposed different options for improving the security of supply of medical radioisotopes in the EU.

3.2. 2010 Council Conclusions and the Commission's response

3.2.1. Council Conclusions: Towards the Secure Supply of Radioisotopes for Medical Use in the European Union

The Council, under the Belgian Presidency, subsequently adopted on 6 December 2010 its Conclusions 'Towards the Secure Supply of Radioisotopes for Medical Use in the European Union'⁶, urging the Commission to define, in close cooperation with stakeholders, a European solution for ensuring medium- and long-term security of supply, for instance by means of a Joint Undertaking (JU). A JU (Article 45 of the Euratom Treaty), already envisaged by DG ENER in the August 2010 Communication, was intended to support the development and implementation of a full-cost recovery methodology for reactor irradiation services and outage reserve capacities and to improve the coordination of reactor operating programmes.

3.2.2. The Commission's response

European Observatory on the supply of medical radioisotopes

Between 2010 and 2011 DG ENER maintained a close dialogue with the stakeholders to discuss the purpose and form of the envisaged JU. A series of meetings were held in Luxembourg and an ad-hoc Inter Service Group on medical radioisotopes, comprising representatives of the Directorates-General for Energy (DG ENER), Health (DG SANCO — now DG SANTE), Research and Innovation (DG RTD), Industry (DG ENTR — now DG GROW), Competition (DG COMP), and the Joint Research Centre (JRC) was set up by DG ENER in June 2011 to coordinate a common approach across different Commission

⁴ 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, COM/2010/0423, 6 August 2010, (http://eur-lex.europa.eu/legal-content/EN/ALL/;ELX_SESSIONID=n9vvTy3WGs0mncQt6ys9BH5s6GxN3q4CfLrpTb3J03Tvh1pTr7Qy!902760657?uri=CELEX:52010DC0423)

⁵ Commission Staff Working Document, SEC(2010) 974, 6 August 2010, (http://ec.europa.eu/euratom/docs/comm_sec_0974.pdf)

⁶ Council Conclusions on 'Towards the Secure Supply of Radioisotopes for Medical Use in the European Union', 6 December 2010, (<http://ec.europa.eu/euratom/docs/118234.pdf>).

services and to evaluate possible solutions. Following a meeting in September 2011, one of the main stakeholders, the Association of Imaging Producers and Equipment Suppliers (AIPES)⁷, provided in mid-November 2011 its position paper on Mo-99/Tc-99m in Europe. As the proposed JU was considered to be too cumbersome and ‘heavy’ for this purpose, AIPES called instead for the establishment of an ‘Observatory’, i.e. a light structure composed of all the main stakeholders who would report to the Commission on key subjects related to the supply of medical radioisotopes. It was agreed that the JU could be considered at a later date if it turned out that the Observatory was not enough to achieve the objectives. The proposal for the creation of an Observatory integrated the recommendations of the OECD/NEA HLG-MR, of which the Commission is a member, the Council Conclusions on medical radioisotopes and the comments made at the Luxembourg stakeholder meetings.

On 30 November 2011, European Commission competent service DG ENER presented the proposal for an Observatory to the Council’s Working Party on Atomic Questions. The idea was supported by all Member States.

A meeting between AIPES and the Commission services to discuss the creation of the Observatory was held on 12 January 2012 in Brussels. The structure, operating modalities and allocation of the tasks, including to Commission services, were agreed upon.

Following these arrangements the Observatory was formally created at its first plenary meeting held on 29 June 2012 in Brussels, at which its mission statement was endorsed⁸.

The main aim of the European Observatory on the supply of medical radioisotopes is to bring all relevant information to the attention of decision-makers in the EU, national governments and official bodies in order to assist them in defining strategies and policies for their implementation. The Observatory follows the OECD/NEA principles established by the HLG-MR⁹ and focuses on the specificities of their European implementation.

⁷ <http://www.aipes-eeig.org/>

⁸ http://ec.europa.eu/euratom/docs/radioisotopes_observatory_mission.pdf

⁹ <http://www.oecd-neo.org/med-radio/statement.html>

The Observatory has four general strategic objectives:

- support secure Mo-99/Tc-99m supply across the EU,
- ensure that the Mo-99/Tc-99m supply issue is given high political visibility,
- encourage the creation of a sustainable economic structure for the Mo-99/Tc-99m supply chain, and
- conduct periodic reviews of the Mo-99/Tc-99m supply chain and capacities.

To achieve these objectives the Observatory functions through four Working Groups (WG):

- (a) WG1 — Reactor scheduling and Mo-99 supply monitoring,
- (b) WG2 — Cost recovery mechanisms for the EU,
- (c) WG3 — Management of HEU-LEU conversion and target production,
- (d) WG4 — Capacity and infrastructure development.

The Observatory, originally chaired by, European Commission service DG ENER, and from August 2013 transferred to and chaired by ESA, is composed of representatives of the European Commission services (DGs ENER, JRC, RTD, GROW and SANTE as an observer), ESA, OECD/NEA, various industry stakeholders grouped within AIPES (research reactor operators — irradiators of uranium targets, Mo-99 processors and Mo-99/Tc-99m generator manufacturers) and the European Association of Nuclear Medicine (EANM). DG COMP, though not represented in the Observatory, scrutinised the process in terms of competition law.

The plenary meetings of the Observatory are held twice per year, and meetings of the WGs about four times per year. The last two plenary meetings were held on 7 July 2014 in Paris and on 27 March 2015 in Luxembourg.

(a) Working Group 1 — Reactor scheduling and Mo-99 supply monitoring

The WG1 ensures effective coordination of reactor schedules to avoid and mitigate Mo-99 shortages and has established for this purpose an Emergency Response Team (ERT), composed of representatives from reactors, processors and generator manufacturers. The ERT was activated for the first time in November 2012, due to the extended shutdown of the HFR reactor in Petten. The ERT quickly responded to information regarding the HFR outage and managed to avoid a potential shortage

between April and June 2013. In November 2013 the ERT was activated for the second time due to another extended shutdown of the HFR reactor, lasting until February 2014, and temporary closure of the Mo-99 production facility in Petten until April 2014. In order to keep supply at the maximum possible level, the ERT convened a series of meetings during this period to discuss and implement all possible mitigation measures to avoid severe shortages (e.g. increasing production capacity at another Mo-99 processing facility (IRE-Belgium) and activating additional irradiation capacity at the BR-2 reactor in Belgium and the LVR-15 reactor in Czech Republic).

The great efforts and the efficiency of the actions launched from 2012 to 2014 for supplying nuclear medicine radioisotopes should be fully recognised. All European research reactor operators and their staff, with the continuous support of radioisotope processors, generator manufacturers and service providers such as transport companies, have worked remarkably well together to coordinate and ensure the necessary continuity of medical radioisotope production and supply to the medical community. Non-European research reactors and processors have also been heavily involved in this process.

Another important measure taken by the WG1 was the establishment of a Joint Communication Team (ESA, OECD/NEA and AIPES) in April 2014, aiming at providing prompt communication to governments in case of supply interruptions. The communication protocol and news release template were agreed between the Observatory members. According to these arrangements and in case of future supply shortages, the governmental representatives of EU Member States will be informed via ESA through the Council's Working Group on Atomic Questions (AQQ) and via DG SANTE through the Health Security Committee (HSC)¹⁰. The latter is a cooperation and coordination body concentrating on health-related threats and is the key mechanism for coordinating health security

¹⁰ http://ec.europa.eu/health/preparedness_response/risk_management/hsc/index_en.htm

efforts at EU level, established under Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013¹¹.

(b) Working Group 2 — Cost recovery mechanism for the EU (cost methodology, drug reimbursement process)

One of the key principles of the HLG-MR policy approach is that all Mo-99/Tc-99m supply chain participants should implement full-cost recovery (FCR). This would provide the economic incentives to develop Mo-99 related infrastructures and to fully finance operating costs. Seeking a consistent approach to how costs are identified, the HLG-MR developed a methodology as described in the NEA Guidance Document published in February 2012¹². That document identifies the essential elements that should be included when determining the full cost of Mo-99 irradiation services, including a reasonable proportion of facility common costs, and how these elements should be allocated between various missions in the case of multipurpose facilities.

Within the Observatory, the issue of FCR is dealt with by WG2. Seeking information on the implementation of FCR, this Group surveyed the European radioisotope market in 2012. The survey showed that most supply chain participants have begun to implement FCR but it is being done at different speeds in different countries. There are still a number of issues which prevent the application of FCR. The success of FCR is highly dependent on consistent application of the principle by all actors.

To facilitate progress with FCR the WG2 organised a European Workshop for Mo-99 Irradiation Services with all European reactor operators and processors and key ministry officials responsible for health, economy and research reactors in EU Member States. The workshop was held on 24 September 2013 in Luxembourg, giving participants the opportunity to discuss the next steps in the process of implementing FCR in Europe and to discuss also the unbundling of payments for radioisotopes from

¹¹ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:293:0001:0015:EN:PDF>

¹² <http://www.oecd-neo.org/med-radio/guidance/docs/full-cost-recovery-molybdenum-99-irradiation.pdf>

radiopharmaceuticals and from diagnostic procedures¹³ (as a tool to support the implementation of FCR).

At the workshop it was agreed that the Observatory would analyse with the EU countries supplying irradiation services (Belgium, France, the Netherlands, Poland, Czech Republic and Germany¹⁴) the possibility of working on a timeline for implementing FCR through an intergovernmental agreement. A special meeting of government representatives from the supplying countries was organised and hosted by the Dutch Ministry of Economic Affairs in March 2014 in The Hague, at which a draft joint statement on an ‘Initiative for sustainable medical radioisotopes supply in Europe’ was discussed. Due to the complexity of this subject, however, no agreement on the text was reached at the meeting, although participants shared an overriding interest in improving the security of supply and agreed to work further on a joint political statement with the long-term goal of proposing a consistent European policy approach. Following on from that meeting, a new draft statement was tabled by the Dutch Ministry and a technical working group involving all the above-mentioned countries was set up. Discussions in the working group are ongoing with a view to finalising the joint statement as soon as possible.

(c) Working Group 3 — Management of HEU-LEU conversion and target production

Besides addressing the ongoing concerns related to long-term reliability of the medical radioisotope supply chain, all current producing countries have agreed to the principle of converting from HEU to LEU targets for Mo-99 production. This is in line with the work plan of the 2010 Washington Nuclear Security Summit based on important nuclear security reasons originally expressed in the framework of the Global Threat Reduction Initiative (GTRI)¹⁵. As a result, there is a need to focus on non-

¹³ <http://www.oecd-nea.org/med-radio/discussion/docs/unbundling-payments-radiopharmaceuticals.pdf>

¹⁴ Commissioning of the facility for Mo-99 production at the FRM-II research reactor in Garching (Germany) is foreseen for 2017.

¹⁵ <http://nnsa.energy.gov/mediaroom/factsheets/reducingthreats>

HEU-based production of medical radioisotopes, i.e. to convert from HEU to LEU targets for Mo-99 production in existing and new facilities.

In this context, the radioisotope processors within the EU are making progress in converting to non-HEU-based methods. As this is a technically and economically challenging operation it is very important to secure continuity of supply of Mo-99 throughout the process of conversion.

The WG3 has studied the risks that could occur during the HEU-LEU conversion process in respect of targets used for radioisotope production. The group started by developing a generic description of the production process, then for each process step the risks were identified, followed by assessment of the potential impact. Lastly, potential mitigating actions were determined, including recommendations for the radiopharmaceutical industry and policy makers. The report¹⁶ drafted by the WG3 was distributed to the AQG members, following the ESA presentation given at the AQG meeting held on 25 September 2013.

In order to prevent risks related to the existence of a sole target manufacturer at EU level and to address all the risks identified in relation to LEU conversion, WG3 recommended that target stocks be increased at the reactors, especially during the conversion process. This will require close dialogue between the manufacturer (AREVA-CERCA) and the European reactor operators. The Observatory offered to act as a platform for discussion.

In order to facilitate timely HEU to LEU conversion, WG3 recommended that transportation and nuclear competent authorities expedite container approval and transportation licences for LEU and that drug regulatory agencies expedite review of new LEU-based Mo-99 sources.

Further to this recommendation, it was agreed that the Observatory would draft a letter on the issue of regulatory approval of containers and transportation licences for LEU in the EU Member States. It would be addressed to HERCA — the association of Heads of the European Radiological protection Competent Authorities¹⁷ and EACA — the

¹⁶ <http://ec.europa.eu/euratom/docs/WG3%20report.pdf>

¹⁷ <http://www.herca.org/>

European Association of Competent Authorities for the Safe Transport of Radioactive Material¹⁸.

As far as the authorisation of a new LEU-based Mo-99 by drug regulatory agencies is concerned, European Medicines Agency (EMA) representatives were invited to the Observatory meetings to present and discuss:

- firstly — a process for getting drug regulatory approval of radiopharmaceuticals, and
- secondly — an expedited review of variation applications for switching from HEU to LEU.

The option of *Grouping & Work Sharing* (Articles 7 and 20 of Regulation (EC) No 1234/2008 as amended by Regulation (EU) No 712/2012), which could potentially accelerate authorisation of a new LEU-based Mo-99 in the EU, was explained to the European stakeholders, including the regulatory framework and timelines for the approval process for variations to national marketing authorisations via the Coordination group for Mutual recognition and Decentralised procedures — human (CMDh)¹⁹. A CMDh representative attended the Observatory meeting held in March 2015 to discuss the perceived regulatory issues from the industry perspective in order to explore how these can be handled in the most coordinated way among EU Member States.

Additionally, at the request of WG3, the processors based in the EU agreed to regularly update the Observatory with their schedules of conversion to non-HEU processes. Such information is instrumental in monitoring overall progress with HEU-LEU conversion in Europe and defining European needs on HEU/LEU material.

(d) Working Group 4 — Capacity and infrastructure development

The main objective of the Observatory's WG4 is to examine Mo-99 production capacity and infrastructure developments for both reactors and processing facilities. The Group, having reviewed current and future

¹⁸ <http://www.euraca.eu/>

¹⁹ <http://www.hma.eu/cmdh.html>

supply and demand data compiled by the OECD/NEA, as well as independent marketing and industry data, came up with the report²⁰ endorsed by the Observatory at its meeting in July 2014. In the report the WG compiled a qualitative assessment of the state of play of the infrastructure and the challenges that lie ahead to meet the demand for Mo-99 in the future.

According to the report, current European demand is about 25 % of global demand, reaching 125 000 Ci per year (6-day²¹). The future trend is estimated at somewhere between zero growth and growth of 1.8% per year from 2015 to 2020, and of 0.4 % from 2020 to 2030.

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

There are currently eight reactors producing the majority of the global supply of Mo-99. Other local producers operate on a small scale (around 5 % of the total global volume). These eight reactors routinely supply irradiated targets to five Mo-99 processing facilities that distribute them to Mo-99/Tc-99m generator manufactures in Europe, the United States, Asia, South Africa, South America and Australia.

However, the current supply chain for Mo-99 is fragile, as the shutdown of one or more of the major irradiators or processors might cause a shortage of supply that the current infrastructure capacity might not cover. This situation could become worse in the short term, given that three important irradiators are scheduled to be definitely or temporarily shut down this year (the licence of OSIRIS reactor in France expires at the end of 2015,

²⁰ http://ec.europa.eu/euratom/docs/WG4_Report.pdf

²¹ A commonly used unit of measure in the industry is the 6-day curie (Ci), defined as the radioactivity of Mo-99 six days after the end of the processing component of the supply chain, when the bulk Mo-99 leaves the processing facility.

the BR-2 reactor undergoes a major 16-month refurbishment programme started in March 2015, and the NRU reactor in Canada will cease routine Mo-99 production in October 2016²²). In the longer term, the HFR reactor in the Netherlands is planned to be shut down in 2024, BR-2 in Belgium in 2026, LVR-15 in Czech Republic in 2028, and MARIA in Poland in 2030.

Provision thus needs to be made for new capacity to replace the production of the current capacity as it is taken out of the market when the corresponding reactors are shut down. The replacement can be done through Mo-99 produced by fission in new or existing research reactors (which can be adapted), or by other alternative reactor non-fission or accelerator based methods, currently under development. Even though a number of projects are under way, the alternative means have not yet demonstrated the potential at industrial or commercial level to replace the production of Mo-99 through fission. Moreover, there is great uncertainty with regard to the feasibility of some of these new projects, because of the difficulty in financing complex and expensive infrastructure, and the doubts over the feasibility of obtaining a commercial return considering that the current prices of Mo-99 lie below the full-cost recovery levels.

In Europe, four new projects that are scheduled could replace the Mo-99 production of the OSIRIS, HFR and BR-2 reactors: FRM-II (Germany) with a new production capacity of 67 000 Ci (6 days)/y available from 2017 and three new reactor builds: Jules Horowitz Reactor (JHR) (France), currently under construction, planned to start-up in 2019, with a Mo-99 production capacity of 154 000 Ci (6 days)/y²³, MYRRHA (Belgium) with a capacity of 212 000 Ci (6 days)/y scheduled from 2023, and PALLAS (the Netherlands) with a capacity of 312 000 Ci (6 days)/y scheduled from 2024. The latter two reactors are still in the design phase.

In conclusion, the existing European network of reactors is fundamental to ensuring the supply of medical radioisotopes to the market in the foreseeable future. The current capacity should be maintained by

²² Canada will keep the NRU reactor available as a back-up production capacity for Mo-99, as one among a range of possible mitigation strategies in the unlikely event of a shortage between November 2016 and March 2018.

²³ JHR start-up is planned for 2019, but the first full year of Mo-99 production is expected in 2021.

encouraging the necessary investments to refurbish the current fleet if appropriate, and also to replace the capacity that will be lost as the operating reactors reach the end of their lifespan.

3.3. 2012 Council Conclusions and the Commission's response

3.3.1. Council Conclusions: Towards the Secure Supply of Radioisotopes for Medical Use in the European Union

The importance of HEU-LEU conversion of irradiation targets was highlighted in the Council Conclusions on this subject²⁴, adopted on 18 December 2012, which called upon the Commission to propose to Member States a relevant instrument to provide EU support for the conversion of HEU to LEU targets and to identify the needs of research that might be supported by the Euratom Research and Training Programme. Discussing this subject at the Observatory meetings, the stakeholders highlighted an urgent need to ensure availability of HEU during the transitional period up to the (delayed) completion of the conversion process (2017), as the US, supplier of this material, has taken measures to minimise the use of HEU for civilian purposes (non-proliferation and nuclear security reasons). Until the conversion is fully in place²⁵ it will be necessary to guarantee the supply of HEU target material to ensure uninterrupted production of medical radioisotopes.

Another closely related aspect has to do with continuing supply of uranium (both HEU and LEU) for fabrication of fuel for the European research reactors where the medical radioisotopes are produced.

3.3.2. The Commission's response (provided by ESA)

ESA was mandated in 2013 by the Commission to follow the Medical Radioisotopes dossier; and in particular also to assess the requirements for these fissile materials and to explore the possibility of assuring their supply. This has been a topic of discussion with the US and various EU countries in the context of the Nuclear Security Summits and related joint statements as well as in experts'

²⁴ http://ec.europa.eu/euratom/docs/2012_council_radioisotopes.pdf

²⁵ In the Seoul Communiqué from the 2012 Nuclear Security Summit, States were encouraged to take measures to minimise the use of HEU, including through the conversion of research reactors from HEU to LEU fuel, where technically and economically feasible. They were also encouraged to promote the use of LEU targets in radioisotope production (https://www.nss2014.com/sites/default/files/documents/seoul_communique_final.pdf).

meetings on uranium supplies for research reactors and Mo-99 production, organised by ESA and held in Luxemburg in September 2013, and April and September 2014. This subject, together with the interrelated US-driven HEU exchange to achieve a 'net negative' of HEU exports prior to any further exports (HEU minimization), is still at the top of the ESA's agenda and is being actively discussed with the relevant Member States. In this context ESA and US Department of Energy (DOE) — National Nuclear Security Administration (NNSA) signed in December 2014 a Memorandum of Understanding concerning the exchange of HEU needed for supply of European research reactors and radioisotope production facilities.

The conversion of the irradiation targets from HEU to LEU and the increasing use of LEU as reactor fuel result in a higher demand for LEU. The supply of this material should also be ensured. As there is currently no production of such LEU (of 19.75% enrichment) in the EU, the ESA Advisory Committee set up a Working Group in May 2012 to study the feasibility and scope for building European capacity designed to produce LEU metal. The study, endorsed by the ESA Advisory Committee at a meeting held on 14 November 2013, leads to the conclusion that the building of a European enrichment facility is technically and legally feasible as well as, under certain conditions, economically sustainable.

Nevertheless, as this constitutes very long-term planning, ESA, supported by its Advisory Committee, suggested in 2013 as a short-term alternative to sign a LEU framework supply agreement with US (DOE) to ensure medium-term supply of LEU after the conversion. This agreement would cover all the necessary conditions for single users to purchase the required material with a simplified contract and licensing requirements. ESA proposed a ten-year agreement that would be reviewed and updated every five years. At present the detailed conditions for signing such a framework contract and its concept are being discussed between ESA and relevant US authorities.

As far as Euratom research requested in the 2012 Council Conclusions is concerned, following the feedback received at the Observatory meetings, the Commission included in the Euratom Research and Training Work Programme 2014-15a topic on high density LEU fuel for research reactors and targets for the

production of medical radioisotopes²⁶. As a result of the corresponding call for proposals, the Commission awarded a research and innovation action grant to the project HERACLES-CP (entitled “Towards the Conversion of High Performance Research Reactors in Europe”). This project, with an EC contribution of 6.4 M€ (total cost 6.8 M€) is coordinated by TECHNISCHE UNIVERSITÄT MÜNCHEN and involves five partners, of which three are producers of Molybdenum-99 / Technetium-99m isotopes. It is due to start 1st of September 2015.

4. SUMMARY OF ACHIEVEMENTS

The Commission (mainly DG ENER) and ESA have followed up rigorously the three sets of Council Conclusions on medical radioisotopes adopted in 2009, 2010 and 2012. The most important achievement has been the establishment of the European Observatory on the supply of medical radioisotopes in 2012, composed of members from the EU institutions and various industry stakeholders.

The four Working Groups established within the Observatory have made good progress and fulfilled the tasks entrusted to them in accordance with their mandates. In particular, WG1 (with AIPES being a core member) has ensured effective coordination of reactor schedules to avoid potential Mo-99 shortages and established for this purpose an Emergency Response Team (ERT). The ERT quickly responded to the two HFR reactor outages and managed to avoid Mo-99 shortages, particularly from April to May and November to December 2013. WG2 surveyed the European radioisotope market with regard to the implementation of a full-cost recovery methodology and supported the ongoing process towards an agreement between the governments of the European producing countries on sustainable supply of medical radioisotopes. WG3 identified risks that could occur during the conversion from HEU to LEU and recommended various measures to prevent the conversion process from causing any discontinuity in the supply chain. In addition, WG3 provided input to the Euratom Research and Training Programme on the subject of fuel for research reactors and targets for the production of radioisotopes. WG4 carried out an analysis of current and future production capacities and of the expected reactor lifetimes, and gave recommendations regarding the infrastructure needs.

²⁶ <http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/2311-nfrp-08-2015.html>

In response to the Council Conclusions on HEU-LEU conversion, ESA undertook a series of specific initiatives, including:

- collection and consolidation of data on European HEU and LEU needs,
- discussion on HEU material supply with the US counterpart and signing a Memorandum of Understanding with DOE/NNSA concerning the exchange of HEU needed for supply of European facilities,
- establishment of a dedicated Expert Group within the ESA Advisory Committee, which has prepared a study on the feasibility and scope for building European capacity designed to produce LEU metal to cover the European demand, and,
- preparation of a LEU framework supply agreement to be signed with US (DOE) to ensure long-term supply of LEU after the conversion, and

Another important development saw the transfer of the dossier on medical radioisotopes from DG ENER to ESA in mid-2013. In view of ESA's mission regarding the security of supply of uranium, anchored in the Euratom Treaty, the observatory role of ESA was enhanced to cover all aspects of the supply of medical radioisotopes in the EU²⁷. This was done in the light of Council Conclusions adopted in response to increased fragility of the current production chain, which relies on an unsustainably low number of ageing research reactors, and in an effort to obtain the necessary supplies of nuclear material for targets used for radioisotope production and fuel for research reactors. ESA thus took on in 2013 the task of coordinating Commission services' actions undertaken to improve the security of supply of Mo-99/Tc-99m, and was assigned the chairmanship of the European Observatory.

5. CONCLUSIONS AND OUTLOOK

The EU institutions have taken several initiatives to improve the security of supply of medical radioisotopes. Most of these activities revolve around the European Observatory jointly established by the Commission and industry representatives in 2012 to help to implement a policy adopted by the Council, with a view to ensuring the continuity of supply of medical radioisotopes in the EU.

The Observatory, chaired by representatives from the Commission and ESA, has functioned well so far. It has proved to be a successful mechanism for achieving the objectives set by the

²⁷ <http://ec.europa.eu/euratom/ar/last.pdf>

Council; therefore at present there is no need to establish a Joint Undertaking as suggested in the 2010 Council Conclusions.

Notwithstanding all the efforts made, the current capacity remains fragile as shown during the recent unplanned outages of the production reactors and processing facilities. Therefore the medical radioisotope issue still requires full consideration by the EU institutions, Member States, the regulators, the industry and international organisations, namely the OECD/NEA and the IAEA. The following short- and medium-term actions are required.

5.1. Short-term actions

- The Observatory should continue to closely monitor developments related to reactor operations and radioisotope production in order to support reliable and secure supply with a focus on the period 2015-2017 (and beyond in case of delays of the new projects), given that a few irradiators, including three of the most important ones, either entered long-term refurbishment or are scheduled to be shut down or cease Mo-99 routine production during that period.
- The Observatory should further liaise with EMA on the subject of possible expedited review of variation applications for switching from HEU to LEU-based Mo-99. The marketing authorisation holders should make use of the grouping and work-sharing provisions laid down in European legislation for submission of HEU to LEU conversion variations. This would ensure a consistent and harmonised assessment and approval process while making best use of competent authorities' and industry's scientific and regulatory resources while reducing delays and preventing any disruption to patients.
- Member States' competent authorities should ensure that measures related to container approval and transportation licences for LEU targets are implemented in good time to avoid any undue delays. It is recommended that the association of Heads of the European Radiological protection Competent Authorities (HERCA) and the European Association of Competent Authorities for the Safe Transport of Radioactive Material (EACA) include this subject in their discussions.
- The Observatory should further support the European producing countries in their efforts to reach agreement on the joint statement on sustainable

supply of medical radioisotopes in Europe. These measures should lead in the medium term to establishment of a consistent European policy approach.

- As far as European nuclear industry is concerned, all the stakeholders should give particular attention to ensuring operational sustainability of a sole European supplier of research reactor fuel and uranium targets (AREVA-CERCA), which is now implementing an extensive programme of safety upgrades with major investments needed (nearing 3 to 4 years of total revenue).
- ESA should continue to scrutinise potential risks to the security of supply of the HEU and LEU required to produce medical radioisotopes and to fuel research reactors. Neither HEU nor such LEU is currently produced in the EU. ESA should continue to be actively involved in assessing requirements for these fissile materials and exploring the possibilities for ensuring their supply. As we are in a transitional period from HEU to LEU targets and in some cases from HEU fuel to LEU fuel, it is very important to strive to obtain the necessary supplies in order to prevent any shortage in the production of medical radioisotopes.

In this context Member States, even those not producing medical radioisotopes, should fully cooperate in defining and implementing a European solution according to the HEU exchange principle.

- As far as LEU material is concerned, ESA should pursue a relevant framework supply agreement with the US. At the same time, following an in-depth analysis by ESA's Advisory Committee, ESA would be ready to cooperate in the preparation of a proposal for an EU-based facility set up as a Joint Undertaking (Article 45 of the Euratom Treaty) to ensure in the longer term the supply security of LEU metal for research reactor fuel and irradiation targets.
- HEU-LEU conversion will have an impact on the global supply chain — both in terms of costs and as regards available capacity. The 2012 OECD/NEA study on market impacts²⁸ indicates that LEU target

²⁸ <http://www.oecd-neo.org/ndd/reports/2012/7129-leu.pdf>

conversion does reduce the available irradiation and processing capacity. Also, converted LEU-based Mo-99 is more expensive than HEU-based Mo-99. The Observatory should closely monitor the market in this context. The processors based in the EU should continue to regularly update the Observatory with their schedules of conversion to non-HEU processes. Such information is instrumental in monitoring overall progress with conversion in Europe and also in monitoring the related European production capacities.

5.2. Medium-term actions

- The existing network of European reactors is fundamental to ensuring the supply of medical radioisotopes to the EU market for the foreseeable future. Therefore, the EU institutions and all Member States, not only those hosting the current production facilities, should ensure that the current capacity is maintained by encouraging the necessary investments both to refurbish the current fleet, if appropriate, and to replace the capacity that will be lost as the operating reactors reach the end of their lifespan. This is vitally important for projects still in the design phase, like the MYRRHA reactor in Belgium and the PALLAS reactor in the Netherlands.
- Equally important consideration should be given to Mo-99 processing capacity in Europe. Processing could be a limiting factor in Europe when it comes to meeting future demand growth and having enough capacity to respond to events such as unplanned outages. The reactor operators, in their position paper on ‘Scenario for sustainable Mo-99 production in Europe’²⁹ presented in 2011 at the stakeholder meeting in Luxembourg, agreed that existing European expertise should be used in the longer term to build and operate one or perhaps two new Mo-99 processing plants in Europe, as such facilities could potentially create a major bottleneck, with only two of them currently existing in Europe.
- The future sustainability and security of supply of medical radioisotopes should also be fostered through further research. The Euratom research and training programme should thus prioritise further improvement in

²⁹ http://ec.europa.eu/euratom/docs/2011_3_research_reactor_position.pdf

performance of research reactor fuel and targets used to produce medical radioisotopes as well as alternative methods of Tc-99m production.