Analysis of the results of the targeted consultation on European Radioisotope Valley Initiative (ERVI)

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Acronym

CA	Carried added
EMA	European Medicines Agency
ERVI	European Radioisotopes Valley Initiative
ESA	Euratom Supply Agency
GDP	Good distribution practices
GMP	Good manufacturing practices
HALEU	High-Assay Low-Enriched Uranium
IATA	International Air Transport Association
ICAO	International Civil Aviation Organization
ISOL	Isotope Separation Online
JRC	Joint Research Centre
LEU	Low enriched uranium
MS	Member State
OECD/NEA	OECD Nuclear Energy Agency
PET	Positron Emission Tomography
RI	Radioisotope
RP	Radiopharmaceutical
RR	Research reactor
TOURR	Towards Optimized Use of Research Reactors in Europe

1. Executive summary

The targeted ERVI consultation gathered the positions of a number of stakeholders on the ERVI objectives and the specific issues concerning the supply chain of medical radioisotopes. A total of 37 issues were identified, covering both the intrinsic challenges faced at the different steps of the radioisotopes supply chains (supply of source material, enrichment, irradiation, processing, logistics) and the transversal ones faced by the stakeholders (e.g., need to collaboration at national and European level, regulatory issues, support to the research and workforce considerations).

Known issues on the RI supply chain confirmed through consultation results

Before the SAMIRA Action Plan and its ongoing European Radioisotope Valley Initiative (ERVI), different projects[1] allowed for shaping the SAMIRA action plan while identifying potential issues to address to secure a reliable and sustainable supply of radioisotopes in Europe:

- The two SMER [1] studies (Study on sustainable and resilient supply of medical radioisotopes in the EU for diagnostic radionuclides – SMER 1 - 2022 and for therapeutic radionuclides – SMER 2 - 2021),
- The European study on medical, industrial and research applications of nuclear and radiation technology [2] - 2019
- The SAMIRA supply chain study (Co-ordinated approach to the development and supply of radionuclides in the EU) [3] - 2021.

Part of the material gathered during the present consultation confirmed and highlighted known issues previously identified in these past EC-funded projects.

A key issue highlighted in all previous studies is the limited availability of information related to radioisotope supply chain capacity and nuclear medicine demand. Different actions were suggested in the present survey by respondents to improve data collection on the current use of nuclear medicine (Issue #1 in section 3) and the supply chains' present and future manufacturing capability (Issue #2). The European Observatory on the supply of radioisotopes was considered crucial for monitoring demand and supply; different suggestions for expanding its scope were suggested by respondents (Issue #3) to include all key radioisotopes, commercial and research ones, and cover all steps of the supply chain and not only the irradiation step.

Several outputs of the SAMIRA supply chain study concerning actions needed at each step of the supply chain were also confirmed by respondents, such as:

- the need for coordinating efforts on stable isotopes supply (Issue #4),
- the need for the development of new targetry systems (Issue #9),

[1] More details on the SAMIRA Action Plan and its related projects can be found on this webpage https://energy.ec.europa.eu/topics/nuclear-energy/radiological-and-nuclear-technology-health/samira-action-plan_en in the sub-section "Studies and projects – supply of medical radioisotopes"

- the bottlenecks and risks associated with centralised European processing facilities (Issue #18),
- the radioisotopes logistics issues (Issues #20 & #21) and the upcoming challenge of theranostic development (Issue #22),
- the challenge of securing the funding necessary for supply chain infrastructures across Europe (public/private funding and adequate reimbursement mechanisms) (Issue #27).

The radioisotope supply chain industry gathers numerous stakeholders at national, European, and international levels. The need for better communication among these stakeholders was reminded by respondents (Issue #24) while at the same time highlighting the need for involving public authorities in the security of supply discussions (Issue #25).

The strong links between the research, the industry and the end-users were highlighted by previous studies. Respondents confirmed the need to secure a sustainable supply of radioisotopes to support the R&D needs (pre-clinical and clinical studies), which could be done at EU-level (Issue #28), together with coordinating public research efforts in the radioisotope sector (Issue #29).

Finally, respondents recognised the efforts implemented in the frame of past/ongoing initiatives and projects aiming at securing the European supply of radioisotopes and highlighted the need for ERVI to build on these outputs and actively involve stakeholders in the discussions (Issue #26).

New developments impacting the security of supply and associated issues/actions

Recent developments in Europe and worldwide have impacted positively or negatively radioisotopes' security of supply.

The reliance on Russian electromagnetic enrichment capability became a crucial issue since Russia's invasion of Ukraine (Issue #5) in the absence of backup alternatives. The lack of European HALEU enrichment installation raises risks for the same reason (Issue #6), considering the uncertainty of US supply in the medium term (the 2030s).

In the last year, the European supply of ^{99}Mo faced different periods of tension due to technical issues at the irradiation level (cooling water leak in HFR in Jan. 2022, valve issue in BR2 in Nov. 2022, etc.). Ageing installations are more prone to such incidents, highlighting the need for pursuing efforts to address the Long-Term Operation of existing large European irradiation facilities (issue #13). Securing and improving the use of existing installations in Europe for radioisotope supply is crucial for the security of supply. The recent TOURR project (Towards Optimized Use of Research Reactors in Europe) aims to evaluate the current and future needs for research reactors and neutron sources in Europe (October 2020 - September 2023, Euratom R&T programme) and provides recommendations for actions at ERVI's level (Issue #16).

Different public and private-financed projects aimed at improving European supply made significant progress in the last years (e.g., PALLAS reactor funding from Dutch Government, collaboration SCK-CEN/IBA for setting the first European ^{225}Ac commercial supply, etc.). Such projects should be closely monitored at ERVI's level to assess their impact on future supply (Issue #15).

Most of these challenges regard commercial supply. Yet, research infrastructures are more and more considered to have a crucial role to play in the future for securing R&D and clinical trial needs (Issue #11). The PRISMAP project (Production of high-purity medical radionuclides by mass separation) involving major European infrastructures aims at providing a sustainable source of high-purity grade new radionuclides for medicine, owing to a single-entry point using standardised access procedures for all researchers active in this field, including SMEs, global pharma, nuclear centres, hospitals, and universities, (May 2021 - April 2025, Horizon 2020).

New key issues and suggestions for actions

The targeted consultation also enabled the identification of specific issues that had not been addressed specifically in the previous EC studies on radioisotope supply chains, namely:

- the opportunity for coordinating efforts on legacy waste recycling for use as source material for irradiation (e.g., ^{226}Ra for ^{225}Ac supply) (Issue #7).
- the opportunity of coordinating efforts for using existing ISOL facilities in Europe to supply a limited quantity of RI for research use (Issue #8).
- the issues related to the unequal geographical distribution of irradiation facilities across Europe and its impact on RI availability and equal access (Issue #10).
- the risk of future lack of high neutron flux research installations (Issue #14).
- the limitations faced by small, decentralised facilities with recycling of targets and potential coordinated efforts to address these needs at a European level (Issue #19).
- The issue related to monopoly risks for some radioisotopes (Issue #17).
- The need for better communication related to potential or ongoing shortages and supply capacity (Issue #23).

Issues and suggestions for actions beyond ERVI's scope

Securing a safe and sustainable supply of radioisotopes in Europe would imply addressing simultaneously different types of challenges. As defined within SAMIRA Action Plan, ERVI is intended to only focus on production infrastructures and methods (to facilitate access to source materials, improve efficiency and further optimise industrial scale production, and support the development of new production methods). Meanwhile, complementary issues on regulations, workforce, education & training, or on quality and safety considerations related to radiopharmaceutical use could be

addressed through other pillars of the SAMIRA action plan (e.g., SAMIRA Simplerad[2] project under the SAMIRA Quality and Safety pillar), through actions from other DGs (DG SANTE, DG MOVE, DG EAC, etc.) or by European authorities (e.g., ENSREG).

The consultation identified multiple transversal regulatory issues beyond ERVI's scope, linked with the national and European radioisotope and radiopharmaceuticals regulations (Issues #31 & #32), and specific nuclear regulations considerations applicable to radioisotope supply chains such as radioactive waste management, discharge monitoring and dosimetry (Issue #30), transport of radioactive material (Issue #33). Supporting the implementation of specific regulatory requirements for small production centres (Issue #34) and staffing considerations in national/European agencies (Issue #35) were also highlighted by respondents.

Education & Training, and workforce considerations at the radioisotope supply chains level were also identified by respondents as crucial to ensure the security of supply. Different suggestions of actions were proposed by respondents to address workforce shortages in specific areas, such as the radiochemical processing industry (Issue #36), or to secure adequate Education & Training ecosystem in Europe (Issue #37). Such considerations are beyond ERVI's scope but could benefit from other EC initiatives in this area.

[2] SAMIRA Simplerad – "Study on the implementation of Euratom and EU legal bases with respect to the therapeutic uses of radiopharmaceuticals"
https://www.eanm.org/advocacy/eu-related-activities/simplerad/

2. Introduction

2.1. Background of European Radioisotopes Valley Initiative (ERVI)

Nuclear medicine is an essential tool for cancer management, contributing to early cancer diagnosis and prognostic assessments aimed at helping doctors make critical decisions and tailor the treatment to the patient's needs. More than 1500 nuclear medicine centres deliver about 10 million nuclear medicine procedures to patients each year in the EU. Depending on the national practices, up to 65% of these procedures are performed in oncology. Besides cancer, radioisotopes play a vital role in diagnosing cardiac conditions and other diseases.

With its unique supply network, innovative technology developments and strong clinical research commitment, Europe plays a central role in the nuclear medicine domain. The EU is the leading supplier of medical radioisotopes to the world market, with a market share of more than 60% for some of the most widely used radioisotopes. These radioisotopes are used for the preparation/manufacturing of diagnostic and therapeutic radiopharmaceuticals (RP). Some of the most important recent pharmaceutical and clinical developments in radionuclide cancer therapy originated in the EU.

At the same time, the long-term global supply of the necessary radionuclides is not fully secured, with bottlenecks at several steps of the global supply chain. These concerns have increased in recent years, raising the question of dependence of Europe on foreign supplies. Radionuclides supply concerns are even more important now that therapeutic radiopharmaceuticals are directly involved.

In February 2021, the EC adopted the SAMIRA action plan[3], which defines EU actions in priority areas, including securing the supply of medical radioisotopes. The actions on the supply of medical radioisotopes have as their main objective the establishment by 2024 of a European Radioisotope Valley Initiative (ERVI) aiming to maintain a secure, resilient, and sustainable supply of medical radioisotopes to patients across Europe.

ERVI would seek:

- To facilitate access to the source materials needed to produce medical radioisotopes (RI) through both fission and other production methods, aiming at developing domestic production to reduce the EU's reliance on foreign suppliers.
- To improve the efficiency and further optimise industrial scale production of radioisotopes aiming at supply security, flexibility, resilience and sustainability.
- To develop new production methods through networking actors and promoting advanced research on innovative techniques and technologies of production.

[3] COMMISSION STAFF WORKING DOCUMENT on a Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) SWD(2021) final

2.2. Consultation on ERVI's objectives and identification of issues/actions within the supply chains of medical radioisotopes

To progress with the preparation of the ERVI initiative, the European Commission has decided to launch first a targeted consultation to gather the positions of stakeholders on the ERVI objectives and the specific issues concerning the supply chain of medical radioisotopes.

The consultation is part of an overall process of focused interactions with stakeholders, allowing EC to efficiently capture relevant views and tap into a wide range of stakeholders' expertise.

The target groups addressed through this consultation included, as follows:

- Production infrastructures,
- Radionuclides and radiopharmaceuticals industrial players,
- Equipment manufacturers,
- Clinical nuclear medicine bodies,
- Research centres/laboratories,
- Expert groups & Professional associations,
- EU Agencies,
- Patient associations,
- International and third-country organisations.

The online consultation was accessible from the 22nd of August to the 14th of October 2022. The link to the questionnaire was transmitted to a list of identified stakeholders, and respondents were able to forward the link to their network within the sector. In addition to that, different professional organisations contributed to this consultation by disseminating the link to their members at national and European levels.

2.3. Survey respondents

At the end of the survey period, 76 answers were collected from the different types of stakeholders identified (see Figure 1), with a balanced involvement between industrial, clinical and research stakeholders.

Respondents were evenly distributed among Europe (see Figure 2), with strong participation from the countries with an active radioisotopes industry (e.g., Belgium, Netherlands).

The detailed answers from the survey can be found in the report entitled "Results of the targeted consultation on European Radioisotope Valley Initiative (ERVI)".

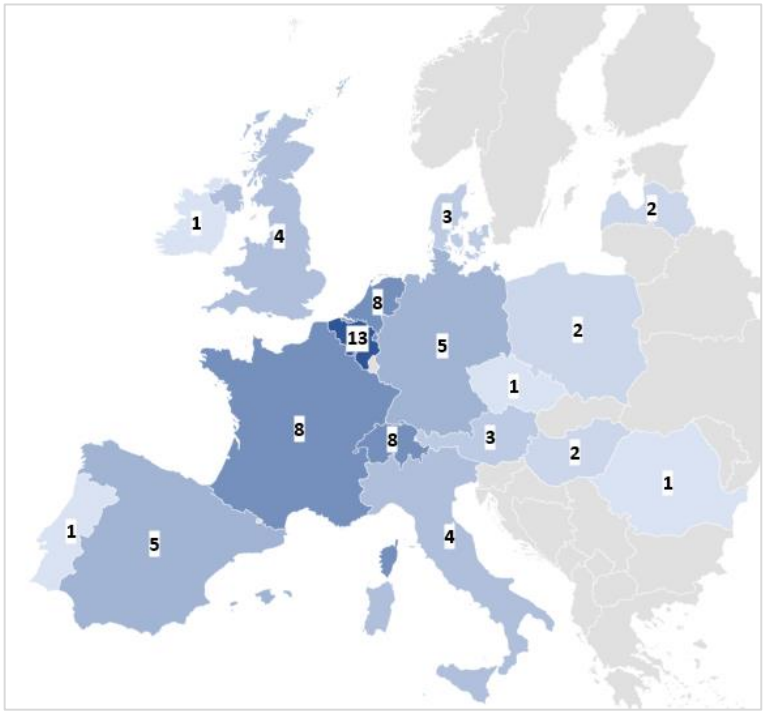

Figure 2: Distribution of the survey respondents by their country of residence

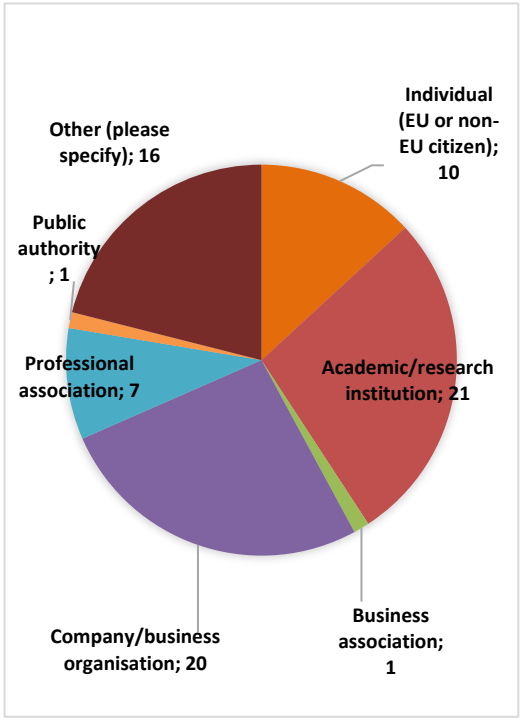

Figure 1: Distribution of the survey respondents by category

2.4. Scientific approach and content of the report

The present report is complementary to the previous one and aims to analyse and summarise the respondents' answers. A significant part of the survey was dedicated to identifying challenges faced by stakeholders in the radioisotopes sector. Respondents were also invited to suggest actions to address these issues, highlighting those that could be implemented at ERVI's level.

The identified challenges and suggested actions were sorted using different complementary approaches:

- In section 3, per overall objective pursued, namely:
  - Developing high-quality evidence on demand and supply (3.1).
  - Ensuring a reliable and sustainable supply of RI at the EU level (3.2) considering each supply chain step:
    - Source material and enrichment
    - Targetry systems and fuel considerations
    - Irradiation
    - Processing
    - Logistics
  - Fostering coordination, communication, and collaboration (3.3).
  - Supporting the implementation of Euratom and EU law (3.4).
  - Ensuring adequate workforce availability (3.5).
  - Supporting European research (3.6).

- In section 4, the issues and identified actions are sorted per radioisotope, allowing the identification of the specific supply chain challenges.

To the largest extent possible, sections 3 & 4 are based on verbatim transcripts. Yet, some statements were completed and updated to consider conclusions from previous studies addressing radioisotope supply chains for clarity and regrouping considerations.

Some of the suggestions provided by respondents went beyond the expected perimeter of ERVI, addressing research, regulatory, or radiopharmaceutical considerations. They are nevertheless included in the present report, as it provides materials for future European Commission actions beyond ERVI's initiative.

In sum, tens of actions/suggestions resulted from the consultation, while 37 were selected for specific discussion within this document.

3. Identification of issues and suggestion of actions

Addressing the issues of security, resilience, and sustainability of supply for radioisotopes in Europe is a broad objective, with technical, financial, and legal considerations to be considered in a holistic approach. Respondents identified multiple challenges that could be addressed as part of the ERVI initiative or through public actions of others DGs and public bodies.

The challenges and suggestions of actions were regrouped under six different categories (the last two being beyond ERVI's scope), namely:

- As ERVI will be a multi-year initiative, medium and long-term planning of actions will be needed. Shaping ERVI's actions will necessitate relying on extensive and reliable **data regarding the supply and demand of radioisotopes** (and radiopharmaceuticals).

Issue #1	Addressing the lack of detailed statistics on nuclear medicine use at the European level
Issue #2	Addressing the lack of disclosed information on European irradiation and processing installations' manufacturing capability
Issue #3	Expanding monitoring of supply to all key radioisotopes, both for commercial and clinical research use

- Radioisotope supply chains rely on industrial, research, and clinical installations adapted for the manufacturing of each radioisotope. **Actions were suggested by respondents to tackle issues at the different stages of supply chains: source material & enrichment, targetry systems and fuel considerations, irradiation, processing, and logistics**.

Issue #4	(Enrichment) Addressing the lack of coordination at the European level for stable isotopes
Issue #5	(Enrichment) Addressing the lack of European electromagnetic enrichment capability
Issue #6	(Enrichment) Addressing the lack of European HALEU enrichment & metallisation installation
Issue #7	(Stable isotopes supply) Addressing the opportunity for legacy waste recycling
Issue #8	(Stable isotopes supply) Addressing the opportunity for using ISOL facilities as alternative suppliers of radioisotopes
Issue #9	(Targetry systems) Addressing the need for new targetry systems
Issue #10	(Irradiation) Addressing the unequal geographical distribution of irradiation facilities across Europe
Issue #11	(Irradiation) Addressing the limited involvement of large accelerators and research installations in securing supply
Issue #12	(Irradiation) Addressing the lack of accelerators exotic beams available across Europe

Issue #13	(Irradiation) Addressing Long-Term Operation of existing large European irradiation facilities
Issue #14	(Irradiation) Addressing the future lack of high neutron flux research installations
Issue #15	(Irradiation) Addressing the risks/opportunities linked with the various irradiation projects under development
Issue #16	(Irradiation) Improving the use of existing research reactors
Issue #17	(Irradiation) Addressing the monopoly risks across radioisotopes supply chains
Issue #18	(Processing) Addressing the bottleneck risks associated with centralised European processing facilities
Issue #19	(Processing) Addressing the limitations linked with recycling of target material for non-centralized facilities
Issue #20	(Logistics) Addressing the bottlenecks of radioisotopes air transport
Issue #21	(Logistics) Addressing customs-related issues delaying and complexifying transport of radioisotopes across Europe
Issue #22	(Logistics) Addressing the challenges linked with the restructuration of the European logistic industry

- Radioisotopes have complex supply chains with multiple stakeholders interacting at all stages. While some radioisotopes rely on local manufacturing, a large part of the market is global, with Europe playing a major role in securing worldwide supply. Thus, ERVI would also need to foster **coordination, communication, and collaboration between stakeholders (industry, public institutions, clinical) at the national, European, and international levels**.

Issue #23	Addressing the need for better communication related to potential or ongoing shortages and supply capacity
Issue #24	Addressing the need for better communication among stakeholders at the European and the worldwide levels
Issue #25	Addressing the need for better involvement of public authorities in the security of supply discussions
Issue #26	Addressing the need to build on past/ongoing public initiatives to prepare for ERVI and involve stakeholders in charge of such projects
Issue #27	Addressing the challenge of securing financing for needed supply chains infrastructures across Europe (public/private funding and adequate reimbursement mechanisms)

- Sustaining the momentum of change within the nuclear medicine sector necessitates maintaining **the excellence of European research on innovative techniques and technologies of production**.

Issue #28	Addressing the need for radioisotope supply to support the research
Issue #29	Addressing the need for coordination of public research in the radioisotope sector

- Radioisotopes (and radiopharmaceuticals) regulatory environment is deemed complex, cumulating nuclear and health regulations. While addressing regulatory issues that fall outside of ERVI's perimeter, several **issues and suggestions for actions related to European regulations**[4] were gathered.

Issue #30	Addressing the issues stemming from targeted radionuclide therapy impact in terms of radioactive waste management, effluents regulations and dosimetry.
Issue #31	Addressing the need for adequate radioisotope regulation in the EU
Issue #32	Addressing the need for adequate radiopharmaceutical regulation in the EU
Issue #33	Addressing the need for adequate regulation of radioisotope transport
Issue #34	Addressing the need for support to small production centres having to implement stringent regulatory requirements
Issue #35	Addressing the need for staffing national agencies in charge of drug approval

- Like any industry, radioisotopes supply chains rely on a specialised workforce that needs to be maintained over Europe. While addressing education and training, or workforce issues, falls beyond ERVI's perimeter, several **issues and suggestions for actions related to E&T and workforce availability**[5] were gathered.

Issue #36	Addressing the workforce shortage at the different steps of the radioisotope supply chain
Issue #27	Addressing the education and training issues at the different steps of the radioisotope supply chain

[4] European regulation considerations are out of the scope of ERVI, as defined within SAMIRA action plan
[5] Workforce and Education & Training considerations are out of the scope of ERVI, as defined within SAMIRA action plan

3.1. Development of high-quality evidence and monitoring of demand and supply of radioisotopes and radiopharmaceuticals at the national and European level

3.1.1. Issue #1 – Addressing the lack of detailed statistics on nuclear medicine use at the European level

Identified issue

The availability and exhaustiveness of nuclear medicine statistics vary among Member States, between official statistics from the Ministry of Health, statistics coming from professional associations, data based on social security reimbursement etc. Moreover, considering the various metrics (radiopharmaceutical used, activity at injection, etc.) needed to efficiently aggregate data at the local, national, or European level, it is currently difficult to precisely assess nuclear medicine use.

Incomplete data prevent identifying the trends and potential differences per country. With improved data, the EU could address the elimination of barriers (source materials, irradiations, processing, and transport) but would also support the improvement of patient treatment in Member States currently underutilising the full potential of nuclear medicine.

Suggested actions

Three actions were suggested, with different timeframes:

- In the long-term, ERVI could act towards better data collection on nuclear medicine use through the establishment of a European centralised database gathering the different needed metrics. This could be implemented through a regulatory requirement, asking end-user organisations (hospitals, clinical centres, research departments), through an anonymised system, to provide information on:
  - (i) the number of procedures and clinical indications,
  - (ii) activity injected
  - (iii) radiopharmaceutical used

  The Swedish experience of SRSA (Swedish Radiation Safety Authority) with the DosReg database should be considered https://dosreg.ssm.se/IsotopStatistik/RegistreringPublik).

- In the short term, ERVI could also launch a specific collaborative work between health authorities to perform an up-to-date evaluation of nuclear medicine use across Europe through the active involvement of MS for the transmission of the reimbursement databases. Such collaborative work could rely on the methodologies used in past EC-funded studies [1] to collect information on nuclear medicine use.

- While beyond ERVI's perimeter, gathering data on the Member States' current medical infrastructure adequacy against the expected rise of targeted radionuclide

therapy (TRNT) would be needed to secure equal access to all European patients to such treatments (e.g., hospital rooms and supporting equipment, radiopharmacy services, etc.).

3.1.2. Issue #2 – Addressing the lack of disclosed information on European irradiation and processing installations manufacturing capability

Identified issue

Irradiation and processing capacity of European radioisotope manufacturing facilities are affected by uncertainties due to commercial considerations and the complexity of evaluating output capacity (e.g., for an irradiation installation, manufacturing capacity depends on the number of targets used per batch compared to the total number of position available, irradiation duration, transport duration considerations, etc.).

This limited knowledge of irradiation capacity prevents from performing precise demand/supply estimates.

Suggested actions

Two actions were suggested:

- ERVI could pursue efforts in performing a global evaluation of supply capacity for the most used or promising radioisotopes. Such modelling exercise could be done in collaboration with industrial and public infrastructures, relying on the work implemented in previous EC-funded studies [1] [2] [3] and international initiatives, such as the one used by OECD/NEA for its report "The Supply of Medical Radioisotopes: Medical Isotope Supply Review: ^{99}Mo/^{99m}Tc Market Demand and Production Capacity Projection".

- Such manufacturing capability could be compared to future needs projections (see issue #1). An end-vision could then be derived at the EU level for defining the needed manufacturing infrastructures and the level of exchanges (import/export) with foreign countries.

  For most used and promising radioisotopes, periodically assessing the demand and supply situation (e.g., within a 5-year framework) would allow for planning for medium-term actions, such as promoting small-scale production of promising RI, fuelling academic research and early clinical trials. End-users could be associated with such modelling exercises.

3.1.3. Issue #3 – Expanding monitoring of supply to all key radioisotopes, both for commercial and clinical research use

Identified issue

For commercial radioisotopes, the European Observatory on the Supply of radioisotopes[6] provides, since 2012, a platform for the stakeholders to discuss, monitor and support the EU supply of widely used medical RI. The observatory currently focuses on ^{99}Mo/^{99m}Tc with limited consideration on recently widely used diagnostic or therapeutic medical radioisotopes.

The manufacturing capability is currently managed in Europe only through the industrial demand side. Investments are generally performed by industrial players once the demand becomes well-established, namely close (or shortly after) market authorisation. Accordingly, for R&D radioisotopes, in the absence of manufacturing capability to foster research activities, clinical trial developments may be delayed or made impossible in Europe (e.g., ^{211}At with very limited availability). To secure clinical trial developments in Europe, monitoring of supply capacity for the radioisotopes not yet at the commercial stage could be valuable.

Suggested actions

Different actions were suggested to improve monitoring, which could be either implemented at ERVI's level or through an update of the European Observatory mandate with close involvement/support from ERVI (ensure the sustainability of the observatory). These different actions of monitoring could gather industrial players, clinical users, and authorities, along with research facilities with manufacturing capability (e.g., PRISMAP members[7]).

The supply monitoring could be implemented with the following objectives:

- *Expanding supply monitoring,* currently mainly limited to ^{99}Mo, *to all key radioisotopes*. While a focus on the most-used radioisotopes should remain a priority, the other strategic radioisotopes of importance could deserve to be closely monitored at the EU level, especially the therapeutic ones whose demand is expected to increase soon (alpha & beta emitters) and those that have not yet reached the commercial stage, needed for clinical trials.

- *Expanding supply monitoring to non-reactor-based radioisotopes, namely the* emerging ones coming from accelerators (^{64}Cu, ^{89}Zr, ^{225}Ac, ^{211}At) and specific sealed sources for which the market is limited (^{192}Ir, ^{106}Ru).

- *Expanding monitoring to the entire supply chain, from enrichment to processing capability*. Monitoring should not be limited to irradiation capacity but could cover enrichment, target manufacturing, processing, etc.

[6] https://euratom-supply.ec.europa.eu/activities/supply-medical-radioisotopes_en
[7] https://www.prismap.eu/

3.2. Actions to support coordination and availability of European supply chains to ensure a reliable supply

3.2.1. Issue #4 – (Enrichment) Addressing the lack of coordination at the European level for stable isotopes

Identified issue

There is no coordination at the European level regarding stable isotope supply. Industrial players or research laboratories directly purchase stable isotopes (sometimes through intermediates). The availability of a given stable isotope mainly depends on commercial interests. In some cases, European centrifugation capacity allows the enrichment of specific isotopes. Yet, the threshold volumes needed to prevent end-users from passing the "minimum" order to launch a separation run.

Being regulated through market considerations, a monopoly situation may appear (e.g., attempts to create a monopoly for ^{177}Lu through the buying of all ^{176}Yb stockpile available), compromising R&D and fair competition.

Suggested actions

One action was suggested:

- Evaluate the interest and feasibility of setting up an independent European entity responsible for procurement, manufacturing, reserve management and distribution of enriched stable isotopes, managed by a European agency, like the National Isotope Development Centre in the US. The perimeter of such an entity could be expanded to radionuclides needed for R&D, which currently represent small market volumes.

  This entity could oversee "joint purchase" at the EU level, or stockpiling source material, as a "joint" resource for Europe, with inventories of materials being kept "up to date" with a "10 years+ vision" and stocks shared with public/private industrials when needed. As the enrichment of stable isotopes may also benefit other industries (e.g., the semiconductor industry), an initiative for setting/developing EU enrichment capacity should also include non-medical stakeholders.

Such a European body could centralise various issues related to enrichment and stable isotopes (see issues #5, #6 and #7).

3.2.2. Issue #5 – (Enrichment) Addressing the lack of European electromagnetic enrichment capability

Identified issue

The European enrichment industry currently lacks electromagnetic enrichment capacity. Enrichment of stable isotopes through this process is presently coming from Russia (e.g., ^{176}Yb). Despite enrichment centrifugation capacity in Europe (Urenco, Orano), some isotopes are only enriched in Russia. To date[8], regarding the heavy stable isotopes (~49 elements out of 65 stables elements that can be enriched), ~37 elements like Yb, for example, are only produced in Russia. Expanding the production scope of the existing EU plant to new elements (~9 new elements like Ni) and the development of new enrichment techniques (~28 new elements like Yb or Gd) is crucial in securing the European supply chain.

Developments are ongoing in the USA to address this issue with strong political and financial support, but no coordinated action at the European level is currently underway.

Suggested actions

Two actions were suggested, with different timeframes:

- In the short-term, coordinate efforts at EU-level to improve access to the installations already implementing isotope mass separation technology (e.g., in Irène Joliot Curie Lab., KU Leuven) to address the limited clinical trials and R&D needs that are currently threatened due to current relation with single Russian supplier (e.g., ^{48}Ca used by GANIL scientific programme).
- In the medium term, support investments into an electromagnetic separation enrichment project necessary for a sustainable supply of stable isotopes in the EU. Both financial and political support would be needed to achieve this objective. A first action that could be implemented through an ERVI working group is the identification of a list of stable isotopes for which self-reliance is needed (^{43,44,46,48}Ca, ^{102,110}Pd, all lanthanide elements such as ^{152}Gd, ^{155}Gd, ^{168}Er, ^{176}Yb, etc. and those not yet available from URENCO or ORANO like Ti, Ni, Ru, Pt...).

[8] As per figures communicated by Orano in the ERVI consultation

3.2.3. Issue #6 – (Enrichment) Addressing the lack of European HALEU enrichment installation

Identified issue

EU has been relying on HALEU (High-Assay Low-Enriched Uranium) supply from Russia/US for ^{99}Mo fission production and research reactors fuel. Continuing to rely on US/Russia delivery will increase tensions for EU supply, considering current geopolitical circumstances and the growing uncertainties on the US delivery capacities beyond 2030.

Given the timescale and coordinated efforts needed to set a European HALEU supply, short-term solutions must be found to secure the EU HALEU supply.

Suggested actions

Two actions were suggested, with different timeframes:

- In the short term, support the creation of a HALEU European stockpile until a sustainable solution is found for a European HALEU production capacity. While this would require flexibility, this also requires further thinking on the relevant instruments and pathways and does not allow self-reliance in the medium to long term.

- In the long term, ERVI or a specific European body (with Euratom Supply Agency - ESA) could coordinate public investment efforts for a HALEU enrichment installation, ensuring the sustainability of such installation. In addition, transversal actions towards an "optimised" use of HALEU could be performed at ERVI's level:
    - to consider recycling initiatives (e.g., RECUMO Belgium[9]),
    - to support non-HALEU alternatives for radionuclide manufacturing,
    - to optimise the use of HALEU[10] to manage limited supply during the construction of new HALEU infrastructure.

[9] https://www.sckcen.be/fr/projets/recumo

[10] A single manufacturer of LEU targets and HALEU research reactors fuel assemblies can be found in Europe (Framatome CERCA). This single source of supply is not considered at risk, yet ERVI could nevertheless work towards ensuring that no supply issues should be expected from this bottleneck in the future, especially regulatory/licensing considerations.

3.2.4. Issue #7 – (Stable isotopes supply) Addressing the opportunity for legacy waste recycling

Identified issue

In addition to the enrichment of "fresh" material, recycling activities to value existing radioactive wastes and legacy material of interest for radioisotope production are not currently investigated at the EU level.

For example, sourcing ^{226}Ra for ^{225}Ac manufacturing is currently seen as an issue. ^{226}Ra is available in large quantities in Europe, but recycling and purification are needed to allow irradiation.

Suggested action

One action was suggested:

- ERVI could initiate public or public/private collaboration to set a European plan to value some radioactive wastes, legacy material or used material, fostering recycling and purification to decrease dependency on foreign supply.

  A first action could be performed to set up a centralised Ra recycling facility, relying on EU public research installations (EC Joint Research Centres - JRC).

3.2.5. Issue #8 – (Stable isotopes supply) Addressing the opportunity for using ISOL facilities as alternative suppliers of radioisotopes

Identified issue

The development of alternative production routes using (e.g., high-energy proton-induced spallation followed by mass separation) could provide small quantities of radioisotopes without the use of highly enriched targets. This implies using Isotope Separation Online (ISOL) facilities and offline mass separation facilities (currently implemented in the EU PRISMAP project).

Suggested action

One action was suggested:

- ERVI could evaluate the interest in developing ISOL facilities in Europe to provide small quantities of high-purity radionuclides for which sourcing of enriched source material is considered an issue. In parallel with other actions towards establishing a sustainable supply of enriched stable isotopes in Europe, this could reduce the shortage risks for some radioisotopes needed in limited volumes.

3.2.6. Issue #9 – (Targetry systems) Addressing the need for new targetry systems

Identified issue

For both accelerator-based targetry systems and reactor-based targetry, there are generally no "generic" target designs, with each manufacturer or irradiation installation having its design requirements. Moreover, upscaling targets productivity would be needed to support nuclear medicine growth.

Suggested action

Two actions were suggested, with different timeframes:

- In the short-term, a gap analysis could be performed to evaluate the needs in new targetry systems, considering the industrial developments underway (GMP and non-GMP targetry systems), along with research projects underway aiming at developing new equipment and methods for target preparation (SECURE project[11], PRISMAP, etc.). A specific ERVI working group could be created to perform this gap analysis.
- In the long term, ERVI could coordinate public/private actions to work towards optimisation and homogenisation of targets not currently available at a commercial scale, through research/industry collaboration, especially for future complex target systems not based on standard electroplating technology.

[11] https://enen.eu/index.php/portfolio/secure-project/ The SECURE project foresees through its WP1 the development of target material handling, optimization and sourcing for alpha and beta emitters and different production routes.

3.2.7. Issue #10 – (Irradiation) Addressing the unequal geographical distribution of irradiation facilities across Europe

Identified issue

Depending on radioisotopes, different supply chains are used, some being centralised, with few installations across Europe (e.g., ^{99}Mo) or decentralised with hundreds of manufacturing sites across Europe (e.g., ^{18}F), for different economic or technical considerations (radioactive decay, irradiation capacity per installation, etc.).

- Centralized irradiation (and processing) facilities are in a limited number of countries, generally those with a strong background in nuclear research (existence of research reactors), such as Belgium or the Netherlands.

- Local production means are generally located close to the largest consumption hubs for economic reasons (large European cities with multiple nuclear medicine services), with significant competition among industrial players. Yet, fewer manufacturing sites can generally be numbered for European regions where demand is more limited.

Across Europe, the distribution of irradiation facilities is rather uneven. Yet the proximity between manufacturing sites, clinical users and research institutions is seen as a prerequisite to foster the development of new practices. Unequal distribution of irradiation means may lead to limit research and clinical developments across Europe while limiting at the same time nuclear medicine use (higher cost, higher supply risks in case of market tensions, etc.).

Across Europe, discrepancies can be found in terms of radioisotope availability and price [1]. The unequal distribution of production means in Europe is one of the drivers of price fluctuations. Allowing equal access to treatments in Europe would necessitate ensuring that produced radioisotopes are available anywhere in Europe and at fair prices.

Suggested action

One action was suggested:

- ERVI could work towards rebalancing the production of radioisotopes in Europe geographically to improve equal access to radioisotopes across Europe.

  ERVI could foster the development of production sites with initiatives aimed at promoting local production for new radioisotopes, avoiding monopolistic positions while providing redundancy of supply. When possible, public efforts should allow for fostering local manufacturing options, like ^{68}Ga onsite production, as compared to centralised European ^{68}Ge/^{68}Ga generators marketed by the industry.

3.2.8. Issue #11 – (Irradiation) Addressing the limited involvement of large accelerators and research installations in securing supply

Identified issue

European radionuclide manufacturing currently relies on research reactors (^{99}Mo, ^{131}I, ^{177}Lu) and small medical cyclotrons (^{18}F) to support commercial radionuclide demand. Despite their manufacturing capacities, large accelerators and research installations are not considered today as key players in radioisotope supply chains.

European accelerators and research installations are currently supporting clinical research by providing limited quantities of radioisotopes that are not produced by the industry. Better coordination of these installations on the model of the NIDC in the US would ensure easier procurement of R&D radioisotopes for all users at the EU level.

Moreover, limited collaboration and exchanges between the research sector and the industry complexify the transition from R&D to commercial manufacturing.

Suggested action

One action was suggested:

- Support the proper integration of large-scale European facilities able to provide non-conventional radioisotopes and new purity grades, such as high flux neutron reactors and new facilities, hadron and electron beam facilities, radionuclide, and isotope mass separation facilities, along with their infrastructure developments.

  Such facilities could be regrouped under a "European medical radionuclide programme or network", securing supply for medical and R&D use. PRISMAP is already an existing platform (funded through EU Horizon 2020) where a consortium of 23 partners in industry and academia is working on creating and making novel radioisotopes accessible. This could be one of the starting blocks for ERVI.

3.2.9. Issue #12 – (Irradiation) Addressing the lack of accelerators exotic beams available across Europe

Identified issue

Aside from the European network of small medical accelerators (medical cyclotrons) used for ^{18}F manufacturing, Europe is lacking more "exotic" beam availability (e.g., 28 MeV alpha beam for ^{211}At manufacturing). In some cases (^{211}At, for instance), short half-lives may hinder centralised manufacturing, making a European network of such facilities necessary.

Suggested action

One action was suggested:

- Support the development of a European network of small and medium accelerators with "non-conventional" beams. In medical institutions, only small cyclotrons can generally be found (only production of diagnostic isotopes, i.e., PET-isotopes) due to limited investment costs. But, if one could apply for an upgrade via EU funding, more cyclotrons could be installed to produce ^{225}Ac, ^{64}Cu, ^{211}At, and ^{89}Zr.

3.2.10. Issue #13 – (Irradiation) Addressing Long-Term Operation of existing large European irradiation facilities

Identified issue

Several large European irradiation facilities (research reactors, large accelerators) are approaching their "end-of-life", and some projects to replace them are ongoing. Yet, it is expected that the European supply of radionuclides will have to continue relying on these facilities in the short term.

Different actions have been launched at the European and international levels to prepare for ageing management (AM) and long-term operation (LTO). The 1st ENSREG topical peer review on ageing management included large research reactors in its scope, and WENRA issued "safety reference levels for existing research reactors", including AM (Issue I) in its scope.

Suggested action

As LTO approval ultimately depends upon national prerogatives (national regulations and licensing rules), implementing transversal actions at the EU level remains challenging. Thus, it is suggested to initiate discussions with Member States and stakeholders involved in LTO/AM of European installations to assess whether ERVI could implement support actions.

3.2.11. Issue #14 – (Irradiation) Addressing the future lack of high neutron flux research installations

Identified issue

With the expected closure of ILL (between 2030-2036), Europe may lack high-flux research reactor installations, leaving a gap for R&D on some radioisotopes.

Suggested action

ERVI could support securing high fluxes (>10^{15} n/cm^2/s) irradiation capacity. Different actions were suggested:

- In the short term, a gap analysis could be performed to evaluate precisely the future expected demand for high neutron fluxes and the future irradiation capacity based on existing/future projects.
- In the medium-term, specific actions in collaboration with the European research reactors network could be implemented to secure high-flux irradiation capacity.
    - For existing installations, back-fitting possibilities could be assessed to create high-flux irradiation positions
    - For future installations, the core design should cover not only the needs for medium flux irradiations of ^{235}U targets (^{99}Mo irradiation) but also aim at the highest possible flux for irradiation of stable isotope targets.

3.2.12. Issue #15 – (Irradiation) Addressing the risks/opportunities linked with the various irradiation projects under development

Identified issue

After the major shortages faced in the 2000s, various initiatives were launched globally to secure radioisotope production. With US-DOE support, many non-reactor projects centred around ^{99}Mo manufacturing emerged in the last years and are currently at different maturity levels (from commercial production to early R&D). These alternative technologies to standard irradiation in research reactors are expected to provide both redundancy (for ^{99}Mo) and complementary manufacturing capacity for some new radioisotopes (e.g., ^{67}Cu through photonuclear manufacturing route).

As Europe is currently exporting a significant part of its ^{99}Mo production, the success or failure of these different projects will impact the European production of radioisotopes. The industry may move from exporting to a local European supply industry. Moreover, such projects may also be localised in Europe (e.g., SHINE Europe).

Thus, close monitoring of these initiatives is needed in Europe to coordinate efforts towards securing a sustainable European supply chain.

Suggested action

One action was suggested:

- Through neutral technical evaluation, the interest in these new technologies could be addressed at ERVI's level to evaluate the interest in supporting these innovative ways of production, using particle accelerators, accelerator-based neutron sources or even power reactors.

  Such evaluation, performed in close collaboration with technology developers, should rely on detailed technical information to evaluate the technology readiness level of these projects and allow ERVI to make decisions regarding a diversified European network of irradiation installations encompassing proven irradiation systems and innovative design projects.

3.2.13. Issue #16 – (Irradiation) Improving the use of existing research reactors

Identified issue

European research reactor fleet is expected to continue to provide irradiation services for radioisotope production during the next decade. Yet, considering recent shortages resulting from the unexpected shutdown of a facility, optimising the irradiation capacity of the different European installations could allow to improve manufacturing capability and decrease shortage risks.

Suggested action

One action was suggested directly in line with the EC-funded project TOURR[12]:

- ERVI could support the dissemination of the conclusions of the TOURR project, to be delivered in 2023. Outputs are expected to provide suggestions of actions and tools aimed at supporting the optimal use of the European research reactors fleet.

3.2.14. Issue #17 – (Irradiation) Addressing the monopoly risks across radioisotopes supply chains

Identified issue

The potential full control of manufacturing capacity by private industrial players with commercial interests tends to drive up prices and create inequalities across EU countries. One of the risks is the exclusive use of production capacity for "large volumes" only, with limited or no manufacturing of radioisotopes to support research.

Suggested action

One action was suggested:

- ERVI could coordinate actions to foster competition and avoid any "monopoly" situation where a single private player owns all manufacturing capacity across Europe.

[12] TOURR is the acronym for "Towards Optimized Use of Research Reactors in Europe" project. It is a coordination action among 9 partners across the European Union (EU), out of which 6 are EU RR Operators.
The main targets of the project are to assess the impact of the decreasing number of RRs, identify future needs (including new neutron sources), draw a roadmap for the upgrade of the existing RR fleet, and develop a model for harmonized resource utilization. Another aim of the project is to evaluate the current and future need for neutron sources and for medical radioisotopes in Europe.

3.2.15. Issue #18 – (Processing) Addressing the bottleneck risks associated with centralized European processing facilities

Identified issue

For short-life RI, each irradiation facility (cyclotron) is equipped with a dedicated processing laboratory, with no bottleneck to be expected.

For long-life RI, there is currently a limited number of installations in Europe for the centralised production of radioisotopes (IRE and Curium ^{99}Mo processing facilities, ITM processing facility for nca ^{177}Lu). These installations are processing irradiated targets from different research reactors and create a bottleneck risk. Whereas some of them are being replaced, other installations are ageing and necessitate investments and modifications to fulfil the latest safety standards (e.g., seismic requirements).

Suggested action

Different actions were suggested at EU-level to ensure the redundancy and the sustainability of centralised processing facilities:

- In the short term, a specific ERVI working group could perform a scoping exercise to assess in collaboration with the different stakeholders:
    - The status of European processing capacities (capacity, timeframe, anticipated evolutions, etc.)
    - The actions needed to maintain or develop European processing capacities (Long-Term Operation, new projects, etc.), with a specific focus on promising radioisotopes (e.g., ^{225}Ac), where the private industry may be reluctant to invest.
- In the long term, ERVI could support specific actions identified by the working group to secure European processing capacity.

3.2.16. Issue #19 – (Processing) Addressing the limitations linked with recycling of target material for non-centralized facilities

Identified issue

The material used in targets (for instance, enriched ^{64}Ni for ^{64}Cu production, ^{226}Ra for ^{225}Ac production) sometimes represents a major share of the overall cost of a radioisotope. Thus, recycling or retrieving target material is a necessity for cost optimisation.

Large processing facilities can generally include complex recycling and purification steps in their installations, while the infrastructures in small production centres may prevent such activities. This can ultimately prevent small production centres (for instance, local cyclotron centres) to produce the corresponding radioisotopes, limiting supply capacity for clinical use.

Suggested action

One action was suggested:

- For certain rare target materials, the recycling efficiency could be improved by pooling and recycling used targets in a central target lab. Such a lab could also cope more easily with residual radio-nuclidic impurities and waste than the network of distributed cyclotron target labs. ERVI could support the creation of a recycling facility through public investment (joint action) to support small producers (especially public ones). This action would improve the use of enriched stable isotopes and mitigate import needs.

This action could be mutualised with issue #7.

3.2.17. Issue #20 – (Logistics) Addressing the bottlenecks of radioisotopes air transport

Identified issue

Radioisotopes air transportation agreements are currently negotiated at the industrial level, each player having its contractual agreements with a limited number of airlines. In case of air traffic disruptions (e.g., during the COVID-19 crisis), there are not always alternatives in place to adapt international delivery.

Suggested action

One action was suggested:

- Some agreements with airlines could be established at the European or Member States level (like in the US) for the transport of radioactive medical material. A dedicated annotation on the packages could be specified. For this, a consensus among Member States is strongly needed.

3.2.18. Issue #21 – (Logistics) Addressing customs-related issues delaying and complexifying transport of radioisotopes across Europe

Identified issue

Transport by truck, even over long distances, is generally preferred due to difficulties in securing flights, considerable paperwork for export and import licenses, and delays due to customs authorities not being familiar with radiopharmaceuticals.

Transportation and customs regulations often contradict the just-in-time requirement applicable to radioisotope products. In many EU member states, customs regulations state that dangerous/hazardous goods have to settle/wait at customs to prove safety requirements for further national delivery (e.g., irradiated material outside of Europe being shipped to Europe for processing, like ^{176}Yb capsule sent back to Germany at ITM manufacturing plant). Such idle time is detrimental to the quantity of product delivered, especially for short-lived isotopes.

Suggested action

One action was suggested:

- ERVI could coordinate actions with competent authorities to improve awareness of regulatory bodies/customs that radiopharmaceuticals are crucial for the diagnosis and treatment of severely ill patients and must not stay for too long at customs before they can be transported further on, especially not in situations of shortage, where such issues would exacerbate the situation. Specific actions at the national level aiming at accelerating custom verifications could be supported by ERVI. Clearance should not be country specific.

3.2.19. Issue #22 – (Logistics) Addressing the challenges linked with the restructuration of the European logistic industry to cope with the delivery of "patient doses" for new nuclear medicine uses

Identified issue

The current European logistic/transport industry mainly delivers "bulk" volumes of RI and RP that will be later used for patient dose preparation in radiopharmacies promptly integrated within nuclear medicine departments. The development of new practices (e.g., theranostic, targeted alpha therapy) may lead to the restructuring of logistics practices through the direct delivery of ready-to-use" patient doses from the centralised manufacturing plants to the end-users, thus drastically increasing the number of packages to be handled by the industry.

Suggested action

One action was suggested:

- Support the development of a European transport fleet and creation of regional/national hubs for the transport of radiopharmaceuticals in compliance with GMP/GDP (Good manufacturing and distribution practices), as the market is shifting (e.g., for therapeutic applications) from radioisotope transport to radiopharmaceuticals transport (small amounts of radioactivity will need to be shipped to many places, which differs from current distribution schemes with large amounts being delivered to a limited number of sites).

3.3. Actions to support coordination, communication and collaboration at the European and international levels between industry stakeholders, institutions, and national authorities

3.3.1. Issue #23 – Addressing the need for better communication related to potential or ongoing shortages and supply capacity

Identified issue

The problems caused by radioisotope shortages are serious, threaten the health of patients and have far-reaching consequences for European health systems. To minimise patient impact, all supply chain players, including healthcare professionals, wholesalers, manufacturers, and competent national authorities, have the obligation and responsibility to collaborate more closely in terms of resolving shortage problems. Especially wholesalers and manufacturers must communicate more effectively about likely and current shortages. Shortage management strategies need to be developed.

Aside from issues related to radioisotope shortages, some radionuclides and radiopharmaceuticals (e.g., DaTSCAN) currently have limited manufacturing capability. This can lead to the cancellation of orders which have been placed and the subsequent cancellation of patient appointments at short notice.

Suggested action

Two actions were suggested:

- In the short term, ERVI could work with the different stakeholders (through a dedicated working group) to define, through a position paper, the content and channels to be used for information exchange on shortages between end users (nuclear medicine, radiopharmacy and medical physics community), authorities and supply chain actors. Such communication should be carried out promptly and contain insights on how imminent the issue is, the expected duration of the shortage and whether alternatives are available.

  This position paper could also take specific recommendations towards industrial players to ensure that manufacturing capacity is reflected within orders capacity.

- In the medium term, ERVI could coordinate/harmonise the recent initiatives, such as the new European Shortages Monitoring Platform and the planned extension of the mandate of the European Observatory on the Supply of Medical Radioisotopes, should consider the specificities of in-house preparations related to shortages and the technical requirements of radiopharmaceuticals to ensure that all patients across can have timely access to needed medical products.

3.3.2. Issue #24 – Addressing the need for better communication among stakeholders at the European and the worldwide levels

Identified issue

Across Europe, there are currently different initiatives and working groups working on RI supply, either through industrial associations, clinical associations, or the research sector. Like any industry, a strong interaction is needed among stakeholders to secure supply and prepare for the future evolutions of the market. As nuclear medicine is a fast-paced development market, such interaction is even more needed.

Some examples highlighting the need for interaction are given hereafter:

- Clinical research cannot progress in the absence of close collaboration between
    - research and industrial stakeholders developing radioisotopes supply & radiopharmaceuticals development,
    - and the clinical side.
- The European radioisotope industry currently exports a significant share of its production. Some countries are currently relying partially (or fully) on European manufacturing capability for their RI/RP use (e.g., the United Kingdom). A secured and sustainable supply of RI/RP should thus include non-EU members.

Suggested action

Two actions were suggested:

- One transversal action to foster interactions at all levels through ERVI actions. Some examples are given below
    - The security of supply considerations should include in the discussions non-EU countries dependent upon European supply chains that manifested interest in collaborating with the EU
    - Improve networking between institutions (both production and research of radionuclides) for facilitated translational research and pre-clinical/clinical studies and staff/expert training in specific fields and production methods application.
- In the medium term, ERVI could set specific communication channels, working groups and "events" to foster the exchange of knowledge across all stakeholders directly or indirectly concerned with RI supply and foresee future evolutions of nuclear medicine and radioisotopes supply, such as:
    - Annual ERVI congress gathering all stakeholders (clinical, industrial, end-users, etc.).
    - Regional observatories so that best practices can be shared and promoted, and these should feed into one central organisation.
    - Topical working groups at the EU level to address specific challenges related to RI supply.

3.3.3. Issue #25 – Addressing the need for better involvement of public authorities in the security of supply discussions

Identified issue

Radioisotope manufacturing supply chains are generally little-known by the public. Aside from the small European medical cyclotrons network, a limited number of countries gather crucial manufacturing installations (Belgium, Netherlands, France, etc.). Such lack of visibility impacts the capacity of the sector to communicate its needs to secure supply and perform the right investments at the EU scale.

Moreover, on several transversal issues related to nuclear regulation, specific channels among authorities could be of great interest. For example, not all countries have already issued clear directives for the use and handling of each radioisotope in the clinical environment (incl. risks, issues, good practices, etc.).

Suggested action

One action was suggested:

- In the medium term, once established, ERVI could organise specific meetings (or set working groups) to periodically gather authorities to discuss
    - the security of supply at the European level and follow actions on securing supply chains to foster MS involvement and foster the future necessary investments.
    - Transversal regulatory issues, like radioactive wastes or good practices for radioisotope handling in a clinical environment, could be discussed and circulated within the regulatory community.

3.3.4. Issue #26 – Addressing the need to build on past/ongoing public initiatives to prepare for ERVI and involve stakeholders in charge of such projects

Identified issue

Different public-funded projects are currently underway and are directly linked with the different ERVI's objectives, such as

- SECURE (developments in the design of irradiation targets, production routes for existing and new isotopes in nuclear therapy and diagnostics)[13],
- TOURR (optimised use of research reactors in Europe), and
- PRISMAP (novel radionuclides and novel production technologies)

These projects shall be considered opportunities for the development of ERVI and could provide key inputs while setting up ERVI.

Suggested action

Two actions were suggested, with different timeframes:

- In the short term, monitor through the ERVI stakeholders' group the progress of all EC initiatives in the field of RI manufacturing. Representatives of ongoing projects could be invited periodically to present their achievements. Actions to directly support the implementation or outputs of such ongoing projects could be supported through ERVI, providing long-term follow-up.

- In the long term, some projects and initiatives could even be expanded. ERVI could identify further needs of public-funded projects or expand the perimeter of existing ones (e.g., an extension of PRISMAP to stable isotope mass separation facilities).

[13] https://cordis.europa.eu/project/id/101061230

3.3.5. Issue #27 - Addressing the challenge of securing financing for needed supply chains infrastructures across Europe (public/private funding and adequate reimbursement mechanisms)

Identified issue

The existing European radionuclide industry and installations (research reactors, accelerators, processing facilities, etc.) rely either on:

- fully private industrial installations,
- or private installations with indirect public support (e.g. industrial players located within public research centres and benefiting from support installations for waste management,
- and fully publicly funded installations and players.

For most European countries, the reimbursement of most of the medical radioisotopes (or radiopharmaceuticals) is included within the reimbursement of the overall procedures, despite the fact they represent only a minor share of the total cost (a few per cent). This negatively impacts the capacity to address cost evolutions (e.g., inflation and new investments in irradiation/processing facilities). Despite reimbursement considerations being beyond ERVI's scope, and having already been addressed by previous EC studies, how the cost of goods could appropriately be passed through the entire supply chain is a question that remains unanswered.

Suggested action

Different actions were suggested:

- In line with European Union public investments rules, ERVI should promote a fair level playing field and fair cost-sharing for radionuclide manufacturing facilities across supply chains, where when needed, public financing at the national or European level is not negatively impacting private industrial investments.
- Support European actions to develop a fair cost-sharing and/or financing scheme for existing and new irradiation facilities (e.g., fixed mark-up fee/levy per Ci to cover the cost of irradiation, waste management and decommissioning). Such practice would generate cash for promoting research as well.
- Support national actions with public health authorities to update reimbursement mechanisms through the establishment of specific reimbursement for medical radioisotopes and examinations. ERVI could lead the actions related to the evaluation and definition of reference prices, covering supply chain costs.

3.4. Maintaining excellence of European research on innovative techniques and technologies of production.

3.4.1. Issue #28 – Addressing the need for radioisotope supply to support the research

Identified issue

There are well over a hundred radioisotopes that may become important for healthcare (and other applications). Whether they will eventually be used is, to a large extent, a matter of availability for (pre-)clinical research and routine clinical use later on.

Ensuring the availability of radioisotopes for research is a strong driver for progress in nuclear medicine and molecular imaging. In the absence of such an existing supply chain (or in the absence of strong commitment from the industry to cope with future demand), investments and research may be slowed down.

Suggested action

Two actions were suggested:

- In the long term, support the research on developing manufacturing processes for new radionuclides (irradiation, processing, etc.) through close collaboration between industry, research, and clinical sector. This could be implemented through EC funding of research programs from academics and industry, with academic research programs developing new manufacturing methods, while industrial players involved in the projects would be responsible for scaling-up and industrialisation of developed technology to ensure sustainable commercial supply (like what is done through the US DOE Isotope Program).
- In the long term, aside from fostering collaboration, creating a European equivalent of the US National Isotope Development Centre that supplies radioisotopes and enriched stable isotopes for R&D needs is a key element in maintaining a leading role in the development of nuclear medicine and molecular imaging.

3.4.2. Issue #29 – Addressing the need for coordination of public research in the radioisotope sector

Identified issue

In the absence of overall and holistic coordination of public research across Europe, developments may not follow clinical interests with the risk of putting aside research fields for which a need will appear in the future.

Regarding R&D implemented in the frame of public financing, it is also needed to protect intellectual property. EURATOM initiatives do not allow the latter and are currently limited to radioisotopes (despite ongoing improvements). The "blurry" lines between healthcare, nuclear energy, and nuclear science in this domain complexify collaborations among public bodies for unlocking funding and agreeing on who should provide the right funding.

Suggested action

Different actions were suggested:

- Collaboration between ERVI and DG in charge of innovation for the coordination of research efforts on radioisotope production (enrichment, irradiation, processing, etc.), including public financing. ERVI could help in the prioritisation of efforts in line with demand/supply considerations.

  The R&D support could be differentiated for each supply chain step:

  - For enrichment, the research could be oriented towards developing new enrichment methods (e.g., mass separation coupled with laser ionisation).
  - For targets, the research could be oriented towards the most complex ones, such as ^{226}Ra targetry systems for ^{225}Ac manufacturing.
  - For processing, the research could be oriented towards improving processing techniques, developing automation, and developing processing techniques for new radioisotopes.

- Considering the US NIDC experience, the coordination of R&D efforts could be done with industry inputs. An approach could be collecting specific user needs and triggering R&D actions through dedicated calls for proposals or through direct negotiation with national labs that master appropriate technologies. This would allow the EU to pool R&D resources.

3.5. Coordinated implementation of relevant Euratom and EU law, and preparation of future regulatory evolutions

The content of the following sub-chapter (sections 3.5.1 to 3.5.6) is based on consultation results, yet the issues and actions identified are beyond the scope of ERVI. They are nevertheless included in the present report as they could be supported through other pillars of the SAMIRA action plan, through actions from other DGs (DG SANTE, DG MOVE, etc.) or by European authorities (e.g., ENSREG).

3.5.1. Issue #30 – Addressing the issues coming from targeted radionuclide therapy impact in terms of radioactive waste management, discharge regulations and dosimetry.

Identified issue

Radioactive waste management and discharge systems of nuclear medicine departments are submitted to national regulations for nuclear installations. The expected development of targeted radionuclide therapy or theranostic may lead to an overall increase of radioactive material handled in nuclear medicine services, impacting namely effluents discharges, raising infrastructure issues related to long-lived isotopes trace impurities (^{68}Ge, ^{225}Ac, ^{177m}Lu for CA ^{177}Lu, etc.).

The methods and tools to properly measure activity and dosimetry of new radionuclides remain to be developed (e.g., alpha activity measurement in effluents or patient dosimetry for new radionuclides). This can limit the development of new treatments and negatively impact patient access to treatment.

Suggested action *(to be implemented outside of ERVI)*

Two actions were suggested:

- Assess at the national and European levels the adequacy of infrastructures and radioactive waste release/discharge management with current regulations and define future needs in terms of infrastructures or regulations adaptation.
- Coordination with national authorities to define standards for radionuclides measurement and support the development of corresponding methods/tools to avoid regulatory impediments when treatments reach the market.

3.5.2. Issue #31 – Addressing the need for adequate radioisotope regulation in the EU

Identified issue

Different issues related to radioisotope regulations were highlighted:

- Annex 3 of GMP is not sufficiently clear and raises challenges in manufacturing radioisotopes according to GMP standards. This can pose a significant barrier to the introduction of new radiopharmaceuticals to the market because of the ambiguity of the GMP-regulated scope. For example, cyclotron production is outside of the remit of GMP, and chemical synthesis is part of GMP, but the steps in between ('processing') can be less clear. Interpretation of where GMP starts to apply differs according to the countries. For example, if GMP-grade copper is needed to make a product in the UK, this can be extremely difficult to source, as GMP is not considered to apply to earlier parts of the production process in other countries.

- Due to current regulations, it can be challenging to obtain a license to explore the use of a certain radionuclide in a clinical environment (as a physicist, for example). There is currently no "graded approach" in the administrative tasks, depending on the objective or the purpose of the exploration.

- European and national regulations address all radioisotopes without distinction on their use (imaging or therapeutic) or their physical characteristics (half-life, type of emissions).

Suggested action (to be implemented outside of ERVI)

Different actions were suggested that could be tackled by regulators (either at the national or European level through ENSREG) or by other DG.

- Supporting the implementation of GMP Annex 3 through specific clarifications and homogenisation of good practices across the EU. A specific guideline could clarify the areas in which differences can be found at the European level.

- A specific regulatory framework could be developed, allowing exemptions when no "clinical" impacts are at stake. Namely, if there is no clinical use in the exploratory phase of an endeavour (like, e.g., calibration of equipment, determination of the sensitivity of measuring, ...), the licensing for a technical use should not dive into pharmaceutical or clinical-related regulatory problems (which sometimes are huge and trigger different authorities or bodies). By that, one could gain a lot of time for doing plain and useful research.

- Amending regulations on radioisotopes to better address the intrinsic specificities among them (manufacturing and logistics challenges differ among radioisotopes). This would also allow addressing specific issues that could be raised in the future (e.g., alpha emitters handling).

3.5.3. Issue #32 – Addressing the need for adequate radiopharmaceutical regulation in the EU

Identified issue

Different issues related to radiopharmaceutical regulation were highlighted:

- Radiopharmaceuticals are currently regulated at the European and national levels with specific requirements such as GMP manufacturing, the need for market authorisation even for the clinical development phase and other specific local constraints.

- A large proportion of radiopharmaceutical development is being undertaken by non-commercial entities, like hospitals, research institutions and universities. When no radiopharmaceuticals ready-to-use are commercially available, applications of radiopharmaceuticals in daily practice are highly dependent on small-scale preparations that are compounded in-house under the responsibility of the nuclear medicine department or a hospital pharmacy. There is currently no distinction between commercial and non-commercial preparations of medical products within European regulations.

- Radiopharmacists use authorised kits and combine them with authorised radionuclide precursors (EU Directive 2001/83) to compound the final radiopharmaceutical ready for use. These kit-based radiopharmaceutical preparations are developed and validated by the marketing authorisation holder of the kit, including adequate quality control procedures. Therefore, kit-based preparations of radiopharmaceuticals are treated specially by current legislation: the final radiopharmaceutical does not need a separate marketing authorisation when prepared in-house and the preparation process is exempted from the scope of GMP annexe 3.

- In vivo use of radionuclides depends upon two types of regulations systems that work independently: pharmaceutical and radiation protection.

Suggested action *(to be implemented outside of ERVI)*

Different actions were suggested that could be tackled by regulators (either at the national or European level through ENSREG) or by other DG.

- A specific study is currently ongoing under the Quality and Safety pillar of the SAMIRA action plan, the "SAMIRA study on the implementation of the Euratom and the EU legal bases concerning the therapeutic uses of radiopharmaceuticals". It is suggested that the outputs of this study are used to work towards updating the European best practices and regulations regarding the therapeutic uses of radiopharmaceuticals. Different topics of action could be identified (e.g., modification of legal/regulatory hurdles on the use of radioisotopes as starting material for radiopharmaceutical production (complex manufacturing, not cold kits-

based manufacturing, the harmonisation of handling limits, import requirements, etc.)

- Making a distinction between commercial and non-commercial preparations of medical products could be investigated to set specific regulations for the small-scale preparation of radiopharmaceuticals. Industrial Good Manufacturing Practice (GMP) principles are not suitable for this type of preparation, and the revision of the pharmaceutical legislation should establish clear non-industrial standards for small-scale preparations that consider, on the one hand, the scientific and technological advancements related to novel and complex radiopharmaceutical preparations and on the other hand the specificities of preparations in hospital pharmacies or nuclear medicine departments. Disproportionate increase of quality assurance processes that are not fit for purpose and measures that impede innovation should be avoided, while at the same time, patient safety and high-quality standards for the in-house preparation of radiopharmaceuticals by non-commercial entities should be upheld.

- With the development of more complex preparations, a clear distinction between starting materials could be introduced, including radionuclides/ radionuclide precursors for kit-based preparations and complex radiopharmaceutical preparations. Current gaps in legislative guidance in this regard have led to misinterpretations of such requirements, ultimately impacting the supply negatively. The demand for marketing authorisation could be strictly limited to starting materials for reconstitution and kit procedures and not for starting materials, including radionuclides and active ingredients used in complex radiopharmaceutical preparations.

- Evaluate the interest in developing a special regulatory system with combination rules. Differences could come from the use of in vivo therapeutic or in vivo imaging.

3.5.4. Issue #33 – Addressing the need for adequate regulation for radioisotope transport

Identified issue

This issue is complementary to Issue #21 (§3.2.18) but deals with regulatory issues that are outside of ERVI's scope.

Different issues related to radioactive transport regulation (used across Europe for radioisotopes and radiopharmaceuticals transport) were highlighted:

- Transportation of radioactive material above certain activity thresholds needs to be done by licensed companies. In several countries, the procedure to get and keep such licenses is deemed too constraining and expensive.

- In terms of regulations associated with transport, the differences among countries complexify transportation rules for radioisotopes. The lack of common/harmonized transport rules across Europe generates idle time within the overall delivery process, which indirectly can lead to important losses of material due to radioactive decay.

Suggested action (to be implemented outside of ERVI)

Different actions were suggested that could be tackled by regulators (either at the national or European level through ENSREG) or by other DG.

- Evaluating the interest and the feasibility of setting a centralised European registration and licensing process to simplify inter-countries radioisotopes transportation.

- Verification and consolidation of the transport regulations, which are mainly managed at the national level and not at the European level, in particular in these fields:
    - Security/maliciousness (e.g., sources)
    - Airport-related activities (handling, inspections...)
    - Custom rules: harmonisation of the documents (import/export) required by the different national safety authorities

- Specific actions towards licensing of radioactive packages were suggested:
    - type B(M) packages currently require validations in each crossed country. It could be more efficient if a type B(M) license delivered by 1 European country is valid across all the European countries, at least for medical use.
    - A1 & A2 limits are not necessarily listed within transport regulations; a redefinition of such coefficients based on the latest data and simulation tools could allow setting more appropriate limits for type A packages.
    - harmonisation of ICAO (International Civil Aviation Organization) and IATA (International Air Transport Association) divergences between European countries.

3.5.5. Issue #34 – Addressing the need for support to small production centres in implementing stringent regulatory requirements

Identified issue

Regulatory requirements (national and European) are sometimes very demanding for small irradiation and manufacturing sites and prevent the development of local manufacturing sites that would be beneficial for the patients.

Suggested action *(to be implemented outside of ERVI)*

One action was suggested:

- Audits and support missions gathering European manufacturing experts could support best practices dissemination and allow small local installations to fully comply with regulatory requirements.

3.5.6. Issue #35 – Addressing the need for staffing national agencies in charge of drug approval

Identified issue

Each country has its agency delivering drug approval. Due to the size of the market, they are very few experts in the therapeutic use of radioisotopes (usually one person in each agency who has other topics to cover). This is also the case for EMA.

Suggested action *(to be implemented outside of ERVI)*

One action was suggested:

- Mutualizing these competencies at a European level in the EMA and designing a European regulatory framework would accelerate the development of these drugs in Europe while relieving pressure on national agencies.

3.6. Actions to support adequate workforce availability, education and training at all stages of the supply chains

The content of the following sub-chapter (3.6) is based on the consultation's results. Yet, these issues and actions identified are beyond the scope of ERVI. They are nevertheless included in the present report as they could be supported through other pillars of the SAMIRA action plan, through actions from other DGs (e.g., DG EAC) or by European authorities. Several European instruments could be used to support E&T for radioisotope supply chains (e.g., ERASMUS, MSCA, etc.).

3.6.1. Issue #36 – Addressing the workforce shortage at the different steps of the radioisotope supply chain

Identified issue

The development of nuclear medicine as a potential "first-line treatment" in the future will necessitate an adequate workforce at all levels of the supply chains and the clinical level. As the radioisotope industry requires very specialised skills, it is currently seen as challenging by the industry to hire appropriate personnel.

Some areas currently face shortages of European professionals:
- Isotope enrichment
- Irradiation (isotope handling, hot cell operation, etc.)
- Processing (radiochemistry).

Suggested action (to be implemented outside of ERVI)

Different actions were suggested:

- In the short term, perform an assessment of the current nuclear medicine industry workforce (excluding the clinical side, where an ongoing study is underway: EU-REST[14]) to identify gaps, training needs and existing national/European training courses.

- In the longer term, support specific education & training actions through European tools in the most critical areas to ensure that the workforce will meet the demand for new radionuclides use, with specific considerations addressing the ageing of the radioisotopes community.

[14] http://www.eurosafeimaging.org/projects/eu-rest

3.6.2. Issue #37 – Addressing the education and training issues at the different steps of the radioisotope supply chain

Identified issue

Radioisotope supply chains employ specialised workers covering multiple industrial and technical backgrounds (radiochemistry, radiation physics, etc.). Education and training (E&T) issues may appear to train the specialised workers in the sector.

Specific needs for E&T were highlighted during the consultation, for example, in radiochemistry. There is currently a lack of radiochemistry education courses in Europe. Some countries do not train students in this field, or when available, education is limited to fluorine chemistry. Yet, knowledge of the radiochemical separation of metallic elements will be needed to support new radioisotope development.

Suggested action (to be implemented outside of ERVI)

Different actions in the long term were suggested:

- Coordination at the EU level on the training needs in the different fields related to radioisotope supply (e.g., in the radiochemical field), potentially through collaboration with ENEN (European Nuclear Education Network) or at the ENEF level (European Nuclear Energy Forum).
- Development in collaboration with radiochemistry professionals of specific actions to ensure E&T in the radiochemical field. Such as:
    - Establish standardised guidance on the courses needed for BSc/MSc, etc., in radiochemistry, and assess the interest of a specific Master in the field.
    - Establish dedicated professional tutoring/training (like the former ENSTTI in nuclear safety).
- Launch actions to improve the attractiveness of the discipline to students, potentially through synergies between nuclear physics and chemistry communities,
- Transversal collaboration is a key success factor in ensuring the success of European R&D, as competencies differ among research laboratories, specialities, supply chain steps and radioisotopes expertise. Academic research could be supported through the establishment of partnering among academic sites, encouraging consortium between nuclear research centres and supporting the exchange of people in the scientific community through grants, to develop multidisciplinary and multinational research teams.

4. Specific considerations per radioisotopes

Among the various radiopharmaceuticals in use (or under development) at the European level, the study entitled 'Co-ordinated Approach to the Development and Supply of Radionuclides in the EU' identified a series of radionuclides of interest for medical applications.

The ERVI consultation requested respondents to identify, for each radioisotope, the supply chain steps (source material, enrichment, irradiation, processing, transport) for which an action is deemed necessary and suggest actions that would have a positive impact on the sustainability and the security of supply.

Issues and actions resulting from this isotope-specific survey often echo the issues and actions listed in section 3 of this report, but some specific actions have been highlighted.

In the perspective of a future prioritisation of these issues and actions, the isotopes have been split into four categories. The successful development of a radioisotope requires a shift of its supply chain from R&D needs towards "maturity". The main development challenge is the capacity to afford such a transition, from the manufacturing of limited quantities of radioisotopes in research installations to commercial facilities satisfying stringent regulations (GMP) while satisfying commercial needs for the benefit of European patients.

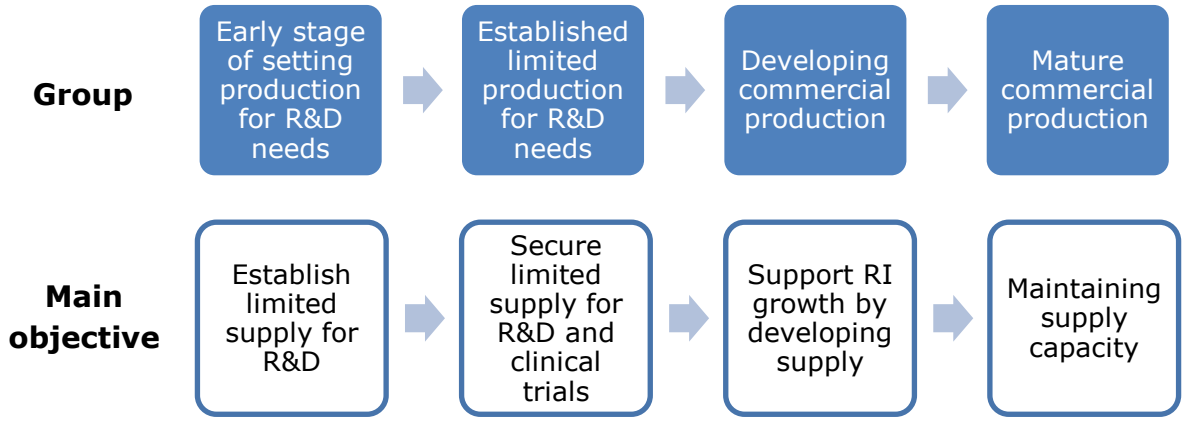

Figure 3: Breakdown per category of maturity level for RI supply chains

Depending on the level of maturity of each supply chain, the actions to be proposed at ERVI's level will address different stakeholders (industry, research sector) or volumes (large commercial needs or limited R&D volumes).

The following table provides a ranking of the respondents' answers regarding the most critical steps of the supply chains, using this breakdown in four categories (highlighted in blue and white alternatively). As can be seen, this breakdown corresponds fairly well with the existence of market authorisation or the number of ongoing clinical trials regarding the isotope under interest.

Table 1: respondents' views on the identification of supply chain steps that need actions to maintain (or set) a secured and sustainable supply chain (M.A. stands for Market Authorisation)

	Status of prod.	Use	M.A.* (EU or US)	Clinical studies	Nb of resp.	Source material	Enrichment	Irradiation	Processing	Transport
^{99m}Tc	Mature commercial production	SPECT	Yes	500	57					
^{131}I		Therapy Beta	Yes	60	37					
^{123}I		SPECT	Yes	40	36					
^{18}F		PET	Yes	1000	24					
^{90}Y		Therapy Beta	Yes	80	24					
^{223}Ra		Therapy alpha	Yes	50	21					
^{60}Co		Sealed sources	*n.a.*		13					
^{192}Ir		Sealed sources			10					
^{125}I		Sealed sources			8					
^{68}Ga	Developing commercial production	PET	Yes	250	49					
^{177}Lu		Therapy Beta	Yes	90	49					
^{64}Cu		PET	Yes	25	46					
^{225}Ac	Established limited production for R&D needs	Therapy alpha	No	15	47					
^{67}Cu		Therapy Beta	No	10	33					
^{89}Zr		PET	No	40	29					
^{124}I		PET	No	20	28					
^{166}Ho		Therapy Beta	No	10	23					
^{188}Re		Therapy Beta	No	10	23					
^{212}Pb		Therapy alpha	No	10	20					
^{211}At	The early stage of setting production for R&D needs	Therapy alpha	No	10	39					
^{44}Sc		PET	No	10	36					
^{155}Tb		SPECT	No	10	35					
^{161}Tb		Therapy Beta	No	10	33					
^{47}Sc		Therapy Beta	No	10	28					
^{149}Tb		Therapy alpha	No	10	25					

< 25%
[25-50%]
[50-75%]
>75%

Colour code indicates the % of respondents considering that actions would be needed to secure supply chains

The tables in the following sub-sections, 4.1 to 4.4, identify the main supply chain challenges for each radioisotope of the four categories, providing additional rationales for the actions described in Chapter 3.

4.1. Radioisotopes with mature commercial production

The radioisotope supply chains included within this category are those for which an existing commercial supply has been developed in the past. The industry is generally considered mature, with an established manufacturing process. The main challenge for these supply chains is to maintain manufacturing capability.

Table 2: Radioisotope supply chains with mature commercial production

RI	Issues (and suggestions of actions, if relevant)
^{99m}Tc ^{99}Mo	- ^{99}Mo irradiation and processing is a recurring challenge; in particular, securing irradiation capacities will remain a challenge if no new irradiation installations are available in Europe. - The current strong reliance on research reactors for ^{99}Mo/^{99m}Tc production is an issue for the security of supply. Supply is threatened by the ageing fleet, with expected increases in downtime and current delays of replacement projects in Europe (either fission or non-fission based). - Production by fission is expected to remain the standard for at least one more decade; thus, securing LEU supply by a decade is a key challenge as US LEU supply is expected to run out in the 2030s at the latest. - Non-fission alternatives may remove the constraint of building new research reactors, yet enrichment considerations for ^{100}Mo have to be solved (need for enrichment, processing and recycling)
^{131}I	- ^{131}I suffers from a significantly "too low price" on the market, not compatible with the cost of production without subsidies. Its production as a by-product of the ^{99}Mo production allows supply to be sufficient most of the time, but its use is increasing, and ^{99}Mo production by fission may be decreasing. - Irradiation of Te in research reactors is an alternative production route for ^{131}I, but the volatility of Te and I compounds makes this route risky for today's research reactors with limited release margins.
^{123}I	- From a user's perspective, ^{123}I irradiation and processing capacities seem to come to a limitation and should be expanded. New medium-energy protons accelerators are needed in Europe. - Support for the photonuclear production route from ^{124}Xe, could be a way to increase supply capacity. Yet source material supply is an issue. Strengthen developments towards photonuclear production of isotopes could be a 3rd pillar of radioisotope supply (after research reactors and proton accelerators)
^{18}F	- The supply of ^{18}O water should be closely monitored, despite the existence of different worldwide suppliers (incl. Russia), to prevent any shortage in the future. The risks linked with such full dependency on both enrichment and supply could be investigated specifically. - Despite having a good cyclotron network in Europe, there are still some areas where it is difficult to get ^{18}F for reasonable costs due to

RI	Issues (and suggestions of actions, if relevant)
	long transport routes that also impact the overall quality of ^{18}F (absorption effects in glass vials, activity concentration, etc.)
^{223}Ra	- Only source of production is the HFIR due to complex processing restricted to specialised laboratories able to handle radon emissions. No supply in Europe.
^{192}Ir	- Limited supply can become an issue, as irradiation necessitates very high flux reactors to achieve the highest specific activities and avoid the need for enriched starting material. Irradiation in Europe is mainly done in a single research reactor (HFR), while the remaining is imported from Russia. Limited supply capacity can become an issue for therapeutic applications. Availability of ^{192}Ir is considered at risk; actions are needed to secure supply.
^{201}Tl	- Despite being still popular for heart studies (and as an alternative in case of ^{99}Mo shortage), a limited supply of this radioisotope can be observed in Europe

4.2. Radioisotopes with developing commercial production

The radioisotope supply chains with developing commercial production are those for which the industry is currently scaling up the manufacturing capacity to support future or ongoing market growth. The main challenge is guaranteeing a sustainable and secured supply.

Table 3: radioisotopes supply chains with developing commercial production

RI	Issues (and suggestions of actions, if relevant)
^{68}Ga	- Facilities and workforce required to produce ^{68}Ga radiopharmaceuticals are limited in Europe, negatively impacting the capacity to meet demand domestically. - Supply of ^{68}Ge is currently limited in Europe, with dependence on Russia. Ongoing private initiatives by ^{68}Ge/^{68}Ga generator manufacturers are underway and could solve this issue. Yet, this should be closely monitored, while investment in medium energy cyclotrons could also be useful for other radioisotope manufacturing. - As part of the ^{68}Ga manufacturing process, the release limits for ^{68}Ge are currently seen as "too strict" by manufacturers, impacting the costs of radiopharmaceutical production. - While different industrial players chose ^{68}Ge/^{68}Ga generators, pursuing efforts in setting local manufacturing options in small medical cyclotrons would allow for backup manufacturing solutions and could be more adapted for limited needs in some regions of Europe.
^{177}Lu	- Considering the significant increase in clinical use and the limited number of suppliers along with European irradiation capacity and lack of European enrichment for stable isotope (^{176}Yb), the ^{177}Lu supply should be closely monitored and direct actions taken in collaboration with the industry to work towards securing supply. - Enrichment of ^{176}Yb relies mostly on Russian enrichment units, and the growing demand already exceeds the offer.

RI	Issues (and suggestions of actions, if relevant)
	- Upscaling of both irradiation and processing capacities is key to meeting the projected radioisotope needs within the next 5 to 10 years. - Transport of larger quantities of radioisotopes in type B containers remains challenging due to the limited number of authorised containers.
^{64}Cu	- The supply of ^{64}Cu is insufficient in Europe (currently, only one producer with marketing authorisation with limited capacity, and demand is expected to rise). - ^{64}Cu has 12.6 hours half-life that would allow the creation of centralised manufacturing centres of radiopharmaceuticals (cyclotron to produce the isotope + radiolabelled drug manufacturing), from which end users would be supplied. - Despite more "limited" yields, liquid targets for ^{64}Cu manufacturing would be valuable for local, small production batches.

4.3. Radioisotopes with established production for R&D needs

Radioisotope supply chains with established production for R&D needs are those for which a supply has been secured, but only at the R&D level that currently allows supporting (fully or partially) clinical trials and research underway. The main challenge here is to start planning for future commercial manufacturing scales by developing cost-effective, industrially scalable processes.

Table 4: radioisotopes supply chains with established production for R&D needs

RI	Issues (and suggestions of actions, if relevant)
^{111}In	- Due to prohibitive cost, it is almost not available anymore in Europe
^{89}Zr	- There is currently only one main irradiation and processing site in Europe with regular commercial supply. As the demand is expected to rise, there is a need to support and coordinate efforts to secure additional suppliers. - The partial EU dependency on China for stable isotope supply must be monitored to avoid future shortages.
^{124}I	- There is no longer a European supply of GMP grade ^{124}I, which is impacting clinical trials. Public actions are needed to set new GMP sources of supply.
^{166}Ho	- ^{166}Ho is difficult to produce for reactors due to the extreme sensitivity of the carrier spheres in radio-embolic therapy. Low gamma flux and temperature control are required. - The current price for the product is incompatible with the production costs.
^{225}Ac	- The production and processing of alpha-emitters are challenging and often require different infrastructures than the production and processing of other radionuclides. This is due to the generation of long-lived waste, possible very high radiotoxicity of by-products (^{227}Ac for ^{225}Ac production) or complex targets production (^{226}Ra for cyclotron route). - While the required activities are generally lower for targeted alpha therapy, the specificities of the ^{225}Ac supply chain make this one a

RI	Issues (and suggestions of actions, if relevant)
	dedicated category calling for the support of complementary infrastructures and expertise (e.g., available in a consortium such as PRISMAP with JRC-Karlsruhe, Arronax, CERN-MEDICIS, as well as biomedical institutes skilled in the developments of such radiopharmaceuticals). European collaboration should be fostered on this subject. - Considering the significant increase in clinical use and the limited number of suppliers, supply risks are expected, especially in case of lag of European initiatives. - Access to ^{226}Ra is currently a major impediment for ^{225}Ac manufacturing.
^{211}At	- Only two facilities (Nantes already and GANIL soon) are currently able to produce this isotope. Due to its rather short half-life, it will be difficult to cover EU demand with these two facilities. - A fleet of 30 MeV alpha beam accelerators (not available today) is required for the sustainable production of ^{211}At. Need for coordinated efforts at the EU level for investments in such facilities. - In parallel with establishing supply, R&D on Astatine chemistry remains needed.
^{212}Pb	- The current supply chain is sufficient to cover the R&D demand (only research). In the case of approval of radiopharmaceuticals for therapy, there might be problems with raw material supply and processing facilities within the EU (currently, only one facility in the EU – small-scale production).
^{57}Co	- ^{57}Co is one of the most widely used radionuclides for the manufacturing of medical sources. They are needed for the calibration of key equipment (SPECT/dose calibrators). Today's production is mainly located in Russia, raising an indirect risk to nuclear medicine applications. - As the element has a 270-day half-life, replacement needs are frequent, and the ability to create long-term storage is very limited.

4.4. Radioisotopes at the early stage of setting production for R&D needs

Radioisotope supply chains at the early stage of setting production for R&D needs are those without established supply, for which minimal quantities of radioisotopes can be sourced, currently preventing starting clinical trials and R&D activities.

Table 5: radioisotopes at the early stage of setting production for R&D needs

RI	Issues (and suggestions of actions, if relevant)
^{149}Tb	- Production is hampered by the limited availability of high energy (>500 MeV) proton beams combined with radioactive mass separators. - The route to produce it in significant quantities with sufficient purity is not fully established yet, and the same applies to extraction from the irradiated targets and the recovery of the highly enriched target material that is needed.
^{155}Tb	- The production of ^{155}Tb is now exclusively done with the combination of high-energy cyclotrons/proton accelerators and mass separation

RI	Issues (and suggestions of actions, if relevant)
	facilities and relies on access to enriched targets in enough quantities and purity grades. Timely online operation of the main isotope mass separation facilities (present such as CERN-MEDICIS and future ones, such as non-exhaustively, ISOL@Myrrha, SPES) is key for its development and a proper share of the facilities for the medical programme should be earmarked. - The enriched material (gadolinium) is currently procured in Russia. ERVI should support the EU domestic enrichment infrastructure. Furthermore, post-irradiation processing technology requires dedicated separation technology. As all medical Tb isotopes are in the early R&D stage, support from ERVI might be a condition to explore the full potential of these isotopes.
^{161}Tb	- Source material and enrichment of ^{161}Tb precursor is limited (^{160}Gd) - As ^{161}Tb production requires the same level of neutron fluxes as for ^{177}Lu, ^{99}Mo, etc., there is a risk of future competition among radioisotopes for irradiation, which could be driven by selling prices, impacting negatively already established radioisotopes generating less return for the irradiators.
^{44}Sc	- No commercial supply is currently available; clinical developments should be closely monitored to set supply in due times - Efforts towards the development of ^{44}Ti/^{44}Sc generators could be supported publicly, considering the interest of generators to allow centralised manufacturing and decrease logistics issues.

5. Conclusions

5.1. Summary of issues raised in the consultation

Introduction

The targeted ERVI consultation gathered the positions of a number of stakeholders on the ERVI objectives and the specific issues concerning the supply chain of medical radioisotopes. A total of 37 issues were identified, covering both the intrinsic challenges faced at the different steps of the radioisotopes supply chains (supply of source material, enrichment, irradiation, processing, logistics) and the transversal ones faced by the stakeholders (e.g., need to collaboration at national and European level, regulatory issues, support to the research and workforce considerations).

Known issues on the RI supply chain confirmed through consultation results

Before the SAMIRA Action Plan and its ongoing European Radioisotope Valley Initiative (ERVI), different projects[15] allowed for shaping the SAMIRA action plan while identifying potential issues to address to secure a reliable and sustainable supply of radioisotopes in Europe.

- The two SMER [1] studies (Study on sustainable and resilient supply of medical radioisotopes in the EU for diagnostic radionuclides – SMER 1 - 2022 and for therapeutic radionuclides – SMER 2 - 2021),
- The European study on medical, industrial and research applications of nuclear and radiation technology [2] - 2019
- The SAMIRA supply chain study (Co-ordinated approach to the development and supply of radionuclides in the EU) [3] - 2021.

Part of the material gathered during the present consultation confirmed and highlighted known issues previously identified in these past EC-funded projects.

A key issue highlighted in all previous studies is the limited availability of information related to radioisotope supply chain capacity and nuclear medicine demand. Different actions were suggested in the present survey by respondents to improve data collection on the current use of nuclear medicine (Issue #1 in section 3) and the supply chains' present and future manufacturing capability (Issue #2). The European Observatory on the supply of radioisotopes was considered crucial for monitoring demand and supply; different suggestions for expanding its scope were suggested by respondents (Issue #3) to include all key

[15] More details on the SAMIRA Action Plan and its related projects can be found on this webpage https://energy.ec.europa.eu/topics/nuclear-energy/radiological-and-nuclear-technology-health/samira-action-plan_en in the sub-section "Studies and projects – supply of medical radioisotopes"

radioisotopes, commercial and research ones, and cover all steps of the supply chain and not only the irradiation step.

Several outputs of the SAMIRA supply chain study concerning actions needed at each step of the supply chain were also confirmed by respondents, such as:

- the need for coordinating efforts on stable isotopes supply (Issue #4),
- the need for the development of new targetry systems (Issue #9),
- the bottlenecks and risks associated with centralised European processing facilities (Issue #18),
- the radioisotopes logistics issues (Issues #20 & #21) and the upcoming challenge of theranostic development (Issue #22),
- the challenge of securing the funding necessary for supply chain infrastructures across Europe (public/private funding and adequate reimbursement mechanisms) (Issue #27).

The radioisotope supply chain industry gathers numerous stakeholders at national, European, and international levels. The need for better communication among these stakeholders was reminded by respondents (Issue #24) while at the same time highlighting the need for involving public authorities in the security of supply discussions (Issue #25).

The strong links between the research, the industry and the end-users were highlighted by previous studies. Respondents confirmed the need to secure a sustainable supply of radioisotopes to support the R&D needs (pre-clinical and clinical studies), which could be done at EU-level (Issue #28), together with coordinating public research efforts in the radioisotope sector (Issue #29).

Finally, respondents recognised the efforts implemented in the frame of past/ongoing initiatives and projects aiming at securing the European supply of radioisotopes and highlighted the need for ERVI to build on these outputs and actively involve stakeholders in the discussions (Issue #26).

New developments impacting the security of supply and associated issues/actions

Recent developments in Europe and worldwide have impacted positively or negatively radioisotopes' security of supply.

The reliance on Russian electromagnetic enrichment capability became a crucial issue since Russia's invasion of Ukraine (Issue #5) in the absence of backup alternatives. The lack of European HALEU enrichment installation raises risks for the same reason (Issue #6), considering the uncertainty of US supply in the medium term (the 2030s).

In the last year, the European supply of ^{99}Mo faced different periods of tension due to technical issues at the irradiation level (cooling water leak in HFR in Jan.2022, valve issue in BR2 in Nov.2022, etc.). Ageing installations are more prone to such incidents, highlighting the need for pursuing efforts to address the Long-Term

Operation of existing large European irradiation facilities (issue #13). Securing and improving the use of existing installations in Europe for radioisotope supply is crucial for the security of supply. The recent TOURR project (Towards Optimized Use of Research Reactors in Europe) aims to evaluate the current and future needs for research reactors and neutron sources in Europe (October 2020 - September 2023, Euratom R&T programme) and provides recommendations for actions at ERVI's level (Issue #16).

Different public and private-financed projects aimed at improving European supply made significant progress in the last years (e.g., PALLAS reactor funding from Dutch Government, collaboration SCK-CEN/IBA for setting the first European ^{225}Ac commercial supply, etc.). Such projects should be closely monitored at ERVI's level to assess their impact on future supply (Issue #15).

Most of these challenges regard commercial supply. Yet, research infrastructures are more and more considered to have a crucial role to play in the future for securing R&D and clinical trial needs (Issue #11). The PRISMAP project (Production of high-purity medical radionuclides by mass separation) involving major European infrastructures aims at providing a sustainable source of high-purity grade new radionuclides for medicine, owing to a single-entry point using standardised access procedures for all researchers active in this field, including SMEs, global pharma, nuclear centres, hospitals, and universities, (May 2021 - April 2025, Horizon 2020).

New key issues and suggestions for actions

The targeted consultation also enabled the identification of specific issues that had not been addressed specifically in the previous EC studies on radioisotope supply chains, namely:

- the opportunity for coordinating efforts on legacy waste recycling for use as source material for irradiation (e.g., ^{226}Ra for ^{225}Ac supply) (Issue #7).
- the opportunity of coordinating efforts for using existing ISOL facilities in Europe to supply a limited quantity of RI for research use (Issue #8).
- the issues related to the unequal geographical distribution of irradiation facilities across Europe and its impact on RI availability and equal access (Issue #10).
- the risk of future lack of high neutron flux research installations (Issue #14).
- the limitations faced by small, decentralised facilities with recycling of targets and potential coordinated efforts to address these needs at a European level (Issue #19).
- The issue related to monopoly risks for some radioisotopes (Issue #17).

- The need for better communication related to potential or ongoing shortages and supply capacity (Issue #23).

Issues and suggestions for actions beyond ERVI's scope

Securing a safe and sustainable supply of radioisotopes in Europe would imply addressing simultaneously different types of challenges. As defined within SAMIRA Action Plan, ERVI is intended to only focus on production infrastructures and methods (to facilitate access to source materials, improve efficiency and further optimise industrial scale production, and support the development of new production methods). Meanwhile, complementary issues on regulations, workforce, education & training, or on quality and safety considerations related to radiopharmaceutical use could be addressed through other pillars of the SAMIRA action plan (e.g., SAMIRA Simplerad[16] project under the SAMIRA Quality and Safety pillar), through actions from other DGs (DG SANTE, DG MOVE, DG EAC, etc.) or by European authorities (e.g., ENSREG).

The consultation identified multiple transversal regulatory issues beyond ERVI's scope, linked with the national and European radioisotope and radiopharmaceuticals regulations (Issues #31 & #32), and specific nuclear regulations considerations applicable to radioisotope supply chains such as radioactive waste management, discharge monitoring and dosimetry (Issue #30), transport of radioactive material (Issue #33). Supporting the implementation of specific regulatory requirements for small production centres (Issue #34) and staffing considerations in national/European agencies (Issue #35) were also highlighted by respondents.

Education & Training, and workforce considerations at the radioisotope supply chains level were also identified by respondents as crucial to ensure the security of supply. Different suggestions of actions were proposed by respondents to address workforce shortages in specific areas, such as the radiochemical processing industry (Issue #36), or to secure adequate Education & Training ecosystem in Europe (Issue #37). Such considerations are beyond ERVI's scope but could benefit from other EC initiatives in this area.

[16] SAMIRA Simplerad – "Study on the implementation of Euratom and EU legal bases with respect to the therapeutic uses of radiopharmaceuticals"
https://www.eanm.org/advocacy/eu-related-activities/simplerad/

5.2. Next steps

Upcoming meetings of the ERVI steering group and stakeholders' group

The content of this report will directly feed the discussions of the ERVI steering group (SG) and stakeholders' group (SHG).

The SG and SHG are intended to support the Commission services in taking forward actions for establishing the European Radioisotope Valley Initiative (ERVI) that is entitled to maintain Europe's global leadership in the supply of medical radioisotopes and help accelerate the development and introduction of new radioisotopes and production methods.

The materials collected in the frame of ERVI targeted consultation and through past EC-funded studies will be used to assess the interest of each suggested action and identify the top priority ones to be implemented in ERVI's frame that could improve the sustainability and security of European supply.

For prioritising these suggestions of action, members of the ERVI steering group could be asked:

- Whether DG ENER alone (or in collaboration with other DGs) have a clear added value in implementing the suggestion of interest,
- Whether a SMART objective can be defined for this action/suggestion, SMART standing for:
    - Specific (target a specific area for improvement),
    - Measurable (quantify or at least suggest an indicator of progress),
    - Assignable (specify who will do it),
    - Realistic (state what results can realistically be achieved, given available resources)
    - and Time-related (specify when the result(s) can be achieved).

Example of SMART objective

As an example of a SMART objective for Issue#1: **Develop a European centralised database gathering the different metrics necessary for evaluating European NM needs in the future** (number of procedures with details on clinical indication, activity injected to the patient, radiopharmaceutical used, etc.).

The **indicator of progress** would be the number (or percentage, or EU coverage) of EU medical institutions informing the database. This task would be **assigned to** a European body, for instance, the European Observatory, on the supply of radioisotopes. This task could be **realised with database developers** (belonging to EU, to Eurostat? subcontracted?) with a **2-year duration** for the beta version, then periodically updated by the EU body in charge and disseminated to industry and research for action, and to the public for information about the benefits of NM in the fight against cancer.

Four categories of radioisotopes are defined in section 4 of the present report, which addresses different types of action, different timeframes, and different stakeholders. These categories could be used to help sort the actions, prioritising, assigning and specifying them more in detail.

ERVI feasibility study

As planned within SAMIRA Action Plan, the next step in preparing for the launch of the European Radioisotope Valley Initiative is:

> "The results of the public consultation will be analysed and summarised together with the stakeholder group. For the most important identified objectives, scenarios and potential measures will be developed and examined for feasibility. Co-funding sources and R&D partners will be identified."

Through a specific project to start in the first half of 2023, feasibility studies will be implemented.

Appendix A. Bibliography

Different studies are mentioned within this report; the details for accessing publications related to these projects are given below.

[1] Mario, N., Kolmayer, A., Turquet, G., A, Study on sustainable and resilient supply of medical radioisotopes in the EU, Goulart De Medeiros, M. and Joerger, A. editor(s), Publications Office of the European Union, Luxembourg, 2022, ISBN 978-92-76-49317-4, DOI: 10.2760/911131, JRC128401

Ligtvoet, A., Scholten, C., Dave, A., King, R., Petrosova, L. and Chiti, A., Study on sustainable and resilient supply of medical radioisotopes in the EU, Goulart De Medeiros, M. and Joerger, A. editor(s), EUR 30690 EN, Publications Office of the European Union, Luxembourg, 2021, ISBN 978-92-76-37422-0, doi:10.2760/642561, JRC124565.

[2] European Commission, Directorate-General for Energy, European study on medical, industrial and research applications of nuclear and radiation technology: final report, Publications Office, 2019, https://data.europa.eu/doi/10.2833/511137

[3] Kolmayer.A; Mario.N ; Vallée.A ; Turquet.G ; Co-ordinated approach to the development and supply of radionuclides in the EU - Final report, DOI 10.2833/120792, https://op.europa.eu/fr/publication-detail/-/publication/4599de47-3ac6-11ec-89db-01aa75ed71a1/language-en#