Co-ordinated Approach to the Development and Supply of Radionuclides in the EU

N°ENER/D3/2019-231

Final Report

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Manuscript completed in August 2021.
First edition.

Luxembourg: Publications Office of the European Union, 2021

PDF doi:10.2833/120792 MJ-09-21-436-EN-N

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This report has been prepared by NucAdvisor for and on behalf of the European Commission.

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Acknowledgments

This report has been prepared by NucAdvisor with the support of many industrial players, scientific societies and international organizations, gathering experts at all steps of radionuclides supply in the EU and on a worldwide basis.

Authors would like to acknowledge with gratitude all the participants that contributed to gather information and perspective of development and supply of radionuclides in the EU.

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Acronyms

BT	Brachytherapy
CA	Carrier added
CAGR	Compound annual growth rate
CSF	Cerebrospinal fluid
EANM	European Association of Nuclear Medicine
EMS	Electromagnetic separation
ESIPP	Enriched Stable Isotope Pilot Plant
EU	European Union
FDA	U.S. Food and Drug Administration
FCR	Full cost recovery
GANIL	Grand Accélérateur National d'Ions Lourds (France)
GEP/NET	Gastro-entero-pancreatic neuroendocrine tumours
GMP	Good manufacturing practices
HALEU	High-assay low enriched uranium
HDR/LDR	High/Low-dose rate (brachytherapy)
HEA	High energy accelerator
HFR	High Flux Reactor (Petten-NL)
HLW/ILW/LLW	High, Medium, Low Level (radioactive) Waste
HSA/LSA	High/Low specific activity
IAEA	International Atomic Energy Agency
ILL	Institut Laue-Langevin (France)
LEU	Low-enriched uranium
LINAC	Linear accelerator
MA	Market authorization
MEC	Medium energy cyclotron
MS	(EU) Member State
NCA/CA	Non carrier added, Carrier -added
NDA	New drug application
NDT	Non-destructive testing
NIDC	National Isotopes Development Center (USA)
NM	Nuclear medicine
NMEu	Nuclear Medicine Europe
NPP	Nuclear Power Plant
PET	Positron emission tomography
PSI	Paul Scherrer Institute (Switzerland)
RIVM	Dutch Health and Environment Ministry
RJH	Réacteur Jules Horowitz (France)
RN	Radionuclide[1]
RP	Radiopharmaceutical
RSV	Radiosynovectomy
SAMIRA	Strategic Agenda for Medical Ionising Radiation Applications
SIPF	Stable Isotope Production Facility project (USA)
SMC	Small medical cyclotron
SMR	Small and Medium Size (power) Reactor
SPECT	Single photon emission computerized tomography
TAT	Targeted alpha therapy
TRL	Technological readiness level
TRNT	Targeted radionuclide therapy

[1] The terms "radionuclide" and "radioisotope" are used interchangeably in the present report.

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Abstract

According to the new European SAMIRA Action Plan[2], there is a need to secure the supply of medical radioisotopes in the medium to long term, in order to maintain EU patients' access to vital medical procedures.

The selection of the most representative of current and future-use radionuclides allows to highlight the long-term paradigmatic change towards an increased use of therapeutic radionuclides. Radionuclides supply chains are then extensively analysed. Complementarity between accelerators/cyclotrons and fission/neutron activation installations for producing industrially all necessary isotopes is emphasized, as well as the interest of coordinating the large European Research installations for producing the isotopes necessary for R&D.

If investments are not timely made in Europe for replacement of the ageing production infrastructures and the development of new source materials capabilities (HALEU and enriched stable isotopes), the result will be an increasing dependence of EU on foreign supply.

Diverse options for fostering a sustainable supply of radionuclides in Europe are then presented and screened through a multi-criteria analysis. Possible scenarios for EU rank from relatively low to high investments, inversely proportional to levels of reliance upon foreign supply.

[2] "COMMISSION STAFF WORKING DOCUMENT on a Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) 5.2.2021 SWD(2021) 14 final"

Selon le nouveau plan d'action SAMIRA de la Communauté Européenne[3], la sécurisation à moyen et long-terme de l'approvisionnement en isotopes médicaux est nécessaire afin de garantir l'accès des patients européens à des procédures médicales vitales.

L'identification des isotopes les plus utilisés actuellement et ceux susceptibles de l'être à l'avenir fait ressortir le changement de paradigme vers une utilisation accrue des isotopes thérapeutiques. Les chaînes d'approvisionnement sont analysées en détail. La nécessaire complémentarité entre la production industrielle d'isotopes par accélérateurs/cyclotrons et celle par fission/activation neutronique est mise en avant. De même, l'intérêt de coordonner les grandes installations de recherche européennes pour la production d'isotopes aux fins de R&D est souligné.

Si des investissements ne sont pas faits à temps en Europe pour le remplacement d'installations vieillissantes et le développement de nouvelles capacités de production d'isotopes et de matériaux-source (isotopes stables enrichis et HALEU), le risque/inconvénient majeur pour la sécurité d'approvisionnement en radio-isotopes médicaux sera une dépendance accrue aux importations.

Diverses options pour assurer un approvisionnement fiable et durable au sein de l'Europe sont alors présentées et analysées selon une analyse multicritères. Les scénarios possibles pour l'Europe s'échelonnent d'investissements relativement faibles à des investissements importants, inversement proportionnels au degré de dépendance de l'Europe aux importations.

[3] Voir référence page précédente

Executive Summary

According to the new European SAMIRA Action Plan[4], there is a need to secure the supply of medical radioisotopes in the medium to long term in order to maintain EU patients' access to vital medical procedures.

The objective of the present study was to fill gaps in the available information on the supply chains for the main established and novel radionuclides that have, or are expected to have, significant uses in Europe. The work also had the goal of preparing the ground for long-term European co-operation in this area.

The study had to meet the following specific objectives:

a. identify the main radionuclides currently in use in the European Union, and the main radionuclides expected to be used by 2030, with a particular focus on the radionuclides used in medicine;

b. identify the existing and emerging methods and technologies for production of the radionuclides covered under (a) and fully describe the main elements of their respective supply chains;

c. identify the main suppliers of source materials and technologies for production of radionuclides covered under (a) and the facilities which are part of the above supply chains;

d. develop scenarios and concrete options for sustainable and secure supply of radionuclides covered under (a) in the EU.

Accordingly, among the large number of radionuclides with development potential, a selection of nuclides has been carried out in consensus with the Steering Group of this study, and confirmed owing to an analysis of the ongoing clinical trials at a global level. It turns out that, during the next 2 decades:

- for SPECT imaging, ^{99m}Tc should continue to be the work-horse;

- for PET imaging: despite high growth expected for ^{68}Ga, ^{18}F should keep its current leader position; ^{64}Cu, ^{89}Zr and ^{124}I are challengers;

- use of radionuclides for targeted therapy will drastically increase. For the β-emitters: sharp growth is anticipated for ^{177}Lu, particularly under its non-carrier added (NCA) form; ^{131}I, ^{90}Y, ^{223}Ra should continue to be largely used. Use of ^{166}Ho and other RN should develop. R&D progresses for α-emitters (^{225}Ac, ^{212}Pb, ^{211}At), as well as for new theranostics pairs based on Terbium and Scandium.

[4] "COMMISSION STAFF WORKING DOCUMENT on a Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) 5.2.2021 SWD(2021) 14 final"

Current and future EU needs for the most important isotopes are quantified.

The isotopes-specific supply chains are analysed in detail, from source material procurement up to processing of the radiochemical ready for radiopharmaceutical labelling, to identify the main security of supply challenges that they raise.

Six findings conditioning security of supply are substantiated in this study.

1) Accelerators/cyclotrons and fission/neutron-activation installations are complementary in the long term, as covering different isotopes-scopes:

   a) accelerators/cyclotrons are particularly necessary for accompanying the anticipated development of PET imaging isotopes and, in a more distant future, for ^{225}Ac;

   b) fission/activation installations are particularly needed for the future industrial bulk of neutron-activation-produced therapeutic isotopes, including NCA ^{177}Lu.

2) If reduction of EU reliance on foreign supply is targeted, new investments are necessary in both domains, cyclotrons/accelerators and fission/activation installations, as the capability of existing installations to fulfil EU needs will deteriorate seriously. Indeed, current cyclotrons fleet will be unable to supply emerging PET isotopes. From 2035 onward, according to the life extension possibilities of BR2, HFR, Maria and LVR15, reactor's production capacities will decline. From 2040, only RJH and FRMII will remain online if no new large installations are built. Their capacities are unable to cover fully EU needs, not only for ^{99}Mo, but overall for essential therapeutic β-emitters nuclides such as NCA ^{177}Lu, ^{131}I, etc.

3) Regarding investments in large installations, several options can be envisaged: a photonuclear-based installation like SMART or an European version of Northstar, a fission-based installation like SHINE, a research reactor or a power reactor. However, the production scopes of the different options are not equivalent.

   a) Whereas a research reactor is able to produce simultaneously, in a proven and industrial manner, all nuclides generated by fission and neutron activation, both medical and industrial, it is not the case for developing options:

      i) for SMART, Go/No Go decision is scheduled by end of 2022. SMART would be able to produce essentially ^{99}Mo and, in the future, certain accelerator-produced isotopes such as ^{225}Ac. An alternative photonuclear-based installation, on the model of the US-Northstar using IBA's Rhodotron® technology could be envisaged as well, but with the same production scope;

ii) SHINE is currently being licensed in the US only for ^{99}Mo, ^{131}I, ^{133}Xe production.

b) Using power reactors, particularly CANDU reactors, is an interesting way to produce isotopes and is being developed in Canada. But not all the operators are ready to take the risk of perturbing their primary power production in case of potential malfunctions of the isotopes production. In addition, only 2 CANDU reactors exist in Europe, operated by Nuclearelectrica in Romania, which currently does not plan to produce other isotopes that ^{60}Co.

4) Other critical points from a security of supply point of view are HALEU supply and the enrichment of stable isotopes:

a) HALEU is essentially supplied by the US, which anticipate possible shortages beyond 2030. The ESA Advisory Committee's Working Group on European production of low-enriched (19.75%) uranium was re-instated in spring 2021 and mandated to continue the work based on the recommendations given in the 2019 ESA report. The group will explore the necessary conditions for establishing European production capacity for HALEU to respond to the EU needs for the research reactors fuel and medical radioisotopes production;

b) concerning stable isotopes, achieving satisfactory yields will necessitate the use of costly enriched targets, which raise a dual problem: their production and their recycling. Developing cyclotrons radionuclides production will increase the need for gaseous centrifugation-enriched materials, and European capabilities will have to be expanded (Urenco, and Orano as possible new entrant). For other source materials such as enriched ^{176}Yb for NCA ^{177}Lu production, Russian electromagnetic installations are currently the main supplier, but with limited capacities. Securing such EMS-enriched isotopes for the EU would necessitate investments (either in a EU EMS-enrichment capacity or through the development of alternative manufacturing routes).

5) Co-ordination between large European research installations is key for supplying R&D isotopes and promoting new production routes. The PRISMAS-MAP initiative federates many European research and industrial organizations for producing R&D and rarer isotopes, on the model of the US National Isotopes Development Center; such kind of initiatives are to be supported.

6) Life extension and revamping of existing installations is to be considered whenever possible, as it is currently the case for BR2, HFR, Maria and LVR-15.

Based on these findings, four typical cumulative long-term scenarios are defined. With regard to their favourable cost-benefit ratio, strong coordination between large European research installations and life extension of existing installations are

assumed in the four cases. The four scenarios are analysed against a series of criteria, starting with security of supply.

- Scenario A: EU supply is based on accelerators/cyclotrons and existing installations, appropriately life-extended whenever possible. In this scenario, the EU can envisage self-reliance for all imaging isotopes including the emerging PET isotopes like ^{68}Ga, but not for the main SPECT imaging isotope ^{99m}Tc. Self-reliance can also be envisaged for developing therapeutic nuclides, namely the α-emitters, but not for the fission/neutron-activated therapeutic isotopes (NCA ^{177}Lu, etc.), which are the most interesting in the perspective of beating certain cancers in the next two decades. Import will then be necessary, and import possibilities of these isotopes will largely depend upon the success of the North American projects (SHINE, NorthStar, CANDU, etc.).

- Scenario B.1: In addition to accelerators/cyclotrons, EU supply relies on large industrial installations based on emerging production routes like SMART or SHINE. In this case, self-reliance can be envisaged for ^{99m}Tc as well, but not for all therapeutics[5] such as NCA ^{177}Lu. Like in scenario A, EU will have to rely on imports for these isotopes.

- Scenario B.2: In addition to cyclotrons/accelerators, at least one new research reactor is built in Europe. In this case, EU self-reliance can be envisaged for all necessary isotopes, in a proven manner. Such option allows to maintain the EU export position and open new export opportunities as well.

- Scenario C: With the addition of own capabilities for HALEU and stable isotopes enrichment, the EU reduces its reliance on foreign supply to a minimum.

The second set of criteria deals with investment effort. The number of installations of each type necessary for achieving EU self-reliance is first evaluated. Using unit costs for each installation type, orders of magnitude of investments are established. Though many uncertainties remain for emerging production routes (CAPEX, production yields, etc.), it turns out that:

- For scenario A, investment could be graded and optimized according to needs, development of production routes and the opportunities to co-produce several isotopes in a single installation. However, despite unit costs being relatively low, new investments in cyclotron installations (SMC & MEC) would induce very high investments due to the number of installations needed, especially for short half-life isotope production preventing long-distance shipping. Corresponding investments could amount to hundreds

[5] Pending evidence that SHINE is able to produce them in an efficient manner.

M€ for a new MEC network (~10 MEC) to more than 1 billion € for a full new SMC network (200 SMC across the EU).

- As cyclotrons/accelerators and large installations are complementary, total investments are additive. A scenario B.1 unit like SMART could represent a 200-300M€ additional investment, whereas a scenario B.2 new research reactor could cost more than 1 billion €.
- For scenario C, securing stable isotopes enrichment in the EU, along with securing HALEU supply would necessitate an additional investment of several hundred M€.
- However, the optimisation of all these new investments remains to be done, when more information will be available concerning the market needs and the performance of the emerging production installations.

Given the complementary production scope of the installations, a large fission/neutron activation installation remains necessary if reduction of EU dependence to foreign supply is targeted. Finally, the larger the investment, the larger the reduction of EU reliance on foreign supply.

Private initiatives can generally be relied upon for graded investments in relatively low-unit-price cyclotrons. However, such private initiatives are conditional upon the existence of a market. For large installations (centralized accelerators and fission-based ones), fully private initiatives might not be practicable, due to the known difficulty of implementing full cost recovery, the high investment costs (several hundred M€) and the relatively long durations for design, construction and licensing (pre-production).

In all cases, due to the many players involved in the investment decisions and the influence of the global market, the risk of investments not being made in a timely manner is high. Coping with such situations may thus require a mix of public incentives and private initiatives[6].

Besides their EU security of supply merits, each scenario also presents other advantages, namely for maintaining European innovation momentum in many promising domains.

However, conditioning all four scenarios is the fact that developing nuclear medicine benefits for beating cancer requires that Europe relies on all the necessary skills, that nuclear careers become appealing again for students and that public acceptance is ensured.

[6] The US domestic 99Mo production program, launched in 2009 and not yet completed, is a good example of such an approach and the amount of time that its implementation requires.

Lastly, this study opens up additional subjects of discussion and/or further investigations. Among others:

- strengthen reliability of input data (EU RN needs, performances and costs of the diverse technologies and processes, workforce needs, waste generation, etc.);
- optimize the installations-mix in Europe (cyclotrons, accelerators, large industrial installations) versus relevant criteria;
- pursue investigations downstream of the supply chain, in the radiopharmaceutical domain.

1. 2030 vision for radionuclides use in the European Union for health and industrial applications

Radionuclides are part of European citizens' daily life, whether for medical or industrial applications. The medical sector relies on them to assess bodily functions and to diagnose and to treat diseases. They are a part of several types of equipment used in medical and industrial applications, in the latter case mainly as sealed sources to perform non-destructive testing (NDT), materials processing, irradiation of goods, measurements, etc.

Nuclear medicine is offering new opportunities because of major recent breakthroughs:

- molecular biology advances offer today an exceptional range of targeted molecules that can be labelled with a radionuclide for both diagnostic imaging and radiotherapy: this is the beginning of theranostics;
- both fast computing and Artificial Intelligence have boosted productivity and reliability in NM imaging procedures;
- hybrid cameras now offer a unique diagnostic tool for clinicians by merging the morphological image of radiology with the functional scan of nuclear medicine;
- new semiconductor and detectors now offer lower dosimetry and better efficiency.

Most of these applications do not have alternatives, which strengthens the need for sustainable supply of radionuclides in EU.

Radionuclide supply chains are complex manufacturing processes that have to deal with radioactivity issues (safety, radiation protection, waste management), often combined with additional requirements (pharmaceutical constraints in the case of nuclear medicine). Due to their unique characteristics (half-life, physical production routes, emission types, chemical characteristics, etc.) supply chains are highly nuclide-specific. A large enough selection of nuclides of interest is thus necessary in order to identify correctly the challenges for Europe's long-term supply. This is the subject of the Chapter 1.

1.1. Radionuclides have become essential components of European citizens' daily life

Since the discovery of radioactivity more than a century ago, the use of ionizing radiation has continuously increased, with the development of innovative tools for exploring matter, improving health, supporting industrial processes and supplying reliable and low-carbon energy. Ionizing-radiation applications take advantage of x-rays, neutrons, α, β, or γ-emissions from nuclear reactions for developing new applications.

Using radionuclides, as sealed or unsealed sources, is currently the most widespread approach for generating α, β, or γ-emissions. Radionuclides are extensively used in health, industrial and research applications (as summarized in the following figure). Over the years, Health has become the largest radionuclides user, both for diagnostic and therapeutic applications. With the expected development of therapeutics applications, radionuclides will be more and more used in the Health sector. Aside from that, they are also largely used in industry for sterilization, non-destructive testing and environmental applications.

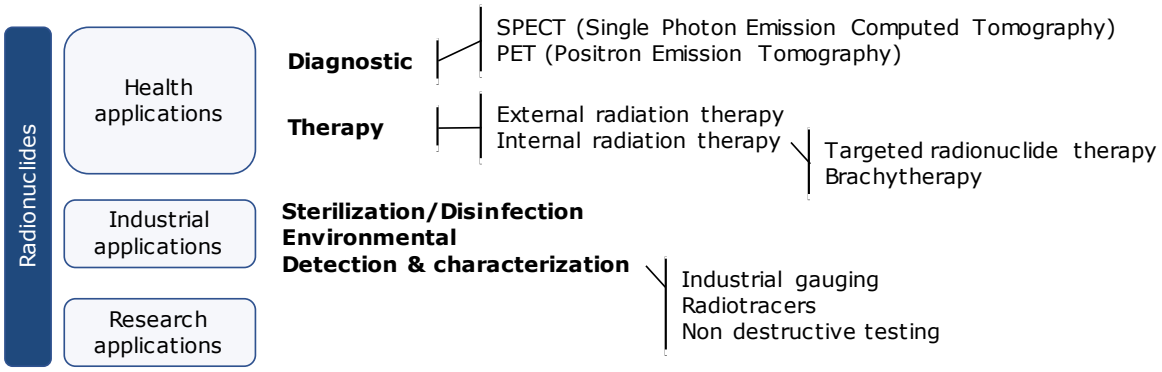


Figure 1: Landscape of applications using radionuclides

The major progress being made by nuclear medicine (NM) today is explained by its operating mechanism, which is directly based on the biological and metabolic activity of pathologies. In diagnosis, NM provides a functional image of a pathology that complements the morphological image of radiology. In therapy, NM makes it possible to target and destroy malignant cells using specific biological vectors of the pathology labelled with appropriate radionuclides.

This chapter aims at identifying the current most-used radionuclides in the medical sector (§1.2) and in the industrial sector (§1.3), both through qualitative and quantitative analysis of the European landscape. Each radionuclide identified is then assessed individually (§1.4) through different criteria (current use & trend, current supply chain status, interest and future perspectives), leading to the selection of the most promising radionuclides (§1.5) for analysis of their respective supply chains.

1.2. An overview of medical radionuclides uses

1.2.1. Nuclear medicine relies heavily on radionuclides for diagnostic and therapeutic applications

Radionuclides are used in the health sector either as radiopharmaceuticals (unsealed sources) to assess bodily functions and to diagnose or internally treat diseases, or as sealed sources in therapy applications (either external or internal therapy). Nuclear medicine is of less frequent use than other imaging modalities, and mainly oriented towards oncology, aside from heart and pulmonary imaging (~10-15 million procedures per year in EU, as compared to 600 million x-ray procedures, 40 million Magnetic Resonance Imaging procedures, and 60 million Computed Tomography procedures per year in the EU[7]) and therapy technologies used in modern health paths.

Radionuclides can be directly injected as ionic species (e.g. thallium cation ^{201}Tl) but are generally attached to molecules (e.g. organic compounds, peptides or antibodies) specifically targeting organs or specific cell types. Radionuclides can also be used as sealed sources or bound to specific materials (e.g. glass spheres) for their sole radiation properties in therapeutic applications.

Nuclear medicine uses radionuclides for imaging and therapeutic applications. Imaging and targeted radionuclide therapy (TRNT) use the same principle: a chemical compound is selected for its binding ability with a specific target (ideally a receptor only existing in the targeted cancer cells) which is linked to a radionuclide. The particle or photon emitted during decay is used for locating cancer cells (imaging) or directly destroying them (therapy).

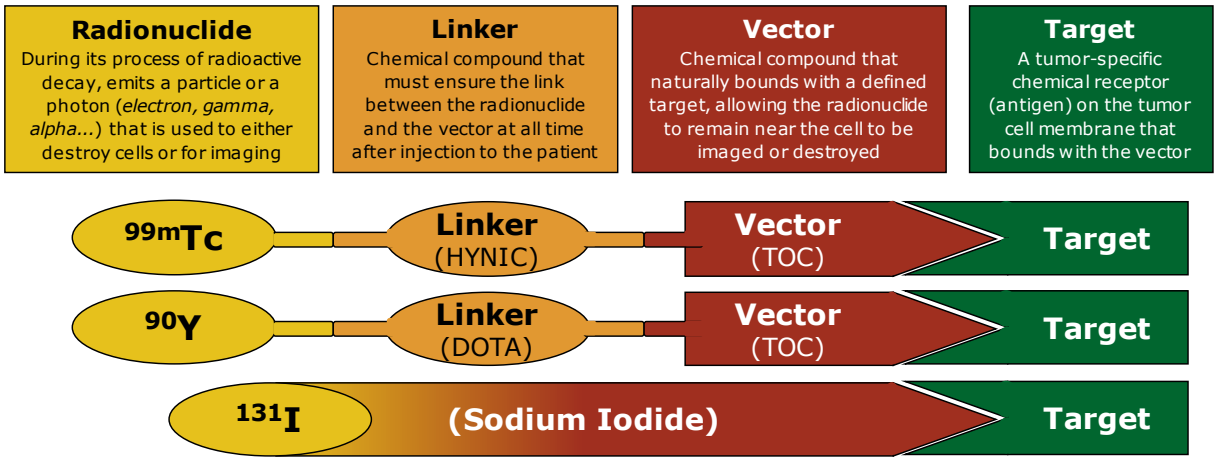


Figure 2: Principle of targeted radionuclide uses in medicine – Source: NucAdvisor

[7] SAMIRA 2019 study: European Study on Medical, Industrial and Research Applications of Nuclear and Radiation Technology. Final Report. Contract ENER/17/NUCL/SI2.755660. MJ-03-19-070-EN-N

In imaging applications, the radionuclide emission profile orients its use either for SPECT (Single Photon Emission Computerized Tomography) or PET (Positron Emission Tomography) imaging.

Radionuclides used for targeted therapeutic applications are either α-emitters, β-emitters, or Auger electron emitters. Depending on their emission profile, their interactions with cells varies (size of volume of interaction, intensity of energy delivered, etc.) Thus, their selection is performed according to the type of treatment envisaged.

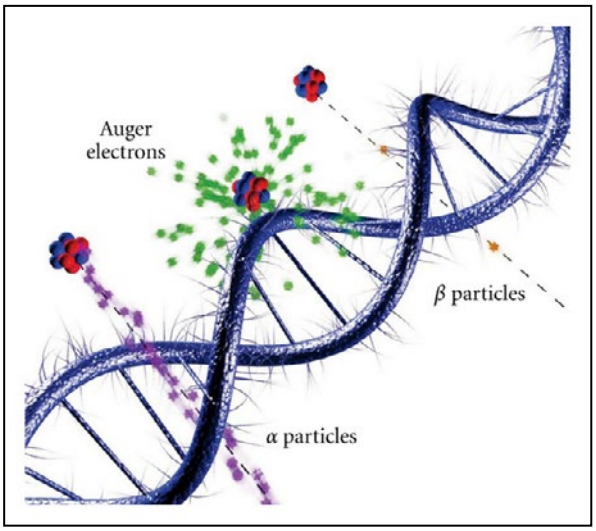


Figure 3: Types of therapeutic radionuclide interaction

Radionuclides have demonstrated high therapeutic efficiency, in comparison to ionizing electromagnetic types of radiation (X-rays and γ-rays), providing stronger destruction to biological systems for a given radiation dose.

In addition to targeted radionuclide therapy, other forms of therapy use internal or external sealed sources (brachytherapy or external radiation therapy) as well as materials loaded with radionuclides to deliver treatments.

1.2.2. EU nuclear medicine currently relies on more than 100 radiopharmaceuticals for diagnostic and therapeutic applications

The common NM imaging modalities (SPECT and PET) use a large variety of radionuclides, whose frequency of use differs widely. Aside from the key radionuclides for SPECT and PET modalities, respectively ^{99m}Tc and ^{18}F, which currently account for more than 90% of medical procedures in the EU[8], several others have more limited use but great value.

The identification of radionuclides under use in the EU can be performed through a screening of the various publications describing the current state of the art in the nuclear medicine sector, and national statistics for some Member States.

The European Nuclear Medicine Guide[9] by EANM (European Association of Nuclear Medicine) and "The Birth of Hygiea," a publication (see Appendix A) of the Innovation Working Group of NMEu (Nuclear Medicine Europe, formerly AIPES) both describe in detail the radionuclides and radiopharmaceuticals in use for diagnosis and therapy, for various types of applications.

[8] SMER study
[9] Link to publication https://www.eanm.org/publications/european-nuclear-medicine-guide/

An overview of nuclear medicine current best practices in Europe has been prepared based on these two publications. The complete list of radiopharmaceuticals in use is given in Appendix B, while a summary of associated radionuclides can be found in the following tables.

Applications		Anatomical area or function investigated	Nuclides
Cardiovascular imaging	PET	Myocardial perfusion and viability	^{18}F, ^{11}C, ^{13}N, ^{15}O, ^{82}Rb
	Planar or SPECT	Blood studies, cardiac imaging, deep vein thrombosis, myocardial perfusion and cardiac function	^{99m}Tc, ^{125}I, ^{51}Cr, ^{201}Tl
Gastro-intestinal and renal imaging	Planar or SPECT	Assessment of renal function and transit (kidneys, bladder…), clearance methods, bile acid investigation, colon transit, liver (hepatocytic function), renal cortical imaging and others *(bladder, oesophageal transit, gastrointestinal bleeding, etc.)*	^{99m}Tc, ^{123}I, ^{75}Se, ^{111}In
Neurology imaging	PET	Amyloid plaque accumulation (Alzheimer), brain metabolism, brain perfusion, Parkinson's diseases (Presynaptic dopaminergic transporters)	^{18}F, ^{15}O
	Planar or SPECT	Brain perfusion (incl. stroke), cisternography and CSF leak, Parkinson's diseases (presynaptic dopaminergic transporters)	^{99m}Tc, ^{111}In, ^{123}I
Pulmonary imaging	Planar or SPECT	Ciliary clearance, lung perfusion imaging and ventilation	^{99m}Tc, ^{81m}Kr
Oncology imaging	PET	Adrenal imaging, bone imaging, brain & nervous systems tumours, breast cancer, neuroendocrine tumours (NET), thyroid imaging, prostate cancer, tumour detection and treatment efficiency measurement, tumour localisation (skeleton, brain, etc.), urogenital cancer (incl. prostate cancer)	^{18}F, ^{11}C, ^{68}Ga
	Planar or SPECT	Adrenal scintigraphy, bone marrow, bone scintigraphy, breast cancer, neuroendocrine tumours (NET), non-Hodgkin lymphoma (NHL), sentinel node lymphoscintigraphy, thyroid imaging	^{99m}Tc, ^{123}I, ^{131}I, ^{111}In
Others imaging applications	PET	Infectious diseases	^{18}F
	Planar or SPECT	Blood/platelet survival study, lymphoscintigraphic or sentinel lymph node mapping, splenic function, infectious diseases, imaging of the salivary glands and lacrimal tract, parathyroid imaging	^{99m}Tc, ^{111}In

Table 1: Summary table of current radionuclides used for diagnostics in EU

Applications	Treatments against…	Nuclides
Therapy	Malignant neural crest tumours (pheochromocytoma)	^{131}I
	Neuroendocrine tumours	^{177}Lu, ^{90}Y
	Non-Hodgkin lymphoma	^{90}Y, ^{177}Lu
	Polycythaemia and thrombocythemia treatment	^{32}P
	Primary/secondary hepatic malignancies (hepatocarcinoma)	^{90}Y
	Prostate cancer	^{177}Lu, ^{225}Ac
	Thyroid diseases therapy	^{131}I
	Palliative treatment bone metastases	^{153}Sm, ^{223}Ra, ^{89}Sr, ^{177}Lu
	Radiosynovectomy – polyarthritis	^{169}Er, ^{186}Re, ^{90}Y

Table 2: Summary table of current radionuclides used for therapy in EU

These tables illustrate the wide use of radiopharmaceuticals products, with Planar Scintigraphy, SPECT and PET products available in the EU to assess a large range of bodily functions and diagnose a large variety of diseases, oncology imaging

being one of the key nuclear-medicine applications. Radiopharmaceuticals may have multiple uses ([^{99m}Tc]Tc-sestamibi can be used for myocardial perfusion, for breast cancer detection, for thyroid and parathyroid imaging, etc.), for imaging different organs, since they target specific molecular mechanisms or cells that may be altered in different tissues and disease states. Currently, it is estimated that more than one hundred radiopharmaceuticals have daily use in the nuclear-medicine sector, most of them being labelled with only few radionuclides (^{99m}Tc, ^{18}F, ^{123}I, ^{131}I, ^{68}Ga, ^{177}Lu, etc.).

In the past, the industry focused its developments on radionuclides with sustainable supply chains, such as ^{99m}Tc, ^{18}F. Indeed, the attractiveness of a radiopharmaceutical for the industry is, among other things, closely linked to the radionuclide's availability and its associated supply chain. When considering the long timeframe (from early R&D to market authorisation) of development for radiopharmaceuticals, it is expected that only very few new products shall reach marketing authorisation within the next 10 years.

1.2.3. What are the current trends and statistics of use of radionuclides in the European Union?

Imaging modalities statistics are rather imprecise and unequal among EU Member States, national statistics being almost systematically limited to a total number of procedures performed, with indications on the anatomical region or organ given only in some cases. It is possible, for example, to estimate the number of thyroid and parathyroid imaging procedures performed in a Member State, but without being able to conclude on the radionuclide used (^{123}I, ^{131}I or ^{99m}Tc). Thus, in general it is hardly possible to link the limited statistics available with the radiopharmaceuticals and radionuclides used to perform these procedures.

Some Member States nevertheless publish statistics that can be used as a reference to identify general trends over the EU (see Appendix C for data concerning Sweden, Germany and The Netherlands).

The proportion of use of radionuclides for imaging and therapeutic use (in terms of number of procedures) is given for Sweden, Germany and Netherlands in the following figures:

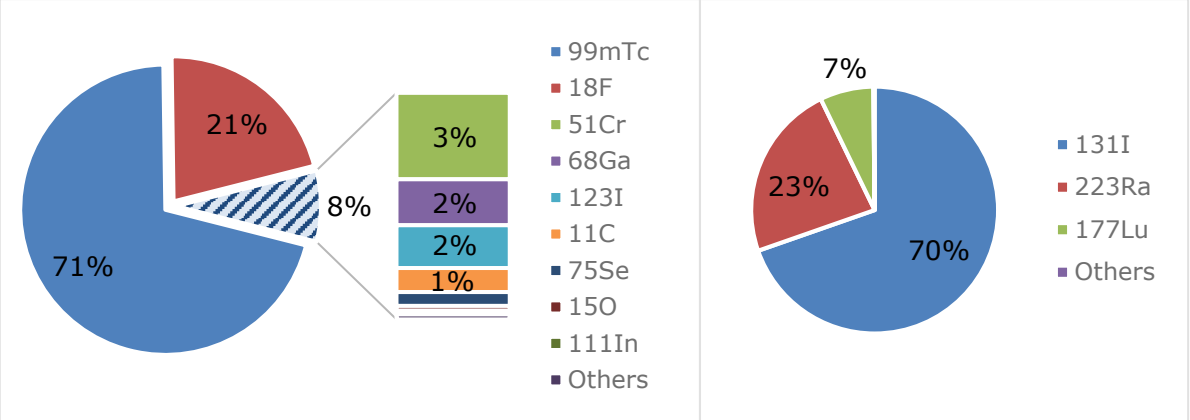


Figure 4: Imaging (Left) and therapeutic (Right) radionuclides used in Sweden in 2018, for a total of ~110,000 NM procedures – source SRSA statistics

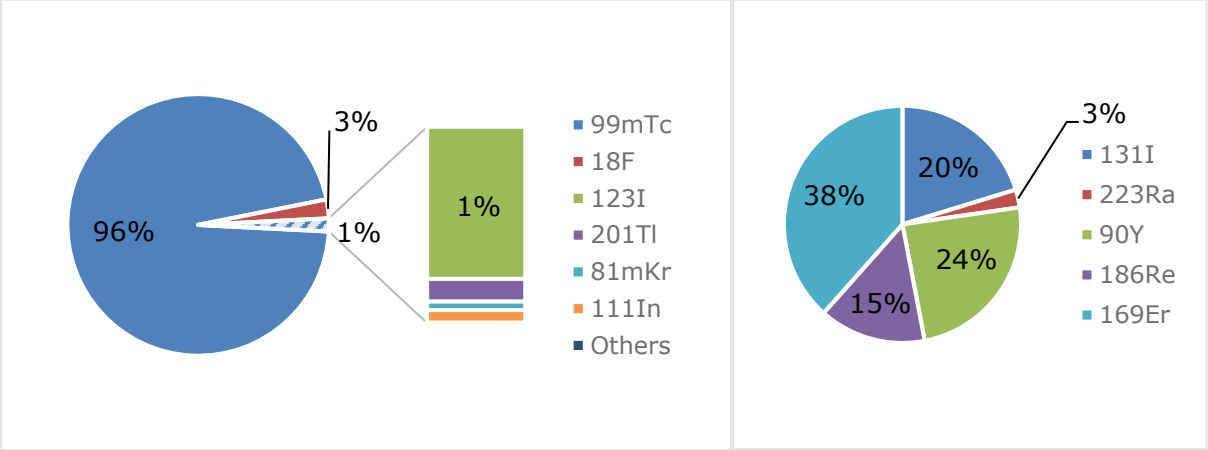


Figure 5: Imaging (Left) and therapeutic (Right) radionuclides used in Germany in 2015 for private nuclear medicine sector and PET imaging performed in public hospitals, for a total of ~ 2 Million NM procedures

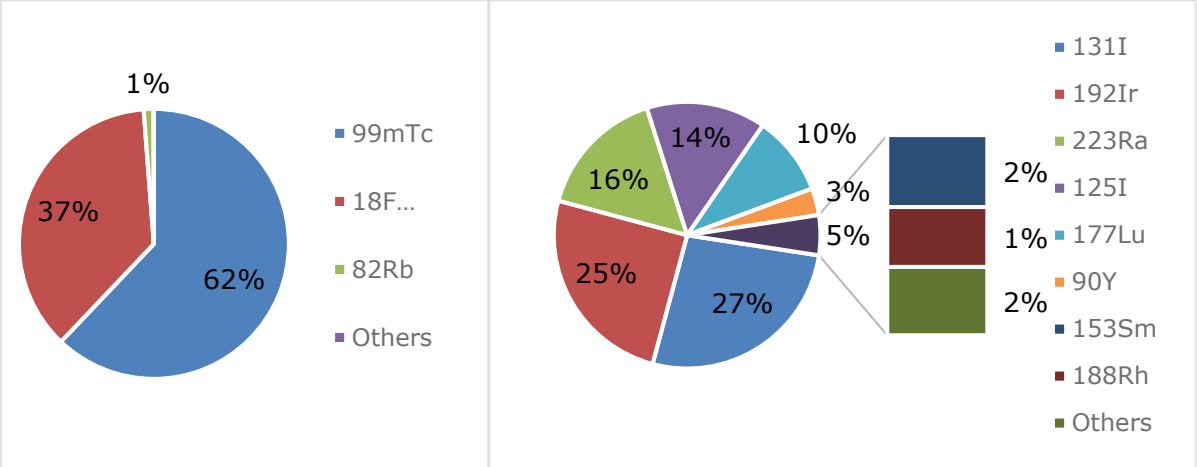


Figure 6: Imaging (Left) and therapeutic (Right) radionuclides used in The Netherlands in 2017, for a total of ~ 360,000 NM procedures

From these countries' samples, various trends for current and future use of radionuclides can be derived:

- ^{99m}Tc and ^{18}F are predominantly used compared to other imaging radionuclides, with a continuous rise of PET observed in the last decade (+45% of ^{18}F procedures between 2015 & 2018 in Sweden) and a stability or slight increase of ^{99m}Tc (when excluding national specificities such as thyroid imaging in Germany);
- different radionuclides emerged over the last decade, with growing trends: ^{68}Ga use for imaging, ^{177}Lu for therapy with Lutathera®'s first market approval in 2018;
- national specificities and best practices lead to different profiles of use: thyroid imaging is for example widely performed in Germany (~50% of SPECT diagnostic procedures in the private sector) whereas it is rather limited in Sweden;
- development of nuclear medicine does not necessarily follow the same trends over the EU, being impacted by regulation, reimbursement mechanisms and professional organizations' recommendations. Up to 2015, PET development in Germany did not follow same trend as for Sweden; the more limited use can be partially explained by reimbursement mechanisms;
- while nuclear medicine imaging is fairly well developed in the EU, with various anatomical or functional investigations made, therapeutic use is currently mainly centred around thyroid therapy (iodine-131) and to a more limited extent inflammation of joints (radiosynoviorthesis).

Regarding the evolutions expected in the next decade, RIVM (Rijksinstituut voor Volksgezondheid en Milieu – Dutch Health and Environment Ministry) provided some trends in its 2017 yearly report on SPECT/therapeutic nuclear medicine use:

- increase for therapeutic radionuclides ^{177}Lu, ^{166}Ho, ^{90}Y, with strong interest for ^{177}Lu, with stable use for brachytherapy (^{192}Ir, ^{125}I) and pain relief (^{223}Ra) radionuclides;
- slight increase expected for ^{99m}Tc.

All the previous observations stem from the analysis of data from three EU countries (Sweden, Germany, and The Netherlands); they are not necessarily representative of the overall EU situation. 2020 data were not accessible, and most figures are historic ones not representative of the latest best practices in Europe (e.g. Germany – 2015 data).

1.3. Overview of industrial radionuclides uses

1.3.1. Industry is a large consumer of sealed sources for numerous uses, from non-destructive testing to gauges

Radioactive sources are used in a wide variety of industrial applications, commonly to measure properties of materials, such as thickness, moisture content, or density; to conduct non-destructive tests during construction; or to control a manufacturing process, such as monitoring the level of liquid in a tank or eliminating static electricity during manufacturing.

With the exception of some specific applications for leak testing and radioactive tracing, the industrial use of radionuclides is almost essentially limited to sealed sources. These sealed sources are used in various equipment for non-destructive testing (NDT), material processing, irradiation of goods, measurement, etc.

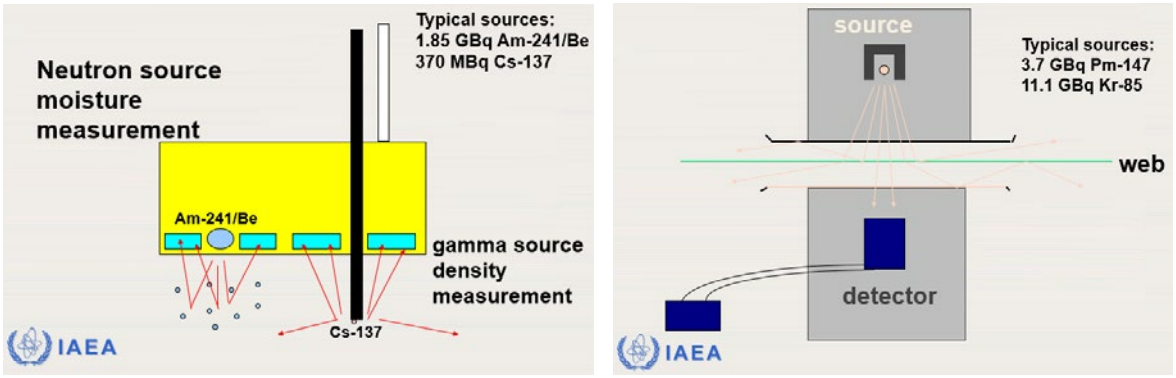


Figure 7: Examples of gauges used in Industry for moisture (Left) and thickness measurement (Right) – Source IAEA

1.3.2. What are the main radionuclides used in the industrial sector?

The industrial use of radionuclides is not directly quantified by EU states. Sealed sources are generally part of specific equipment. This equipment (mobile or fixed) is often used over a long period of time and performs many measurements, tests or irradiation. The identification of radionuclides of interest can sometimes be performed owing to the number and types of sealed sources in use.

Since the promulgation of "Council Directive 2003/122/EURATOM on the control of high activity sealed radioactive sources and orphan sources," the Member States are now obliged to closely monitor the use of sealed sources through delivery of authorization to use. Statistics on the total number of users can be found among Member States, but only overall statistics are gathered regarding the type and models of sealed sources used (e.g. about 100,000 sealed radioactive sources are used in Germany in industry, medicine, research and agriculture[10]).

[10] https://www.bfs.de/EN/topics/ion/daily-life/radiation-sources/radiation-sources_node.html

The IAEA has gathered a large quantity of information related to sealed sources and their applications, especially through the development of the International Catalogue of Sealed Radioactive Sources and Devices (ICSRS).[11]

The IAEA publication "Management of disused sealed radioactive sources. Energy Agency, 2014" describes what are considered as the most-used radionuclides for alpha/beta/gamma emission and neutron sources.

TABLE 1. CHARACTERISTICS OF SELECTED ALPHA/BETA/GAMMA EMITTING RADIONUCLIDES OFTEN USED IN SRSs [19]

Characteristics	^{60}Co	^{137}Cs	^{192}Ir	^{226}Ra	^{241}Am	^{90}Sr (^{90}Y)	^{75}Se	^{125}I
Half-life	5.27 a	30 a	74 d	1600 a	433 a	29 a	120 d	60 d
Alpha energy (MeV)	—	—	—	7.7	5.86	—	—	—
Max beta energy (MeV)	0.31	1.2	0.67	2.8	—	0.55 (2.3)	—	—
Gamma energy (MeV)	1.17 1.33	0.66	0.32 0.47	Up to 2.4	0.06	—	Medium level	0.03
Gamma constant (μSv/h × GBq at 1 m)	360	86	140	220	4	3.5 (Bremss.)	39	39

Figure 8: Characteristics of the most often used radionuclides for alpha/beta/gamma emission Source: IAEA

Detailed European use statistics are not accessible; however industrial processes are widely similar worldwide, and Japanese statistics from the Japan Radioisotopes Association (JRIA) provide an overview of the main trends regarding radionuclides use in industry (Cf. Appendix D).

Based on these elements, the main radionuclides used in the industry can be identified: ^{60}Co, ^{137}Cs, ^{192}Ir, ^{241}Am, ^{85}Kr, ^{63}Ni, ^{57}Co, ^{75}Se, ^{147}Pm, ^{75}Se, ^{169}Yb, ^{252}Cf, ^{226}Ra.

[11] https://www.iaea.org/resources/databases/international-catalogue-of-sealed-radioactive-sources-and-devices

1.4. Not all radionuclides have comparable use and interest for medical and industrial applications

The evaluation of a radionuclide's interest is not limited to its breadth of use; some applications relying on sealed/unsealed radionuclides can be of utmost importance in the absence of alternatives or have very limited markets but crucial applications (e.g. sealed sources used for calibration of medical devices).

Thus, a case-by-case analysis of radionuclides is needed to enable evaluation of:

- current use (common for widely used radionuclides, limited in the case of very specific applications and rare when use is locally restricted and in early R&D), along with future trend;
- current supply chain status (making it possible to differentiate industrial production, following good manufacturing practices & health authorities regulations, from research production limited to clinical trials and compassionate use for medical applications for example). The current main production type is also specified, but could change in the future, considering the emergence of alternative production means (discussed in depth in Chapter 2 for selected radionuclides);
- European interest and future perspectives of use, evaluated on a qualitative basis (current and future market interest, existence of competing radionuclides, supply chain considerations, etc.). These comments are based on literature analysis and expert judgments gathered during discussions with industry and experts in the field of radionuclides.

The radionuclides used in diagnostics (SPECT, PET), therapy, brachytherapy and industrial applications are discussed separately hereafter (classified by mass number). Those highlighted in blue are the ones presenting the greatest interest for European use and have been selected for in-depth analysis (cf. §1.5).

	Current use & trend	Supply chain status	European interest and future perspectives
^{51}Cr	Rare / Decrease	Industrial production (research reactor)	Only used for in-vivo non-imaging procedures and some ex-vivo procedures. No other future applications foreseen. Use of ^{51}Cr should decrease through the years.
^{75}Se	Rare / Decrease	Industrial production (reactor & accelerator)	Only used for bile acid investigation, without new applications foreseen. Its relatively long half-life (120 days) limits its use in nuclear medicine.
^{81m}Kr	Rare / Decrease	Industrial production (generator)	Use for pulmonary imaging, in competition with ^{99m}Tc or ^{133}Xe. Supplied through a generator with a short half-life (~5h), making its use more complex than competing products. Its use should remain limited to centres focused on lung imaging. Interest is declining for this RN.

	Current use & trend	Supply chain status	European interest and future perspectives
^{99m}Tc	Common / Stable to slight increase	Industrial production (generator)	^{99m}Tc will remain the #1 RN, due to its proven mass-production supply chain (production of ^{99}Mo in research reactors, then loaded in generators for ^{99m}Tc milking), the advantage of generators, and its low price and versatility. The ^{99}Mo supply issue can be solved by the large variety of projects and alternatives that should enter the market within the next decade.
^{111}In	Limited / Decrease	Industrial production (accelerator)	Limited future due to high price, limited supply capacity and strong competition with ^{99m}Tc SPECT RP. Potential future therapeutic applications, but with less support than for ^{177}Lu or ^{90}Y. A declining interest can be foreseen. Whenever possible ^{111}In is replaced by ^{99m}Tc if SPECT is mandatory or ^{68}Ga or ^{89}Zr if PET is acceptable.
^{123}I	Limited / Stable	Industrial production (accelerator)	Situation similar to ^{111}In, with limited supply capacity and competition with other RNs. Decreasing interest for ^{123}I is linked to its complexity of use. Whenever possible ^{123}I is replaced by ^{99m}Tc if SPECT is mandatory or ^{68}Ga or ^{89}Zr if PET is acceptable, while some RPs don't have alternatives (mIBG).
^{133}Xe	Rare / Decrease	Industrial production (by-product of ^{99}Mo supply chain)	Used for pulmonary imaging and competing with ^{99m}Tc. ^{133}Xe can only be used in gas form, limiting potential new applications. It is easily produced as a by-product of the ^{99}Mo supply chain. Its use is limited in Europe, where it still has a substantial market share in the US for lung ventilation studies (for diagnosing pulmonary embolism).
^{155}Tb	Early R&D	/	^{155}Tb is currently under early R&D, with a pairing interest with therapeutic isotopes of terbium.
^{201}Tl	Limited / Decrease	Industrial production (accelerator)	^{201}Tl is essentially a more expensive ^{99m}Tc substitute product, used in cardiology. Situation is not expected to change in the future. There was some interest to use more ^{201}Tl in Europe, due to the ^{99}Mo shortage. However globally the use of ^{201}Tl is declining.

Table 3: Radionuclides overview for nuclear medicine SPECT imaging

	Current use & trend	Supply chain status	European interest and future perspectives
^{11}C	Limited / Stable	Industrial production (accelerator)	Limited use due to short half-life (20 min) implies production onsite (small cyclotrons) or in a dedicated ^{11}C centre (production and use on same site).
^{13}N	Rare / Decrease	Industrial production (accelerator)	Interest in cardiology, but limited RN accessibility drastically limit its use and it has a very short half-life (9.9 min). Future use shall remain limited to research applications (except for Japan where some centres are using this tracer as an alternative to SPECT in cardiology imaging). For routine PET applications in cardiology, ^{82}Rb, associated with its ^{82}Sr/^{82}Rb generator, appeared as an alternative for some countries. ^{13}N remains quite common in Scandinavian countries.
^{15}O	Rare / Decrease	Industrial production (accelerator)	Same observations as for ^{13}N. Very short half-life of 2.03 min. There is no real future for ^{15}O-water in cardiology except as a research tool.
^{18}F	Common / Increase	Industrial production (accelerator)	^{18}F should continue to hold the #1 position for PET diagnostic RN. The cyclotron network should continue to enlarge in the next decade to cope with the increasing use of ^{18}F and its associated RP. EU is well covered by cyclotron networks, however with disparities by country, and several EU countries still have no cyclotron.
^{43}Sc	Early R&D	/	^{43}Sc is currently under early development stage for PET imaging, in pairing with ^{47}Sc, but appears less promising considering its more constraining production route.

	Current use & trend	Supply chain status	European interest and future perspectives
^{44}Sc	Early R&D	/	^{44}Sc is currently under early development stage for PET imaging, in pairing with ^{47}Sc.
^{64}Cu	Industrial production (Curium US portfolio)	Industrial production (accelerator)	^{64}Cu is a PET imaging candidate that could also be used as a therapeutic. First NDA for PET RP awarded to RadioMedix/Curium by FDA in September 2020 and should reach EU market at some point. Use in pair with ^{67}Cu is foreseen, but ^{67}Cu therapeutics development are still at R&D stage (pairing use for mid-future).
^{68}Ga	Limited / Increase	Industrial production (generator)	High potential with many RPs under development, should become 2nd most important PET RN. The generators ^{68}Ge/^{68}Ga allow strong flexibility as compared to ^{18}F daily deliveries. ^{68}Ga should not fully replace ^{18}F but should be associated with diagnostic examinations for therapeutic use. Large cyclotrons will be needed for ^{68}Ge production. Existing PET cyclotron network can also be adapted to directly produce ^{68}Ga.
^{82}Rb	Rare / Stable	Industrial production (generator)	^{82}Rb should be available in the near future through a generator ^{82}Sr/^{82}Rb (already available in USA). Applications in cardiology could make it compete with SPECT myocardial imaging agents, but it means investments in PET cameras for cardiologists. The Arronax 70MeV cyclotron (Nantes, France) already produces ^{82}Sr.
^{89}Zr	R&D	Industrial production (accelerator)	^{89}Zr is currently being investigated as a potential future PET diagnostic RN. ^{89}Zr labelled radiopharmaceuticals are still in early clinical stages. Its long half-life (78 hours) represents a major advantage for supply considerations.
^{149}Tb ^{152}Tb	R&D	/	^{149}Tb/^{152}Tb are currently in the early development stage for PET imaging, in pairing with therapeutic terbium isotopes.
^{124}I	R&D	/	RP under development
^{52}Mn ^{55}Co ^{86}Y	R&D	/	Radionuclides under no active R&D but presenting characteristics compatible with PET imaging.

Table 4: Radionuclides overview for nuclear medicine PET imaging

The radionuclides used in therapy are developed in the following tables, with a distinction between α- and β-emitters.

	Current use & trend	Supply chain status	European interest and future perspectives
^{32}P (β)	Rare - Decrease	Industrial production (reactor)	Limited use, no evolution to be expected.
^{47}Sc (β)	R&D	/	Research interest for ^{44}Sc/^{47}Sc pair, currently in early development.
^{67}Cu (β)	R&D	/	Clinical development of ^{67}Cu has been limited in the past due to manufacturing complexity of RN, along with limited supply and lack of chelated vectors. Situation could change in the future, with NorthStar recently announcing sustainable supply for clinical research applications. RN use will remain limited to research in the next decade with high potential.
^{89}Sr (β)	Rare - Decrease	Industrial production (reactor)	Use should remain limited to pain palliation; no dynamic for development of other products. Show unfavourable chemistry and no real interest for the future.

	Current use & trend	Supply chain status	European interest and future perspectives
^{90}Y (β)	Limited - Decrease	Industrial production (reactor)	^{90}Y has various applications in therapy (TRNT, brachytherapy and radio-synovectomy). It is now in competition with ^{177}Lu and its use should decrease in the near future. Nevertheless, it is still widely used and thus should continue over the next decade.
^{131}I (β)	Common - Stable	Industrial production (reactor)	^{131}I is almost only used for thyroid therapy as a standard procedure and such situation should continue. Some RPs are in development and should directly compete with ^{177}Lu RP. ^{131}I is produced as a sub-product of the ^{99}Mo supply chain, making it available worldwide at a limited price.
^{153}Sm (β)	Rare - Decrease	Industrial production (reactor)	Only one RP using ^{153}Sm (Quadramet®), used for castration-resistant prostate cancer and in direct competition with ^{223}Ra-Xofigo®. No promising development for use in therapy underway.
^{161}Tb (β)	R&D	/	^{161}Tb is currently under early R&D, with a pairing interest with therapeutic isotopes of terbium.
^{166}Ho (β)	Rare - Increase	Industrial production (reactor)	Only one radiopharmaceutical available in South Korea, and not approved outside of the country. ^{166}Ho could be used as a palliative treatment. Developments underway with clinical trials in EU.
^{169}Er (β)	Rare - Decrease	/	Use limited to radio-synovectomy, with a decreasing interest through years. There is no development underway for new RP based on this radionuclide. Expected to be replaced by ^{117m}Sn. Upcoming unavailability of the precursor ^{168}Er.
^{177}Lu (β)	Limited - Increase	Industrial production (reactor)	Most promising therapeutic radionuclide, a large number of radiotherapeutics presently in clinical development are based on the ^{177}Lu tracer. The first one reached the market in early 2018 (Lutathera®, ^{177}Lu-PSMA, etc.) for GEP-NET or prostate cancers. Supply chain will need to cope with increasing demand within the next decade (few players currently and limited ^{176}Yb supply).
^{186}Re (β)	Rare - Decrease	/	Use limited to radio-synovectomy, with a decreasing interest through years. There is no development underway for new RP based on this radionuclide. Expected to be replaced by ^{117m}Sn. Interest is declining.
^{188}Re (β)	R&D	/	Interest in therapy, expected possibility to use ^{99m}Tc labelled molecules with ^{188}Re, thus having theranostic pairs. Other advantage lies in the development of ^{188}W/^{188}Re generators.

Table 5: Radionuclides overview for nuclear medicine therapy (β emitters)

	Current use & trend	Supply chain status	European interest and future perspectives
^{149}Tb (α)	R&D	/	^{149}Tb is currently under early R&D, with a pairing interest with therapeutic isotopes of terbium. It also has interest of dual use (both PET imaging and therapy).
^{211}At (α)	R&D	/	Promising radionuclide for Targeted Alpha Therapy. ^{211}At has a simple manufacturing route through cyclotron, and non-problematic decay products. It will need a dedicated network of cyclotrons.
^{212}Pb (α)	R&D	/	Currently under R&D for TAT. Supply would be ensured through by-product of nuclear fuel cycle. Supply chain is already secured with an active player (Orano Med).
^{213}Bi (α)	R&D	/	Promising radionuclide for TAT but could be replaced by ^{225}Ac in the case of a supply chain without impurities. Large advantage of production through generator and without impurities, but daughter products raise issues.

	Current use & trend	Supply chain status	European interest and future perspectives
^{223}Ra (α)	Limited - Decrease	Industrial production (reactor)	Currently only used in Bayer/^{223}Ra-Xofigo® RP for pain palliation in prostate cancer. No development expected with this radionuclide.
^{225}Ac (α)	R&D	/	Most promising radionuclide for TAT, with currently supply chain limitations with important impurities limiting direct use for patients. Interest is growing strongly. As for ^{211}At, a network for production of ^{225}Ac is still lacking.
^{227}Th (α)	R&D	/	Currently in active R&D stage, with clinical trials underway.

Table 6: Radionuclides overview for nuclear medicine therapy (α emitters)

Besides the nuclides applications above, brachytherapy is widely used in the EU; ~800 BT equipment are available across ~600 radiotherapy centres (half of all radiotherapy centres).[12] Regarding permanent implants, it is estimated that several tens of thousands of procedures are performed each year[13] in the EU (^{192}Ir, ^{125}I, etc.) It is estimated that about 10–20% of radiation oncology patients are treated with brachytherapy; 80–90% are treated with external beam techniques.

A limited number of radionuclides are used in brachytherapy; over a dozen radioactive nuclides are used as sealed sources in brachytherapy. The common[14] current sources are ^{60}Co, ^{137}Cs, ^{192}Ir, ^{125}I ^{103}Pd, and ^{90}Sr/^{90}Y. Less common sources are also used, like ^{198}Au, ^{106}Ru and ^{252}Cf, whereas the use of ^{226}Ra and ^{222}Rn has been discontinued because of safety concerns.

	Current use & trend	Supply chain status	European interest and future perspectives
^{60}Co	Rare (in EU) - Decrease	Industrial production (reactor)	High specific activity makes cobalt appropriate for small high activity sources. Less frequent change of source as compared to ^{192}Ir for HDR use. Used in HDR brachytherapy but also in external beam therapy. However mainly used in Third World countries to take advantage of the long half-life. Overall declining interest. Europe would rather use ^{192}Ir HDR brachytherapy.
^{103}Pd	Common - Stable	Industrial production (reactor & accelerator)	Alternative for ^{125}I permanent implants. Its short half-life (17 days) limits its use for permanent implants. Higher dose delivery than ^{125}I, useful for rapidly proliferating tumours. ^{103}Pd is mainly produced by cyclotron. Most of it is done in the US. The facility in Belgium (ex-Ibt – Eckert&Ziegler is closed). No production exists today in EU.
^{125}I	Common - Stable	Industrial production (reactor)	Used for permanent implants. A large part of the LDR seeds are ^{125}I-based.
^{131}Cs	Limited	Industrial production (reactor)	Used in LDR brachytherapy seeds but only made by IsoRay (USA).

[12] "Final report - European Study on Medical, Industrial and Research Applications of Nuclear and Radiation Technology"
[13] "Medical isotopes – Global importance and opportunities for the Netherlands in a European context"
[14] IAEA - IAEA publication (ISBN 92-0-107304-6): "Radiation Oncology Physics: A Handbook for Teachers and Students"

	Current use & trend	Supply chain status	European interest and future perspectives
^{192}Ir	Common - Stable	Industrial production (reactor)	HDR or LDR feasible depending on ^{192}Ir concentration. Easy manufacturing process, small source size and stable daughter product (^{192}Pt). Half-life of 74 days implies frequent recalibrations and replacements (every 3-4 months).
^{198}Au	Limited	Industrial production (reactor)	Limited average photon energy (0.4 MeV) needing limited radiation protection requirements (as compared to ^{137}Cs or ^{60}Co). Limited use, only player manufacturing seeds is Best Medical (USA).

Table 7: Radionuclides overview for brachytherapy and external radiation devices

Regarding radionuclides used in industrial sealed sources, most of the supply comes from a very limited number of governmental facilities in Russia and in the US, while some radionuclides are by-products of the nuclear industry. Supply processes are less demanding than in the medical industry. Whilst use of some nuclides listed below may be limited or very limited, it does not mean that they are not essential for certain vital operations.

	Current use & trend	European interest and future perspectives
^{57}Co	Very limited	Used for calibration of imaging equipment (SPECT and PET systems), rather important use for nuclear medicine, but with very limited market/demand.
^{60}Co	Common - Increase	^{60}Co sources are produced as high specific activity sources for teletherapy, industrial radiography, industrial sources for irradiators (incl. sterilization) and other applications. Due to security and safeguards concerns, current trend is pushing towards ^{60}Co alternatives (USA called for phasing-out). Nevertheless, due to large volume of use and important added value in everyday life (in health, for food, in industry, etc.) and limited alternatives, it is expected that ^{60}Co will remain a key radionuclide used in the industry in the next decade.
^{63}Ni	Limited - Stable	Use limited to electron capture detectors (ECD). ECD is a device used in a gas chromatograph to detect trace amounts of chemical compounds in a sample. Typically, it contains a 10 mCi of nickel (^{63}Ni) metal foil.
^{75}Se	Very limited and stable	Gamma radiography using ^{75}Se is now generally acknowledged throughout the world to provide performance benefits relative to ^{192}Ir in the working range of 5-30mm steel. ^{75}Se has a softer gamma ray spectrum than ^{192}Ir and it has a significantly longer half-life (120 days instead of 74 days). For these reasons ^{75}Se provides real performance benefits and working life advantages, but its use is limited to small width; beyond 30mm, ^{192}Ir as to be used.
^{85}Kr	Limited - Stable	Mainly used for basis weight measurement: a beta radiation beam passes through the paper and is then received by a detector. The signal attenuation on this detector gives the paper density and thus the basis weight. Also used in some consumer products (light bulbs, smoke detectors, etc.) ^{85}Kr will remain limited in the future.
^{137}Cs	Common - Stable	Due to its long half-life (30 years), ^{137}Cs sealed sources have a long period of use (~15 years) as compared to other sealed sources. They are widely used in industrial gauging, thickness and density measurements, but also for sterilization of equipment in medical field. As for ^{60}Co, large consensus to push for alternatives (e.g. for blood irradiators), but alternatives do not offer same quality of use (non-destructive alternatives currently have technical and operational limitations in challenging environments), and ^{137}Cs should remain widely used within the next decade. Some countries are considering banning ^{137}Cs to address terrorist threats.

	Current use & trend	European interest and future perspectives
^{192}Ir	Common - Stable	^{192}Ir is a common industrial gamma-ray source for industrial radiography. Current trend pushes for a replacement of the highest energy gamma sources by lower energy ones: ^{60}Co (1,17-1,33 MeV) by lower energy gamma sources, ^{192}Ir (energy range from 206 to 612 keV) and ^{75}Se (from 66 to 401 keV). Thus, ^{192}Ir should be of interest in the near future for some applications, but ^{60}Co use will prevail.
^{226}Ra	/	No longer used in sealed sources due to various issues (long half-life, radiological problems, radiation protection issues, etc.)
^{241}Am	Common - Stable	^{241}Am sources are both gamma ray and alpha particle emitters, with low energy. They are applied in industrial gauging, including X-Ray fluorescence analysis systems, in the measurement of glass, plastics, rubber and light alloys (for example, thin-section aluminium) for which beta sources are not suitable. They are widely spread in industry. Americium is also used as neutron source (Am-Be) sources.
^{147}Pm ^{169}Yb ^{252}Cf	Very limited and stable	Used in various equipment, with very limited use.

Table 8: Radionuclides overview for non-medical industrial applications

1.5. Identification of strategic radionuclides for EU requiring future stable and sustainable supply

In order to ensure the optimal imaging and treatment solutions for Europe's health sector, the supply of the current and future most important radionuclides must be secured. A consensus among the Steering Group members of this study resulted in a selection of radionuclides of interest. This selection is based on the careful consideration of various parameters: breadth of use, alternatives, innovation needs, relation between research and industry, versatility, demand and costs, pairing use for imaging/therapy. The following figure summarizes the current and future portfolio of radionuclides[15] selected (highlighted in blue):

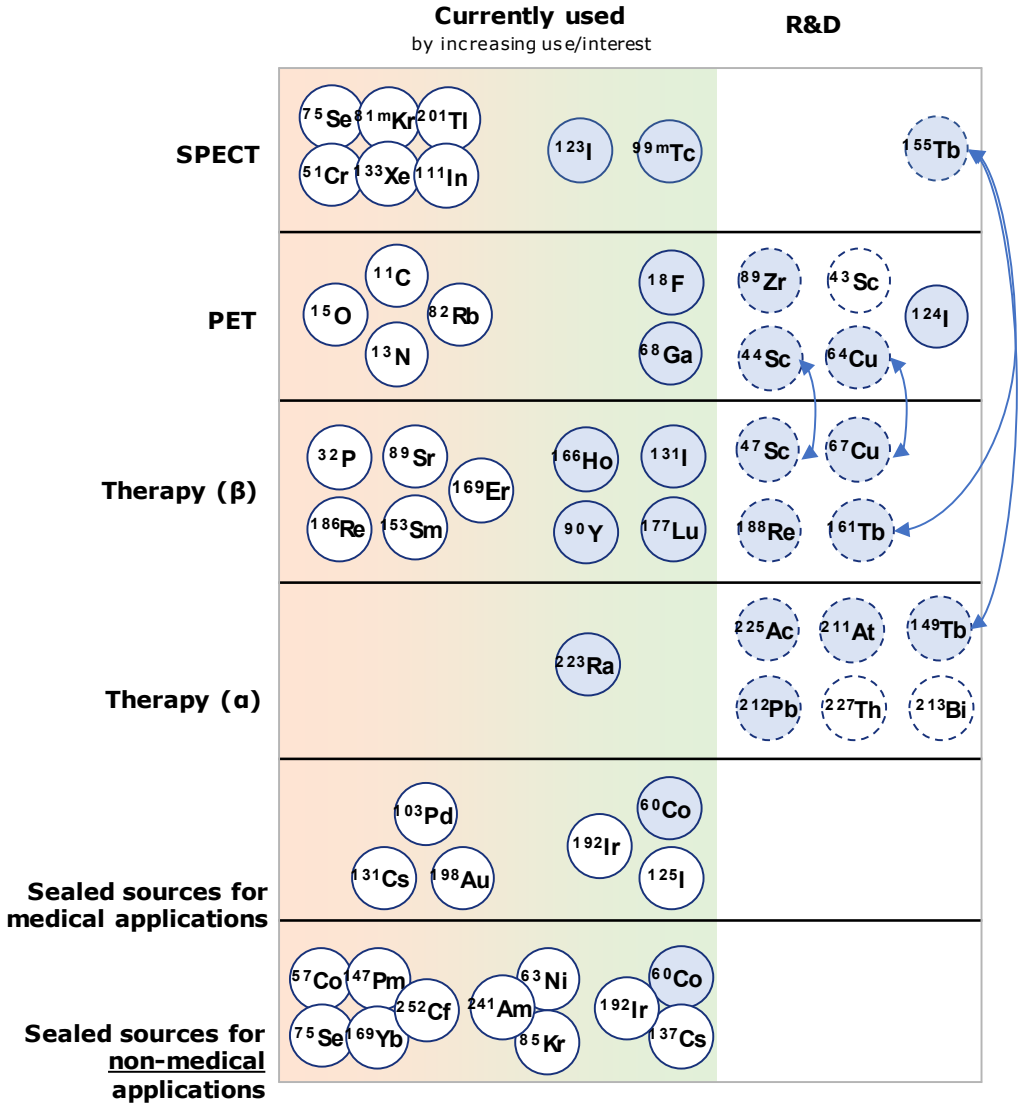


Figure 9: Summary of radionuclides identified per application (radionuclide future pairs identified with arrows) – Source: NucAdvisor

[15] Supply chains of radionuclides in blue are developed in Annexes

This selection is large enough for allowing identification of the typical supply chain challenges the EU will have to face for sustainable and secure supply and innovation needs, namely:

- stable isotope supply and enrichment needs,
- coverage of the typical production technologies (reactors, cyclotrons, accelerators and alternative installations),
- separation/purification challenges involving various techniques,
- involvement of large European research bodies and importance of the academic research supply,
- cooperation between research & industry.

Corresponding supply chains are studied in-depth in the next chapter.

2. Radionuclides supply-chains characteristics and challenges in Europe

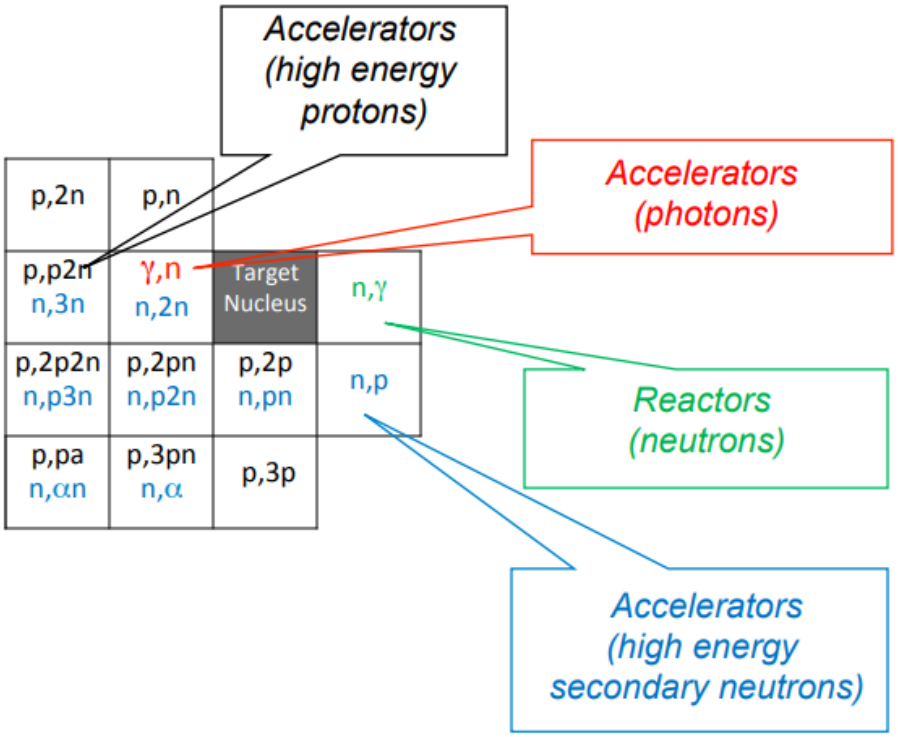
Radionuclides manufacturing relies on a large variety of players and industrial equipment, from stable isotope procurement, enrichment, target manufacturing, irradiation in small/medium/large reactors or accelerators to processing and transportation. Each radionuclide has a quite unique supply chain, depending upon its physical and chemical properties.

Historically the EU has always been an important player in this field, through research centres, irradiation installations and radio-pharmaceuticals companies exporting radionuclides. Yet in some cases the EU relies on foreign supply or must cope with limited production capacity in the absence of adequate tools or industrial capacity.

Radionuclide production often offers various routes having industrial advantages and drawbacks that ultimately impact the quality of product delivered and the market outcomes.

In this chapter the European status of radionuclides supply chains is assessed, allowing identification of future key challenges that could become threats to sustainable RN supply.

Many ways of producing nuclides exist, involving many nuclear reactions, achievable in diverse installations (see illustration below), opening virtually infinite possibilities.



As most of the nuclear reactions are not industrially workable for many reasons, the radionuclides selected within the framework of this study offer a fair representativeness of the multiple types of supply chains that are at an industrial level or are envisaged in the radionuclide sector, allowing for a screening of the challenges Europe has to face – for instance:

- supply chain development status (established industrial production, laboratory-scale production, research, etc.),
- need for enriched target material (distillation, centrifugation, etc.),
- irradiation tools (research reactors, accelerators, nuclear power plants, etc.),
- types of reactions (activation, fission, proton excitation, etc.),
- time constraints (daily "just in time" production, weekly production, etc.),
- European self-reliance capability and shortages risks,
- radioactive transport, containers and regulations.

In order to assess radionuclide supply-chain challenges, this chapter is structured in two parts.

Chapter 2.1. This sub-chapter provides an overview of the supply-chain status for each nuclide considered. The manufacturing routes, current supply chains and their specific challenges are developed in detail in Annexes 1 to 22.

Chapter 2.2. As a complement to §2.1, this sub-chapter includes a transversal analysis at each main step of radionuclide supply chains (enrichment, irradiation, etc.), highlighting common challenges among radionuclides.

2.1. Supply-chain status by radionuclide

In order to identify the key impediments to sustainable supply of radionuclides in the EU, a detailed case study for each radionuclide has been conducted, with the following structure:

- **Radionuclide specificities:** the physicochemical characteristics of each radionuclide are described, allowing identification of key parameters impacting production and use such as half-life and decay(s) type. Main applications for each radionuclide are presented with insight on competing radionuclides, along with an estimate of the current demand and its potential evolution towards 2030.
- **Manufacturing routes analysis:** a detailed assessment of the current and future achievable manufacturing routes is performed, with a transversal comparison, for main specificities (technology readiness level [16], radionuclide quality, economics, target material, installed base capacity, industrial players, etc.).
- **Supply chain:** for already industrially produced radionuclides, an overview of current EU & worldwide supply-chain structure and players is given, allowing for conclusions as to EU supply structure, from target material to radiochemical preparation. For radionuclides without an existing supply chain, the equipment and installations needed to secure supply are highlighted.

This chapter is a summary of the detailed analysis performed in Annexes 1 to 22 for the radionuclides selected in the context of this study. For more details concerning the different manufacturing routes investigated and the description of the current European and worldwide supply chains, refer to the Annexes section.

The two following tables give, respectively, a summary of the different manufacturing routes considered for each radionuclide and a qualitative synthesis of challenges for sustainable production, demand evolution within the next decade and current production capacity.

[16] The detailed classification used to assess the Technology Readiness Level is detailed in Appendix E, based on the European Commission classification used in the H2020 programme

Legend

Manufacturing routes in grey are the ones currently used for radiopharmaceutical production or routine research supply.

SMC: Small Medical Cyclotron
MEC: Medium Energy Cyclotron
HEA: High-Energy Accelerators
CA/NCA: carrier added / non carrier added
EMS: Electromagnetic separation
Centrif: Enrichment through centrifugation

Local: Production close to user (a few hours)
Regional: Production centralized at EU scale or region
Worldwide: Production exported worldwide

TRL 1	Basic principles observed
TRL 2	Technology concept formulated
TRL 3	Experimental proof of concept
TRL 4	Technology validated in lab
TRL 5	Technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies)
TRL 6	Technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies)
TRL 7	System prototype demonstration in operational environment
TRL 8	System complete and qualified
TRL 9	Actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space)

	Existing RP with MA	Reaction(s)	TRL	Purity	Target material	Preferred enrichment	Target form	Target recycling	Irradiation facility	Power/ Energy	Generator	Supply chain scale
^{99m}Tc	Yes (^{99}Mo/^{99m}Tc generators)	^{235}U(n,f)^{99}Mo	9	NCA	^{235}U	Centrif.	Solid	No	Research R.	-	^{99}Mo/^{99m}Tc	Worldwide
		^{235}U(n,f)^{99}Mo	6	NCA	^{235}U	Centrif.	Liquid	Yes	Shine	-	^{99}Mo/^{99m}Tc	Worldwide
		^{235}U(n,f)^{99}Mo	3	NCA	^{235}U	Centrif.	Solid	No	Myrrha	-	^{99}Mo/^{99m}Tc	Worldwide
		^{98}Mo(n,γ)^{99}Mo	9	NCA	^{98}Mo	Centrif.	Solid	Yes	Research R.	-	^{99}Mo/^{99m}Tc	Worldwide
		^{98}Mo(n,γ)^{99}Mo	4	NCA	^{98}Mo	Centrif.	Solid	Yes	Power. R.	-	^{99}Mo/^{99m}Tc	Worldwide
		^{100}Mo(γ,n)^{99}Mo	6	NCA	^{100}Mo	Centrif.	Solid	Yes	Accelerator	40MeV	^{99}Mo/^{99m}Tc	Worldwide
		^{100}Mo(p,2n)^{99m}Tc	8	NCA	^{100}Mo	Centrif.	Solid	Yes	SMC/MEC	20 MeV	*none*	Local
^{18}F	Yes	^{18}O(p,n)^{18}F	9	NCA	^{18}O	Distillation	Liquid	No	SMC	10-20MeV	*none*	Local
		^{20}Ne(d,α)^{18}F	9	NCA	^{20}Ne	None	Gas	No	SMC	10-20MeV	*none*	Local
^{68}Ga	Yes (^{68}Ge/^{68}Ga generators)	^{nat}Ga(p,xn)^{68}Ge ^{69}Ga(p,2n)^{68}Ge	9	NCA	^{nat}Ga ^{69}Ga	None EMS	Solid	No	MEC	20-40MeV	^{68}Ge/^{68}Ga	Worldwide
		^{68}Zn(p,n)^{68}Ga	8	NCA	^{68}Zn	Centrif.	Liquid/Solid	No	SMC	12 MeV	*none*	Local
^{177}Lu	Yes	^{176}Lu(n,γ)^{177}Lu	9	CA	^{176}Lu	EMS	Solid	No	Research R.	Low flux	*none*	Worldwide
		^{176}Yb(n,γ)^{177}Yb→^{177}Lu	9	NCA	^{177}Yb	EMS	Solid	No	Research R.	High flux	*none*	Worldwide
^{90}Y	Yes	^{89}Y(n,γ)^{90}Y	9	CA	^{89}Y	None	Solid	No	Research R.	Low flux	*none*	Worldwide
		Industrial gen - ^{90}Sr/^{90}Y	9	NCA	^{90}Sr	None	*no irradiation needed*				^{90}Sr/^{90}Y	Worldwide
^{131}I	Yes	^{130}Te(n,γ)^{131}Te -> ^{131}I	9	NCA	^{130}Te	Centrif.	Solid	No	Research R.	High flux	*none*	Worldwide
		^{235}U(n,f)^{131}I	9	NCA	^{235}U	Centrif.	Solid	No	Research R.	-	*none*	Worldwide
^{123}I	Yes	^{123}Te(p,n)^{123}I	9	CA	^{123}Te	Centrif.	Solid	No	MEC	20-30MeV	*none*	Regional

	Existing RP with MA	Reaction(s)	TRL	Purity	Target material	Preferred enrichment	Target form	Target recycling	Irradiation facility	Power/ Energy	Generator	Supply chain scale
		$^{124}Xe(p,2n)^{123}Cs$ -> ^{123}Xe -> ^{123}I	9	NCA	^{124}Xe	Centrif.	Gas	No	MEC	20-30MeV	*none*	Regional
^{124}I	No	$^{124}Te(p,n)^{124}I$	9	NCA	^{124}Te	Centrif.	Solid	Yes	SMC	8-12MeV	*none*	Regional
		$^{124}Te(d,2n)^{124}I$	6	CA	^{124}Te	Centrif.	Solid	Yes	SMC	10-14MeV	*none*	Regional
		$^{125}Te(p,2n)^{124}I$	6	CA	^{125}Te	Centrif.	Solid	Yes	SMC	15-21MeV	*none*	Regional
^{89}Zr	No	$^{89}Y(p,n)^{89}Zr$	9	NCA	^{89}Y	None	Solid	No	SMC	10-20MeV	*none*	Regional
		$^{89}Y(d,2n)^{89}Zr$	6	NCA	^{89}Y	None	Solid	No	SMC	20MeV	*none*	Regional
^{223}Ra	Yes	^{227}Ac -> … -> ^{223}Ra	9	NCA	^{227}Ac	None	*no irradiation needed*				Industrial	Worldwide
		$^{nat}Th(p,…)^{223}Ra$	3	CA	^{nat}Th	None	Solid	No	HEA	90-800MeV	*none*	Worldwide
^{225}Ac	No	^{233}U->^{229}Th->^{225}Ac	9	NCA	^{229}Th	None	-	No	-	-	Industrial	Worldwide
		$^{232}Th(p,x)^{225}Ac$	9	CA	^{232}Th	None	Solid	No	HEA	>100MeV	*none*	Worldwide
		$^{226}Ra(d,3n)^{225}Ac$	4	NCA	^{226}Ra	*Unknown*	Solid	Yes	SMC	18,5MeV	*none*	Worldwide
		$^{226}Ra(p,2n)^{225}Ac$	4	NCA	^{226}Ra	*Unknown*	Solid	Yes	SMC	15MeV	*none*	Worldwide
		$^{226}Ra(\gamma,n)^{225}Ra$->$^{225}Ac$	4	NCA	^{226}Ra	*Unknown*	Solid	Yes	Accelerators	High Energy	*none*	Worldwide
		$^{226}Ra(n,2n)^{225}Ra$->^{225}Ac	4	NCA	^{226}Ra	*Unknown*	Solid	Yes	Research R.	-	*none*	Worldwide
^{212}Pb	No	^{224}Ra->^{212}Pb	9	NCA	None	None	*no irradiation needed*				$^{224}Ra/^{212}Pb$	Worldwide
^{166}Ho	Yes (not in EU)	$^{165}Ho(n,\gamma)^{166}Ho$	9	CA	^{165}Ho	None	Solid	No	Research R.	Low flux	*none*	Regional
		$^{164}Dy(n,\gamma)^{165}Dy(n,\gamma)^{166}Dy$->$^{166}Ho$	6	NCA	^{164}Dy	EMS	Solid	No	Research R.	Low flux	*none*	Regional
^{188}Re	No	$^{187}Re(n,\gamma)^{188}Re$	7	CA	^{187}Re	EMS	Solid	No	Research R.	Low flux	*none*	Local
		$^{186}W(n,\gamma)^{187}W(n,\gamma)^{188}W$->$^{188}Re$	9	NCA	^{186}W	Centrif.	Solid	No	Research R.	High flux	$^{188}W/^{188}Re$	Worldwide
^{211}At	No	$^{209}Bi(\alpha,2n)^{211}At$	6	NCA	^{209}Bi	None	Solid	No	MEC	28-29MeV	*none*	Local
		$^{211}Rn/^{211}At$	3	NCA	^{227}Th	*Unknown*	Gas	No	HEA	High	*none*	Regional
^{64}Cu	Yes (in the USA)	$^{64}Ni(p,n)^{64}Cu$	9	NCA	^{64}Ni	Centrif.	Solid	Yes	SMC/MEC	12-16MeV	*none*	Local
		$^{64}Zn(d,2p)^{64}Cu$	3	CA	^{64}Zn	Centrif.	Solid	No	SMC/MEC	10-40MeV	*none*	Regional
		$^{nat}Zn(d,x)^{64}Cu$	9	CA	^{nat}Zn	None	Solid	No	SMC/MEC	10-40MeV	*none*	Regional

^{67}Cu	No	^{67}Zn(n,p)^{67}Cu	9	CA	^{67}Zn	Centrif.	Solid	No	Research R.	High flux	*none*	Regional
		^{70}Zn(p,α)^{67}Cu	9	CA	^{70}Zn	Centrif.	Solid	Yes	SMC	16MeV	*none*	Local
		^{68}Zn(p,2p)^{67}Cu	9	CA	^{68}Zn	Centrif.	Solid	No	HEA	50-425MeV	*none*	Regional
		^{68}Zn(γ,p)^{67}Cu	9	NCA	^{68}Zn	Centrif.	Solid	No	Accelerator	30-60MeV	*none*	Regional
		^{64}Ni(α,p)^{67}Cu	3	NCA	^{64}Ni	Centrif.	Solid	No	Accelerators	30MeV	*none*	Local
^{44}Sc	No	^{44}Ca(p,n)^{44}Sc	3	NCA	^{44}Ca	EMS	Solid/Liquid	Yes	Accelerators	10-15MeV	*none*	Local
		^{44}Ti->^{44}Sc	3	NCA	^{44}Ti	Centrif.	Solid	No	MEC/HEA	40-50MeV	^{44}Ti/^{44}Sc	Worldwide
^{47}Sc	No	^{46}Ca(n,γ)^{47}Ca->^{47}Sc	3	NCA	^{46}Ca	EMS	Solid	Yes	Research R.	High flux	^{47}Ca/^{47}Cs	Worldwide
		^{47}Ti(n,p)^{47}Sc	3	CA	^{47}Ti	Centrif.	Solid	*Unknown*	Research R.	Fast flux	*none*	Regional
		^{48}Ti(γ,p)^{47}Sc	3	CA	^{48}Ti	Centrif.	Solid	*Unknown*	Accelerators	40MeV	*none*	Regional
		^{48}Ti(p,2p)^{47}Sc	3	CA	^{48}Ti	Centrif.	Solid	*Unknown*	MEC/HEA	30-70MeV	*none*	Regional
		^{50}Ti(p,α)^{47}Sc	3	CA	^{50}Ti	Centrif.	Solid	*Unknown*	MEC/HEA	30-70MeV	*none*	Regional
		^{48}Ca(p,2n)^{47}Sc	3	CA	^{48}Ca	EMS	Solid	Yes	MEC/HEA	30-70MeV	*none*	Regional
		^{44}Ca(α,p)^{47}Sc	3	CA	^{44}Ca	EMS	Solid	*Unknown*	Accelerators	30MeV	*none*	Regional
^{149}Tb	No	^{152}Gd(p,4n)^{149}Tb	4	CA	^{152}Gd	EMS	Solid	*Unknown*	HEA	60MeV	*none*	Local
^{152}Tb		^{152}Gd(p,n)^{152}Tb		CA	^{152}Gd	EMS	Solid	*Unknown*	SMC	12MeV	*none*	Local
^{155}Tb		^{155}Gd(p,n)^{155}Tb		CA	^{155}Gd	EMS	Solid	*Unknown*	SMC/HEA	12-60MeV	*none*	Worldwide
^{161}Tb		^{160}Gd(n,γ)^{161}Gd->^{161}Tb		NCA	^{160}Gd	EMS	Solid	*Unknown*	Research R.	High flux	*none*	Worldwide
^{60}Co	n.a.	^{59}Co(n,γ)^{60}Co	9	-	^{59}Co	None	Solid	No	Power. R. Research R.	Low flux High flux	*none*	Worldwide

Table 9: Summary table for radionuclides manufacturing routes – Source NucAdvisor

–	Technology readiness level of manufacturing routes	Main challenges over supply chains	European demand and evolution up to 2030	Current production capacity
^{99m}Tc Annex 1	Fission of ^{235}U in research reactors is currently the preferred production route (TRL9); an accelerated-based neutron source (SHINE) is under development (TRL6). Activation of ^{98}Mo targets in research reactors (TRL9) or CANDU (TRL3) appear as alternatives, along with photonuclear reaction on ^{100}Mo targets in electron accelerators (TRL7). Direct ^{99m}Tc production in SMC is progressing in Canada (TRL 8).	○ For the fission route, the LEU supply for research reactor fuels (and targets) remains a concern to be practically addressed. ○ Non fission routes will need to set up a large supply of ^{98}Mo and ^{100}Mo, along with recycling techniques to improve competitiveness; ○ New irradiation means will be needed within the next 10 years to replace ageing research reactors, need for investments in standard or new technologies (research reactors, accelerators, etc.)	Latest estimates from OECD-NEA evaluate to 9500 6d Ci EOP the weekly demand of ^{99}Mo. This corresponds to roughly 40 million ^{99m}Tc procedures per year, with EU representing roughly 25% of this demand. ^{99m}Tc is expected to remain the most-used radionuclide during the next decade. The market is stable in EU and North America (0.5% CAGR), with main growth expected from Asia and Rest of the World (5% CAGR), resulting in a few percent total growth per year.	Current European production capacity is higher than EU sole demand (EU being a large exporter of ^{99}Mo); the future shutdown of HFR, BR2, LVR-15 and MARIA will need to be replaced by new installations. Current EU production is based only on research reactor ^{235}U fission.
^{18}F Annex 2	^{18}F production is limited to a single manufacturing route: cyclotron production using ^{18}O (TRL9). No technology change or evolutions are expected within the next decade.	○ Just-in-time production of ^{18}F is done through an EU-wide cyclotron network, more dense in western EU (see §2.2.3.2). Need to ensure equal access to ^{18}F across EU; ○ Diversified supply or target material (^{18}O), fully imported from outside EU.	The current worldwide market for ^{18}F labelled RP (produced by cyclotron centre) can be estimated at roughly 1B$ (5 Million procedures per year, with an average cost for FDG dose around 200€), with significant growth expected (from 1 to 6% CAGR depending on world region). EU represents ~20% of world market.	With the exception of ^{18}O enrichment, the European ^{18}F supply chain is almost fully domestic, with a mature cyclotron network operated by EU international players (Curium, AAA/Novartis), using low-energy cyclotrons mostly manufactured by two large players (IBA and GE Healthcare).
^{68}Ga Annex 3	The supply of ^{68}Ga is currently performed through generators (TRL9), that could be complemented in the future with direct production in cyclotrons (TRL8) allowing larger production capacity (i.e. generators have limited daily elution capacity).	○ Generator production relies on the ^{68}Ge supply, mainly coming from commercial manufacturers, but also from public institutes. Capacities were increased in the recent years, but with growing demand for generators, there is a need to develop sustainable ^{68}Ge supply; ○ Industrial direct production route will need solid (best yields) ^{68}Zn target systems, currently under development.	^{68}Ga experienced an important growth in recent years, and generator manufacturers increased their production capacities. An order of magnitude of 1,000 sites worldwide equipped with generators. Generator use is not optimized, and only a few hundred thousand procedures per year are performed with ^{68}Ga. Future TRNT pairing use will increase demand.	Current worldwide production capacity is currently unbalanced between ^{68}Ge manufacturing (outside EU) and generator manufacturing in EU. Curium is world's largest producer of ^{68}Ge. Recent investment in generator manufacturing facilities should solve past tensions on generator supply.
^{177}Lu Annex 4	Two grades of ^{177}Lu are produced: CA & NCA. Both manufacturing routes are routinely used on an industrial basis (TRL9). NCA ^{177}Lu route is expected to become the main supply source, currently produced in research reactors, with potential alternatives (Power reactors, SHINE, etc.)	○ ^{176}Yb for NCA route is currently only enriched by electromagnetic separation in Russian Calutrons. USA (ORNL and National Isotope Development Program) are working on re-establishing such enrichment capacity.	^{177}Lu demand is limited but currently increasing (Lutathera®: 1st RP with Market Authorization had a turnover of 400M$ in 2019). Several hundred thousand patients could benefit from ^{177}Lu treatments in the future. In 2019, over 1,000 patients were treated in Western Europe (UK, DE, ES, IT and FR) with Lutathera.	^{177}Lu is currently produced through two main manufacturing routes that currently coexist providing either CA or NCA grade ^{177}Lu. EU is a large contributor of ^{177}Lu manufacturing, either through irradiation (HFR for CA or BR-2 for NCA), while different players are supplying ^{177}Lu radiochemical or GMP product with market authorization. Russia is the only supply of target material (enriched ^{176}Yb).

–	Technology readiness level of manufacturing routes	Main challenges over supply chains	European demand and evolution up to 2030	Current production capacity
^{90}Y Annex 5	^{90}Y can be produced through two manufacturing routes, either directly, leading to carrier-added ^{90}Y, or indirectly through ^{90}Sr decay, with non-carrier-added ^{90}Y produced. Both routes are currently already used by the European radionuclide industry for ^{90}Y production; no direct "competition" exists between the two, the different product grades being used for different applications.	○ No specific challenges in the next decade	Before the recent development of Lutathera and Xofigo, ^{90}Y Zevalin® was the largest therapeutic agent on the market. ^{90}Y demand remains important, the CA ^{90}Y is largely used for radiosynoviorthesis applications (tens of thousands of procedures in EU), while NCA use is more limited but could increase in the future in case of success of new TRNT products under development. ^{90}Y microspheres for liver treatment are also used.	The two manufacturing routes of ^{90}Y are not in competition, providing two different product qualities used for distinct applications. Strong competition between EU players equipped with generators at pharmaceutical grade.
^{131}I Annex 6	^{131}I has been produced in reactors, either as ^{99}Mo fission route by-product (TRL9) or through ^{130}Te target irradiation (TRL9). With NRU end-of-life joint production with ^{99}Mo became the new standard (IRE, NTP). A growing trend for NCA ^{131}I can be observed, pushing for increased production with ^{130}Te route (already largely produced by MARIA).	○ ^{131}I production is currently partially dependent on ^{99}Mo one; past issues on ^{99}Mo production impacted worldwide ^{131}I supply.	Based on EU statistics of use, an order of magnitude of a few tens of thousands ^{131}I procedures per year in EU can be estimated. A limited growth has been reported from market players.	^{131}I has been produced through the two manufacturing routes during the last 20 years. With NRU end-of-life joint production with ^{99}Mo became the new standard (IRE, NTP). IRE is currently converting its production to LEU. A growing trend for NCA ^{131}I can be observed, pushing for increased production with ^{130}Te.
^{123}I Annex 7	^{123}I is produced in low- or medium-energy cyclotrons through direct or indirect routes, both industrialized (TRL9).	○ The indirect route (^{123}Xe decay) relies on medium/high energy cyclotrons (20-30MeV) less widely available.	^{123}I demand is in the range of tens of thousands of procedures in the EU, far less than ^{99m}Tc imaging. Its use will at least remain stable for the next decade, considering the lack of alternatives and its superiority for thyroid imaging. Parkinson diagnostics with Datscan may change this figure.	The indirect route is preferred for industrial production. However, the limited availability of medium-energy cyclotrons (20-30MeV) dedicated to RN production is a significant limitation.
^{124}I Annex 8	^{124}I can be produced through different manufacturing routes; ^{124}Te target irradiation in cyclotrons has become the standard (TRL9).	○ No specific challenges expected, aside from investment needs to develop supply.	The development of ^{124}I-labelled RP shall remain limited to some slow biological process imaging, making ^{124}I a radionuclide with a limited use as compared to other short half-life imaging PET radionuclides (^{18}F, ^{68}Ga).	Industrial supply of ^{124}I is currently limited in EU; BV Cyclotron VU stopped production in 2020, and ^{124}I is not among Curium's products (despite being previously among IBA Molecular's.
^{89}Zr Annex 9	The proton irradiation route of ^{nat}Y is expected to become the standard production route (TRL9), having no major limitations.	○ No specific challenges expected, aside from investment needs to develop supply.	The development of ^{89}Zr-labelled RP shall remain limited to Immuno-PET, making ^{89}Zr a radionuclide with a limited use as compared to other short-half-life imaging PET radionuclides (^{18}F, ^{68}Ga).	Current production capacity is limited in EU; upon market arrival of ^{89}Zr labelled RP, investment in dedicated production site will be needed.
^{223}Ra Annex 10	Indirect production through ^{227}Ac decay (TRL9) will remain the sole route used for ^{223}Ra. Existing stockpiles can be renewed every few decades through ^{226}Ra irradiation.	○ No specific challenges in the next decade	Aside from research applications, current ^{223}Ra demand is essentially limited to ^{223}Ra-Radium dichloride (Xofigo®). Demand is expected to remain stable over the next decade; no new RP is under advanced development stage.	Current worldwide supply capacity (from ^{227}Ac stockpiles) will be enough to cover demand. No investment needed.

–	Technology readiness level of manufacturing routes	Main challenges over supply chains	European demand and evolution up to 2030	Current production capacity
^{225}Ac Annex 11	Current supply limited to ^{229}Th decay (TRL9), not sufficient for future RP use. Among alternative routes, CA ^{225}Ac produced by spallation of ^{232}Th (TRL9) has limited RP use (production of long-lived ^{227}Ac); cyclotron route is promising but important challenges remain unsolved (TRL4)	○ EU supply limited by stockpiles of ^{229}Th, need to secure more to increase production capacity; ○ For medical use, spallation route would need additional separation step (to isolate ^{227}Ac) such as mass separation technologies (e.g. CERN ISOL); ○ Gathering high-energy proton installations to enable alternative route in EU while setting up an EU cyclotron network (^{226}Ra irradiation), along with solving technical issues linked with ^{226}Ra.	^{225}Ac will play a significant role within the next decade. Current supply capacity is not sufficient to cover increasing needs. Based on figures from the American Cancer Society, roughly 550,000 new patients in the US could benefit from ^{225}Ac treatment.	Current supply capacity is limited to a few hundred patients per year on a worldwide basis.
^{212}Pb Annex 12	A single indirect manufacturing route through ^{224}Ra/^{212}Pb generators (TRL9) is foreseen. Pilot plant for generator production already operational.	○ No major technical challenges remaining for ^{212}Pb supply, except the need to expand production through investment in different production plants worldwide, along with setting up a distribution network.	Demand is currently limited to research and early clinical studies, and should remain limited during the coming years, as the different RPs labelled with ^{212}Pb are still in early development phase.	Production currently limited by the purification step (extraction of ^{228}Th from natural Thorium salts or ^{232}U stockpiles). No limitation foreseen in the future, no issue with Thorium stocks. Need to expand production for ^{212}Pb-labelled RP.
^{166}Ho Annex 13	Two manufacturing routes possible, the CA historic direct one (TRL9), along with the NCA indirect route, currently under development (TRL6/7), that will be preferred for future TRNT applications.	○ International dysprosium supply is facing tensions (China is the sole supplier); ○ Otherwise, no major technical challenges for setting up or expanding both manufacturing routes for supply, aside from the investment needs.	Considering the increasing interest for ^{166}Ho in the last decade, and the different applications already in use (microspheres for liver treatment, TRNT for bone metastases and hepatocellular carcinoma), ^{166}Ho use should continue to grow in the future.	Current production capacity is sized for brachytherapy and RSV needs only.
^{188}Re Annex 14	^{188}W/^{188}Re generators (TRL9) appears as the most convenient and cost-effective route, allowing daily supply of NCA ^{188}Re. The reactor direct route should remain limited to ^{188}Re supply for non-high specific activity applications, and where generator use or supply is not possible. In EU, generator-based ^{188}Re should remain the preferred manufacturing route.	○ The development of pharmaceutical-grade generators is currently the main challenge faced by the industry; ○ Enriched target material should not be a limitation in short term (large stockpiles), but need for sustainable long-term enrichment solution.	^{188}Re demand is currently limited for NM applications, only used for bone pain palliation in EU. Its future demand will be linked to market approval of new RP labelled with ^{188}Re. In the meantime, the availability of a generator will increase demand, fostering clinical developments.	Only two players (in EU) currently manufacture GMP-grade generators (IRE ELIT and ITG GmbH), with a production directly aimed at clinical R&D.
^{211}At Annex 15	Direct production of ^{211}At (TRL5/6) currently appears as the less complex route, while generator production is still in early development (TRL3).	○ The main challenge to be faced for large-scale production of ^{211}At is the need for a α-beam 30MeV cyclotron network.	Demand is currently almost null (due to limited supply), with very limited R&D underway.	^{211}At is part of a few cyclotrons' RN portfolio; no routine production.

–	Technology readiness level of manufacturing routes	Main challenges over supply chains	European demand and evolution up to 2030	Current production capacity
^{64}Cu Annex 16	The standard production route (TRL9) through proton irradiation of ^{64}Ni targets remains expensive due to high cost enriched material, while alternative route in deuterium fluxes (TRL3) could be less costly but is still in early R&D and would result in CA product.	○ The development of an EU-wide MEC cyclotron network will be needed in case of ^{64}Cu-labelled RP, representing a large investment for industry; ○ In order to optimize production costs, improved targetry systems will be needed.	Demand is currently limited to early clinical developments.	In the absence of large demand, there is currently no EU industrial supply of ^{64}Cu. A MEC cyclotron network would be needed (~50 production sites) to cover EU needs.
^{67}Cu Annex 17	Among the different production routes, photonuclear reaction (TRL9) is currently becoming the more advanced route towards industrial production. Production in reactors results in low-quality product, while proton irradiation (TRL9) necessitates high proton fluxes.	○ Securing a high-energy proton network for semi-centralized production of ^{67}Cu in EU, or the development of electron accelerator network of medium energy (30MeV) for ^{67}Cu production; ○ Securing enriched zinc isotope supply for ^{64}Cu and ^{67}Cu production.	^{67}Cu demand has been limited in the past due to scarce supply sources and high production costs. The recent availability of US DoE routine production should foster clinical research and increase demand. Demand will remain limited to clinical trials prior to the market authorization of a first ^{67}Cu labelled RP.	The single routine production of ^{67}Cu is performed through the DoE at Argonne Laboratory (LINAC), and NorthStar (USA) recently announced the development of industrial production capacity of ^{67}Cu for Clarity Pharmaceuticals, in their recently acquired Rhodotron®. In Europe, ^{67}Cu can also be sourced from PSI, but in limited quantities.
^{44}Sc Annex 18	Two manufacturing routes in early development stage (TRL3); the indirect route through ^{44}Ti/^{44}Sc generators appears promising (good yield/purity and limited cost material), but long irradiation needed in high-energy proton flux (50MeV), while the direct route in cyclotron is based on enriched ^{44}Ca (costly and more difficult to enrich).	○ The sustainable supply of enriched ^{44}Ca; ○ The availability of an EU-wide cyclotron network for target irradiation, (α, deuterium or proton); ○ The availability of large proton irradiation facility for ^{44}Ti production or spallation sources; ○ The development of GMP for ^{44}Sc production, along with specific equipment and production processes.	^{44}Sc demand is currently limited to R&D. Considering that ^{44}Sc-labelled RP are only in early development stage, demand should remain low within the next decade.	There is currently no established supply chain for ^{44}Sc, its use being limited to preclinical R&D.
^{47}Sc Annex 19	Currently the indirect route ^{46}Ca(n,γ)^{47}Ca followed by decay into ^{47}Sc, and the photonuclear reaction ^{48}Ti(γ,p)^{47}Sc appear as the most promising production routes, in their early development stage.	○ The sustainable supply of enriched ^{46}Ca and ^{48}Ti; ○ The availability of fast neutron irradiation means, or a network of photon accelerators, currently not widely available at EU scale.	^{47}Sc demand is currently limited to preliminary R&D. When considering that ^{47}Sc-labelled RPs are only in early development stage, demand should remain low within the next decade.	There is currently no established supply chain for ^{47}Sc, its use being limited to scarce preclinical R&D. ^{47}Sc has already been produced in EU at Institute Laue Langevin reactor (France), in spallation-induced neutron source SINQ of Paul Scherrer Institute (PSI), and in BR-2 reactor (Belgium).

–	Technology readiness level of manufacturing routes	Main challenges over supply chains	European demand and evolution up to 2030	Current production capacity
^{149}Tb **^{152}Tb** **^{155}Tb** **^{161}Tb** Annex 20	The supply of the different terbium isotopes is not currently at similar levels of development; ^{161}Tb is the "easiest" one to produce, with a supply close to ^{177}Lu NCA in research reactors. Regarding the 3 others, they can be produced in high-energy proton accelerators (70 MeV) with specifically enriched gadolinium targets or through high-energy proton irradiation of tantalum foil, followed by a mass isotope separation process (ISOLDE/CERN).	○ Supply of enriched target material (^{160}Gd for ^{161}Tb production, or ^{152}Gd for ^{152}Tb, or ^{155}Gd for ^{155}Tb); ○ Availability of high-energy proton flux (up to 70MeV) for ^{149}Tb, ^{152}Tb, ^{155}Tb.	The demand for terbium isotopes is limited, partially due to limited supply sources. It is expected that terbium isotope demand will remain capped by production capacity in the next decade. Through 2030, terbium isotope demand will be restricted to a few preclinical and early clinical applications.	There is currently no routine production of terbium. Aside from ^{161}Tb supply chain in research reactor that could be based on existing installations (with the challenge of enriched ^{160}Gd supply), the other terbium isotopes currently rely on complex manufacturing solutions (scarcely available high-energy proton accelerators, mass separators, etc.), limiting wide-scale deployment.
^{60}Co Annex 21	There is only a single manufacturing route for ^{60}Co, with thermal neutron irradiation of natural cobalt sources (100% of ^{59}Co isotope) in reactors. Depending on the grade of ^{60}Co produced (HSA or LSA), irradiation duration and target systems are different.	○ Increasing production capacity, considering increasing demand. Recent collaboration between Nordion and Romanian CANDU could add a large supply of LSA ^{60}Co in EU.	^{60}Co demand has been increasing through the years; the main market players (Canada and Russia) have taken measures to secure and increase production for the future through additional production sites, thus confirming this growing trend.	Canada and Russia are main suppliers of LSA ^{60}Co. Production of LSA was performed in EU in the past (e.g. in BR-2). HSA ^{60}Co is produced in some EU research reactors. Canada recently started to produce HSA in CANDU reactors.
Indust. RN Annex 22	Most industrial radionuclides developed themselves as by-products of nuclear-industry related processes or are produced in limited quantities through specific production campaigns by state-subsidized installations (USA and Russia).	○ Most applications relying on industrial radionuclides have been in use for decades; main challenge is to maintain these applications as long as no better alternatives are found. Thus it is necessary to secure non-EU supply.	EU demand remains limited as compared to worldwide demand for most industrial radionuclides (mainly used in industrial gauges).	The great majority of industrial radionuclides are not produced in EU.

Table 10: Summary table of radionuclides case studies (Annex 1 to 22) - Source NucAdvisor

2.2. Step-by-step supply-chain analysis

After having characterized in detail in the previous chapter the various supply chains, nuclide by nuclide, the typical steps of any radionuclide supply chain are considered in the present chapter, allowing assessment of the challenges for the EU in a transverse topical manner.

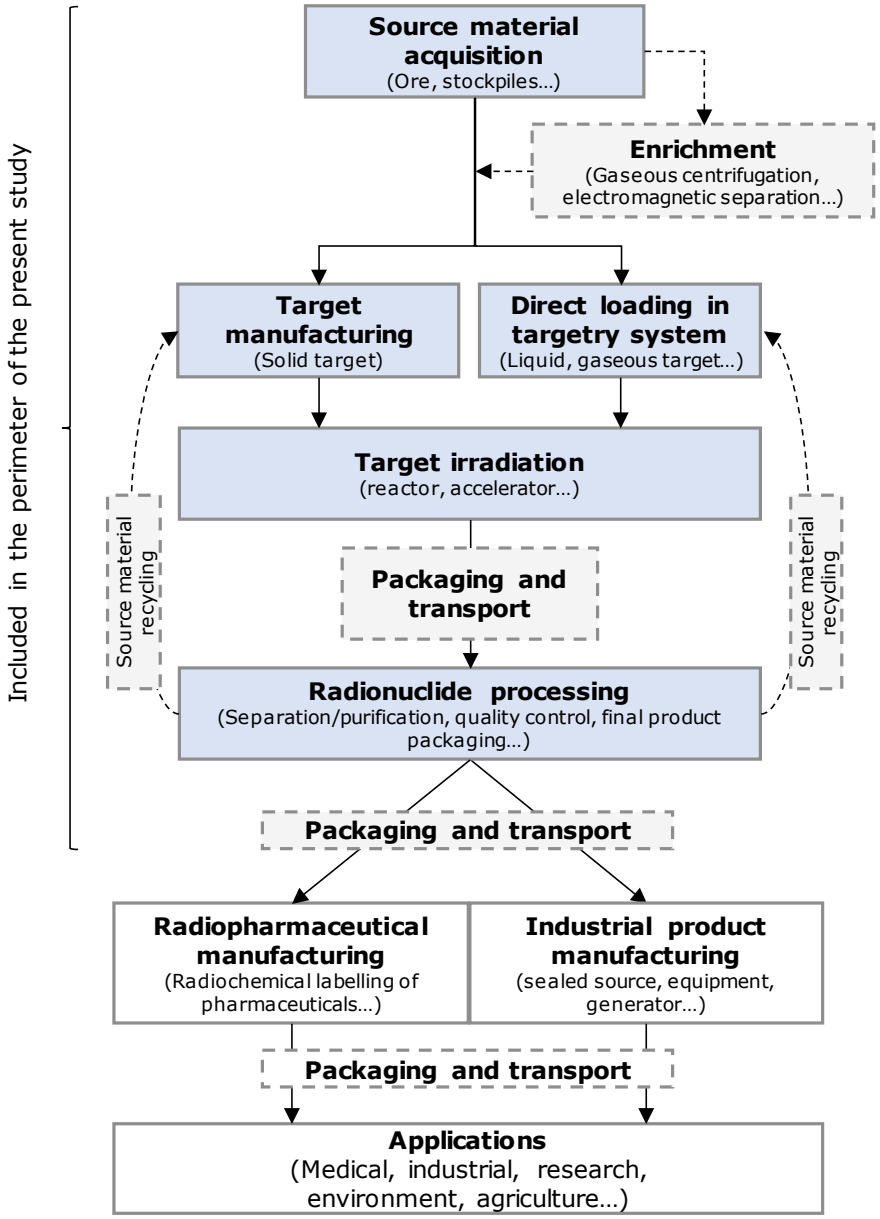


Figure 10: Typical supply-chain steps for radionuclide production

As seen in Chapter 2.1, many nuclear reactions can generally be envisaged for the production of a single radionuclide. Depending on the nuclear characteristics of the target material (neutron cross sections, proton excitation functions, etc.) and the characteristics of the incident beams (neutron flux level in reactors, energy and intensity of the charged particles beams in accelerators), production yields and the

impurities levels[17] are very variable and not all installations are able to produce a given radionuclide with enough efficiency and purity.

Optimizing a radionuclide production is thus a complex task, which requires examining in detail all the supply-chain steps for each manufacturing route identified, as illustrated in the ^{225}Ac example below.

The ^{225}Ac case shows diversity and complexity for selecting a good compromise for setting up an industrial radionuclide supply. An exhaustive ^{225}Ac production routes list is summarized in the table below (see Annex 11 for more details regarding ^{225}Ac production routes).

	Production Method	Facility	Capabilities	Monthly ^{225}Ac Production [GBq (Ci)]
Current Sources	^{229}Th generator	ORNL ITU IPPE	0.704 g (150 mCi) of ^{229}Th 0.215 g (46 mCi) of ^{229}Th 0.704 g (150 mCi) of ^{229}Th	2.2 (0.06) 1.1 (0.03) 2.2 (0.06)
Potential	^{232}Th(p, x)^{225}Ac	TRIUMF	500 MeV, 120 µA	11266.5 (304.05)
		BNL	200 MeV, 173 µA	2675.84 (72.32)
		INR Arronax	160 MeV, 120 µA 70 MeV, 2×375 µA	1002.0 (27.08) 462.1 (12.49)
		LANL	100 MeV, 250 µA	444.0 (12.00)
		iThemba LABS	66 MeV, 250 µA	127.7 (3.45)
Future Sources	^{226}Ra(p, 2n)^{225}Ac	20 MeV, 500 µA cyclotron 15 MeV, 500 µA cyclotron		3983.1 (107.65) 1157.4 (31.28)
	ISOL	TRIUMF (existing) TRIUMF (potential upgrades)		0.37 (0.01) 190.6 (5.15)
	^{226}Ra(γ, n)^{225}Ra	medical linac ALTO	18 MeV, 26 µA 50 MeV, 10 µA	48.1 (1.3) 55.5 (1.5)
	^{226}Ra(n, 2n)^{225}Ra	fast breeder reactor		~37 (1)

Production Method	Comments
^{226}Ra(p, pn)^{225}Ra	Yields insignificant compared to ^{226}Ra(p, n) ^{225}Ac production (10^5× less according to FLUKA simulation)
^{232}Th(p,4n)^{229}Pa	Low cross-section
^{nat}U(p, x)^{225}Ac	Produces ~10× less ^{225}Ac and ^{225}Ra compared to thorium spallation, creates fissile ^{239}Pu and ^{235}U, can handle less beam current than thorium spallation targets
^{232}Th(n, γ)^{233}U	Would take decades for ^{229}Th to build up
^{230}Th(γ, n)^{229}Th	^{230}Th not available in sufficient quantities
Reactor production of ^{229}Th	Potential target materials ^{228}Ac, ^{228}Ra, ^{228}Th, and ^{230}Th not available in sufficient quantities. Production yields from ^{226}Ra irradiation (110 MBq/month/g, or 3 mCi/month/g) too low considering cost and difficulty of ^{226}Ra source production.

Table 11: Diverse ways of producing ^{225}Ac [18]

For ^{225}Ac, many production routes are available for supplementing current sources. The two most promising ones are through ^{232}Th spallation and ^{226}Ra proton irradiation, both of them having advantages and drawbacks. The first necessitates

[17] Due to many competing nuclear reactions
[18] "Development of ^{225}Ac Radiopharmaceuticals: TRIUMF Perspectives and Experiences." Andrew Kyle Henderson Robertson, Caterina Fortunata Ramogida, Paul Schaffer and Valery Radchenko, Current Radiopharmaceuticals, 2018, 11, 156-172

very powerful proton accelerators (LINACs or cyclotrons), whereas the second one uses more modest cyclotrons. The first one co-produces ^{227}Ac impurity, which complicates the post-irradiation processing, whereas the second one uses ^{226}Ra targets, more complex and hazardous to handle than metallic ^{232}Th targets. In both cases, standardized production yields and costs (CAPEX and OPEX) balances need to be established, taking into account the industrial, safety, radioprotection and auxiliary systems aspects. It is therefore particularly difficult to define which route is the best compromise.

As seen in this ^{225}Ac example and in §2.1, each nuclide may have several production routes, each of them having advantages and drawbacks relatively to:

- the abundance of the target material, to be enriched or not,
- the targets specifications: ability to sustain low/high irradiation energy, complexity to design, need for R&D, complexity to handle target material and targetry systems, etc.,
- the irradiation installations specifications: supporting systems complexity and size, operation and construction costs, operating complexity, etc.,
- the impurities related to the production reaction which must be removed after irradiation, necessitating a more or less complex separation process,
- CAPEX, OPEX and costs of goods more or less affordable for producers and end-users.

In the next paragraphs, the typical steps of the various supply chains are examined more in detail.

2.2.1. Target material availability

The target material can be a natural product (water for ^{18}O, or refined ore for the majority of target materials), stem from existing stockpiles (^{233}U-^{229}Th for ^{225}Ac production, or consist of reprocessed fuel fission products like ^{90}Sr for ^{90}Y production). It may also be by-products of other radionuclides production (^{133}Xe produced in parallel with fission-^{99}Mo).

The production of the raw materials necessary – for instance Gallium, Germanium or Iridium – is sometimes concentrated in the hands of one country.

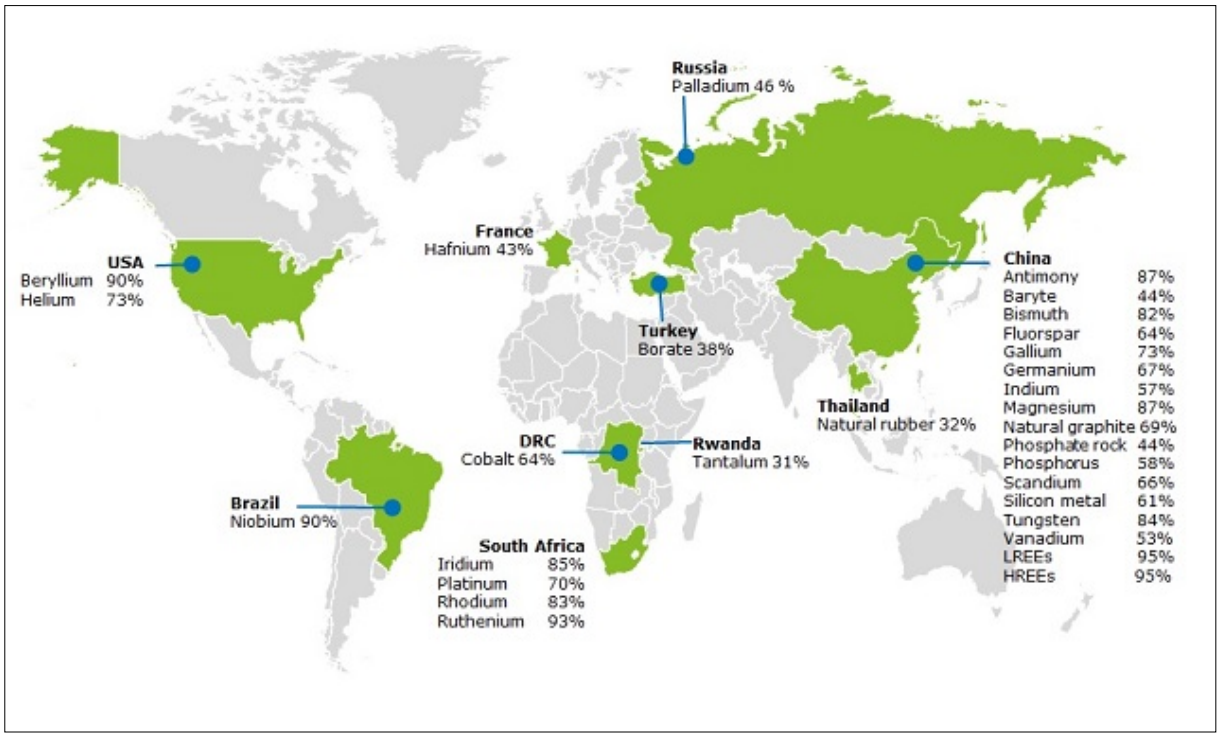


Figure 11: Countries accounting for largest share of global supply of CRMs.
Source: EC – Study on the review of the list of Critical Raw Materials - June 2017

Risks to supply may occur in case of international tensions. For example, between 2007 and 2016, the risk for rare-earth elements peaked in 2011 and 2012 when China halted exports during a dispute with Japan. The supply of rare-earth elements consistently remained among the highest-risk commodities throughout the entire period studied by the USGS.[19]

The question of EU dependency on foreign supplies has been considered at the global industrial level as early as 2008 through the European Raw Materials Initiative.[20] To address this challenge, the European Commission has created a list

[19] https://www.greeNCArcongress.com/2020/02/20200223-usgs.html
[20] https://ec.europa.eu/growth/sectors/raw-materials/specific-interest/critical_en

of critical raw materials (CRMs[21]) for the EU, which is subject to regular review and update (last update[22] in 2017).

Concerning the main radionuclides of interest in the present study:

- The target material for NCA ^{177}Lu is ytterbium, which is among the rare-earth elements. This mineral is found with other rare-earth elements in several minerals. It is most often recovered commercially from monazite sand (0.03% ytterbium). The element is also found in euxenite and xenotime. The main mining areas are in China, the United States, Brazil, India, Sri Lanka, and Australia. World production of ytterbium is about 50 tonnes per year, reflecting that it has only few commercial applications. Reserves of ytterbium are estimated at one million tonnes.[23] Ytterbium ore shortage risks thus seem limited, as opposed to enriched material ^{176}Yb (see next chapter).

- This is less the case for ^{68}Ga, whose production routes necessitate either gallium (generators route) or zinc (direct route), which are more in demand on the market and more prone to shortages. Since 2015, the international zinc supply has been facing shortages (market of 14 million tonnes a year, with yearly shortfalls up to 0.4 million tonnes), due to mine closures and cutbacks at other mines, along with environmental issues in China, that impacted its production capacity.[24]

- The industrial supply of many other target materials for future production of radionuclides currently under development are already at issue: dysprosium for NCA ^{166}Ho, yttrium for ^{89}Zr, bismuth for NCA ^{211}At, etc.

EU current status #1: Even for target materials for which supply risks cannot be excluded, the fraction of material necessary for medical radionuclides production remains generally very small as compared to the other industry needs. Hence, risks linked to target material supply for radionuclide production are limited. Even in the worst case of strong supply risks, given the small amounts of target materials necessary for medical applications, it would always be possible to constitute strategic stockpiles for medical use at the MS or EU levels for the most critical target material. Close surveillance of raw materials supply as it is already implemented in Europe may be sufficient to anticipate any future issues.

[21] CRMs combine raw materials of high importance to the EU economy and of high risk associated with their supply.
[22] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52017DC0490
[23] https://en.wikipedia.org/wiki/Ytterbium
[24] "Shortages, shrinking stocks to energize zinc bulls" – Reuters – March 5, 2019

2.2.2. Stable isotopes enrichment

An increasing volume of enriched isotopes will be needed for RN production.

Highly enriched targets minimize the production of unwanted radionuclides that would ultimately lead to purity and radiological contamination issues (unwanted reactions, half-life not compatible with desired applications, etc.).

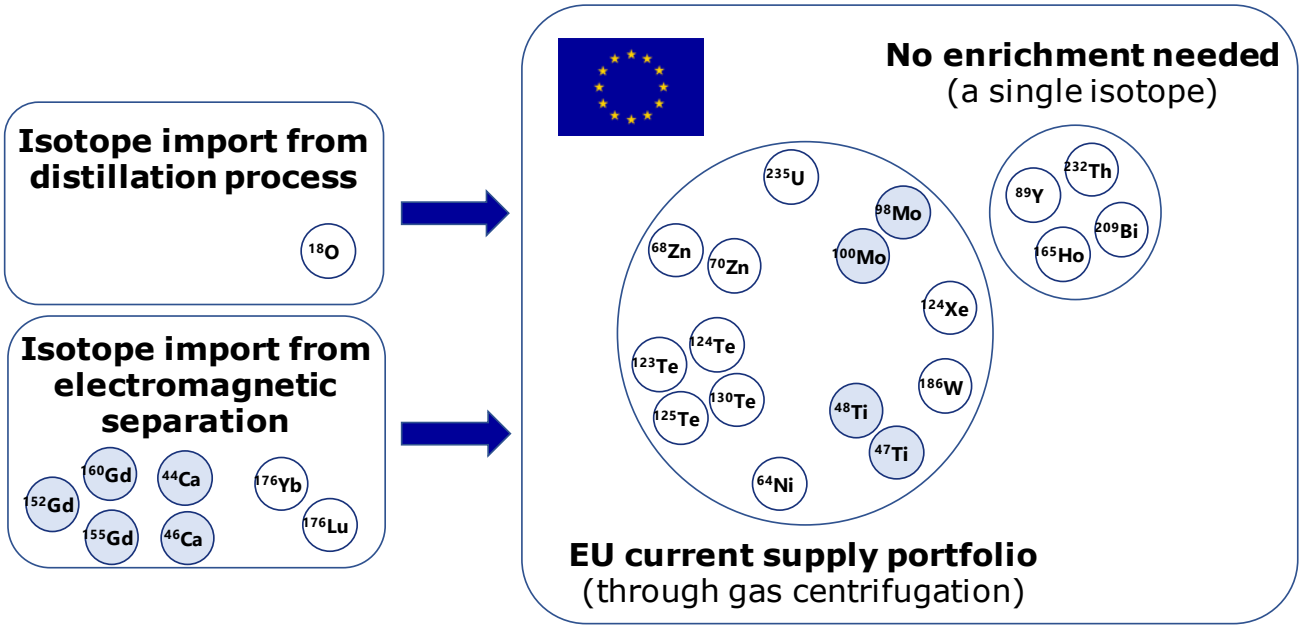


Figure 12: Current European situation for isotopes enrichment (in blue, isotopes that would be needed by 2030 to support research and/or industrial radionuclide production)

The main methods for enriching stable isotopes are:

- distillation and all its variants, which only works effectively when there is a large relative mass difference between the different isotopes of an element. Distillation is therefore only used for the separation of light isotopes (typically oxygen for obtaining ^{18}O);
- gaseous centrifugation, which is the most cost-effective method for separating the isotopes of elements that are too heavy for distillation. A suitable gaseous compound of the element must exist, and is not always available (typically ytterbium and other lanthanides cannot be enriched in this way);
- electromagnetic enrichment (owing to a machine called a "calutron" – see box below). The calutron, a technology known for 70 years, is able to enrich the isotopes of nearly all elements but is costly to operate, and only relatively small quantities can be produced. This technique can also be used for separating radioactive beams "on-line", as in the ISOLDE[25] installation in CERN;

[25] ISOL: Isotope Separation On-Line. On-line separation is when the mass separator is close to the accelerator producing the radioactive beam.

- other methods such as chemical exchange, laser enrichment, photo chemical enrichment and plasma separation are also occasionally used, at least at laboratory scale.

Accordingly, enrichment processes are nuclide-specific:

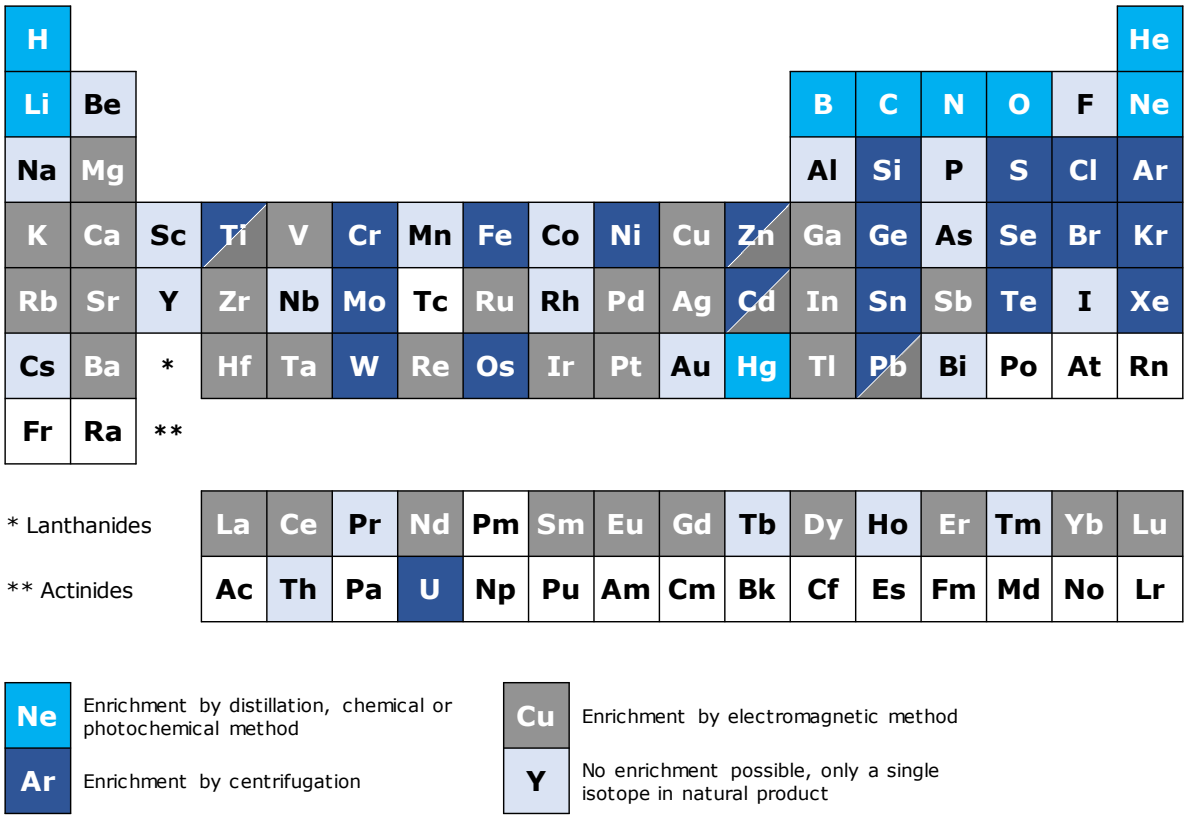


Figure 13: Summary of enrichment technologies used per element - Source: NucAdvisor

Among the radionuclides of interest selected in the context of this study, an increasing need for enriched isotopes is foreseen:

- one of the main stable isotopes of interest is ^{18}O, precursor of ^{18}F, which will continue to be widely used in the near future;
- ^{98}Mo or ^{100}Mo enriched isotopes are necessary for alternative ^{99m}Tc production routes. Alternative supply sources through innovative (electromagnetic separation combined with gas centrifugation) or alternative technologies (laser enrichment) are under consideration (see USDOE-ESIPP below);
- the issue of getting stable enriched ^{176}Yb for NCA ^{177}Lu production is already significant. Russian calutrons are currently the only supplier of enriched ^{176}Yb;
- the same considerations apply for future supply of target material for scandium and terbium radionuclides production (Ca isotopes: ^{44}Ca & ^{46}Ca; Gd isotopes: ^{152}Gd, ^{155}Gd & ^{160}Gd).

Gaseous centrifugation and electromagnetic separation principles

Gaseous centrifugation: Gas enrichment is accomplished by centrifugation and by internal thermal diffusion due to the counter-current motion of the molecules in the centrifuge. The enriched product (lower molecular weight isotopes) and depleted tails (higher molecular weight isotopes) are withdrawn, respectively, by scoops located at the ends of the centrifuge. The process is characterized by large throughput but relatively low separation factors, requiring groups of centrifuges called "stages" to reach high isotopic assays. Since centrifuges have only two output streams, they are best suited for separation of elements with two primary isotopes. Multiple-isotope elements must undergo repeated runs of the product or tails through the centrifuges, in a batch-type process, to separate the middle molecular weight isotopes.

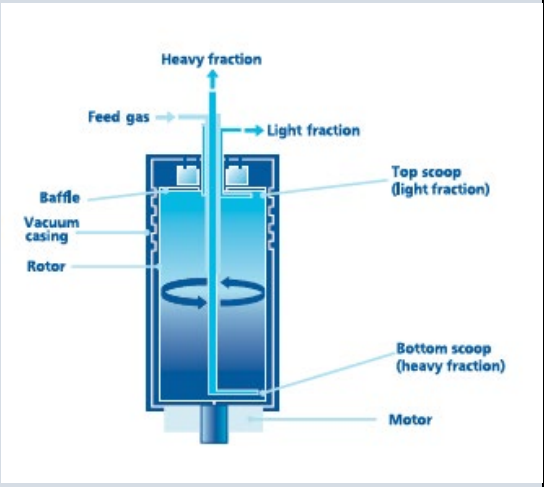


Figure 14: Principle of a gaseous centrifugation cell centrifuge (Courtesy of Urenco)

Source: A Summary of Actinide Enrichment Technologies and Capability Gaps – ORNL 2017

Electromagnetic separation method uses magnetic and electronic forces to manipulate charged isotopic species. In this process a specific source is heated to produce ions flux. The beam of charged particles is passed through a very strong magnetic field. The magnetic field introduces a force on each ion causing it to travel in a circular path, the radius of which is proportional to the momentum of the ion. The heavy ions have a greater momentum than the lighter ions and their beam is bent less than the lighter ions. With a very strong magnetic field there is sufficient beam separation to permit individual collectors to be arranged to accumulate the light and heavy isotopes. Calutrons can separate almost any stable isotope, separate different isotopes simultaneously, and may be used to ionize and separate compounds. However, they remain costly to operate and only relatively small quantities can be produced.

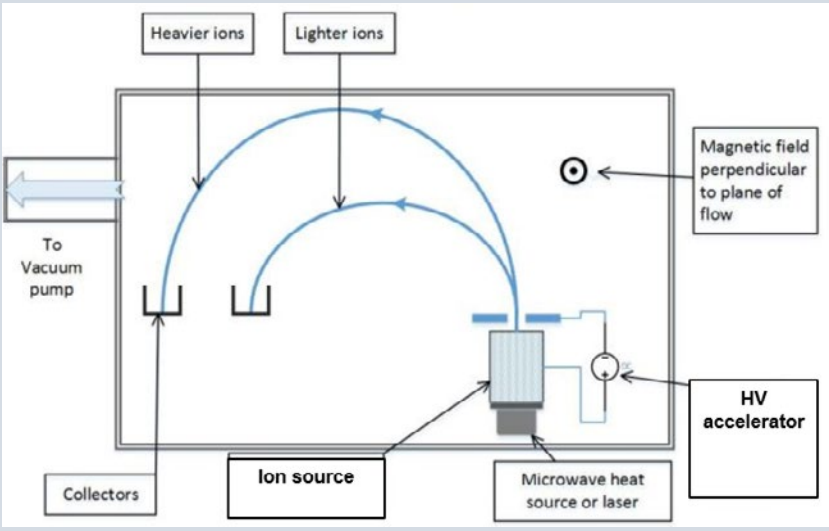


Figure 15: Calutron principle

Source: USNRC Technical Training Center, Uranium enrichment processes module 5.0

EU sustainable supply of ^{18}O is fostered by international competitive environment

Distillation is massively used in the medical field for producing ^{18}O, the base material for ^{18}F. As some limited shortages have been recorded in the past, tensions could nevertheless appear on the market given the developing use of this PET radionuclide. Many processes have been studied in the past to obtain high-purity oxygen isotopes[26] (fractional distillation of water or carbon monoxide, distillation of water combined with thermal diffusion of oxygen gas, cryogenic distillation of nitric oxide and thermal diffusion of oxygen).

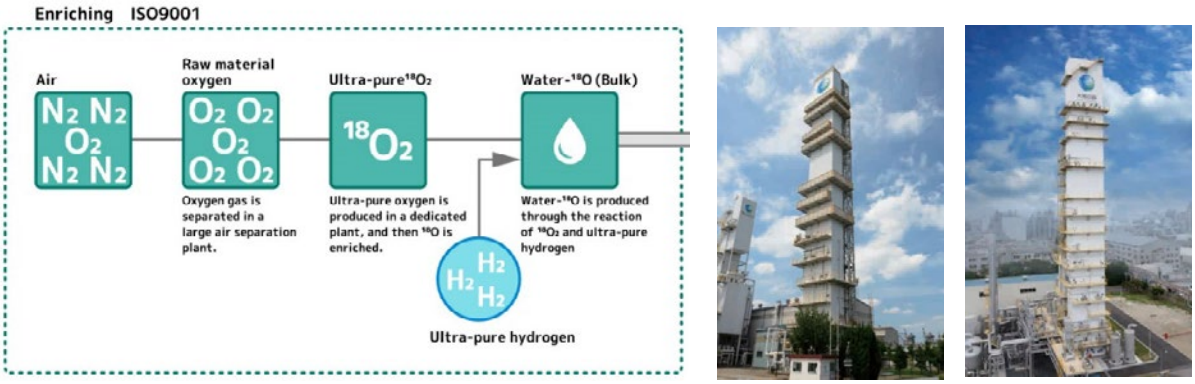


Figure 16: Front-end of ^{18}O manufacturing process (packaging and QA not included) and ^{18}O distillation units 1&2 at Chiba production sites (respectively 100 & 200kg/year). Source: Taiyo Nippon Sanso

2-4 mL of ^{18}O-enriched water are needed per irradiation batch. As opposed to ^{18}F local and regional production, ^{18}O manufacturing is a worldwide competitive market. Production of ^{18}O-enriched water is almost exclusively performed out of Europe, through the standard methods of natural purified water distillation or oxygen distillation. The current worldwide production capacity is estimated at over 2,000 kg/year of oxygen-18 water,[27] the main manufacturers being detailed below. That quantity basically fills the current global needs.

Companies		kg/year
Taiyo Nippon Sanso	Japan	600 [28]
Cambridge Isotope Laboratories Inc	USA	420 [29]
Huayi Isotopes Company	China	150
SRICI	China	100
Center of Molecular Research	Russia	60-80
Klydon	S. Africa	200-230
Marshall Isotopes Ltd	Israel	150
Rotem Industries Ltd	Israel	220-250
Iason GmbH	Austria	*Limited*

Table 12: Worldwide main producers of ^{18}O

The global distribution of oxygen-18 is either ensured by the manufacturer (when locally supplied) or goes through international resellers. Considering that the

[26] "Separation of heavy oxygen isotopes; a survey" (2013) – Gheorghe Vasaru
[27] "Production of stable isotopes of light elements: past, present and future" - A V Khoroshilov 2018
[28] https://www.tn-sanso.co.jp/en/our_technology/water-18o.html on 09/04/2020
[29] "Xenia company's fifth expansion underway" – Dayton Business Journal Apr 16, 2019

installed base of PET cameras in the EU amounts to roughly 900 units (~15% of worldwide 7,500 installed PET cameras[30]), a production capacity of ~300 kg/year of oxygen-18 water would be needed to ensure EU self-reliance in case of external supply deficiencies.

EU current status #2: In the context of an international market with overcapacity, composed of various private industrial players, despite some tensions that have been experienced in the past, the EU's modest needs of ^{18}O (around 15% of global capacity) seem not to be threatened. In the case of a second wave of ^{18}F radiopharmaceuticals use, which would require a large increase in ^{18}O supply, this statement might be revised.

For gaseous centrifugation enriched isotopes, the EU can currently rely on Urenco's installed capacity in the Netherlands

The reference European service provider of stable isotopes enrichment is Urenco.[31] Its catalogue is illustrated below. Urenco's strategy encompasses development of the stable isotope enrichment business from its Dutch base in Almelo.

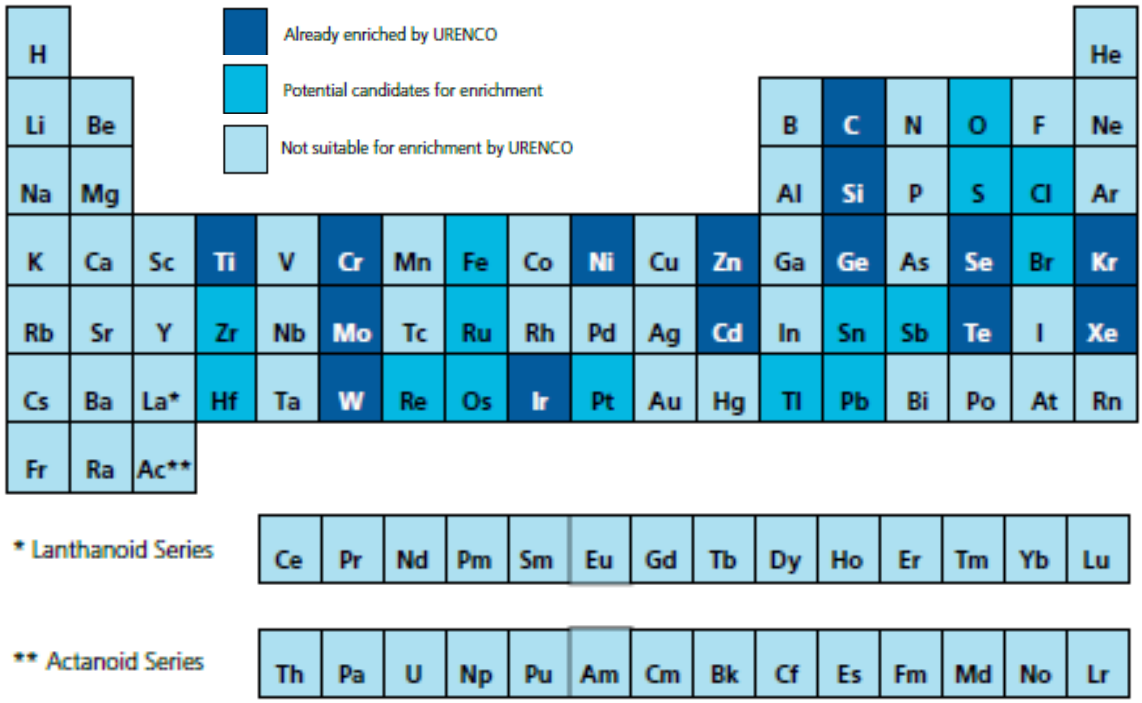


Figure 17: Stable isotopes in the URENCO catalogue (gaseous centrifugation)

The same kind of catalogue exists for the world leader (ECP, Zelenogorsk, Russia). When achievable, centrifuge enrichment is the most cost-effective method for

[30] "How fast will the U.S. market get access to 68Ga?" By Richard Zimmermann and Paul-Emmanuel Goethals – June 2017

[31] Urenco's shares are ultimately held one-third by the UK government (through Enrichment Investments Limited), one-third by the Dutch government (through Ultra-Centrifuge Nederland Limited), and one-third by two German utilities (through a holding company, Uranit UK Limited; shares in its German holding company are indirectly held 50% by E.ON S.E. and 50% by RWE AG).

separating "heavy" isotopes. Gas centrifugation[32] is extensively used for the large quantities market (thousands of kilograms per year, representing a total market of ~25M$), with Russia being the main market player (60%), followed by Urenco (40%) in the EU. Orano has recently announced their ambitions in this domain.

EU current status #3: Urenco is the second-ranking worldwide player in stable isotopes supply. The Russian centrifuge enrichment facility (ECP) has a larger product portfolio than Urenco (roughly 20 products in catalogue). Some stable isotopes not produced in EU by Urenco are thus currently imported (Iron, Tin, Osmium, Lead, Sulphur, etc.) Though Urenco is expected to increase its capacity and product portfolio over the next few years, it is likely that import of Russian isotopes will remain a necessity.

Current reliance on Russian calutrons for electromagnetic enrichment to be solved through innovative and modern technologies (e.g. the ESIPP project from US DOE)

Currently, a semi-industrial operating calutron, started in 1951, exists only in ElektroKhimPribor (EKP) in Lesnoi, Russia. Kurchatov Institute (Moscow) also operates one. These installations are the main global suppliers of ^{176}Yb.

The USA started the development of its own capability in 2009 and put in service its Enriched Stable Isotope Pilot Plant (ESIPP) in Oak Ridge in 2017. ESIPP combines an automated electromagnetic isotope separator (EMIS) and a small cascade of nine gas centrifuge isotope separators (GCIS) that have been specifically designed for stable isotopes. It is also intended to be used for ^{99}Mo production for alternatives routes based on ^{98}Mo and ^{100}Mo (see illustration below).

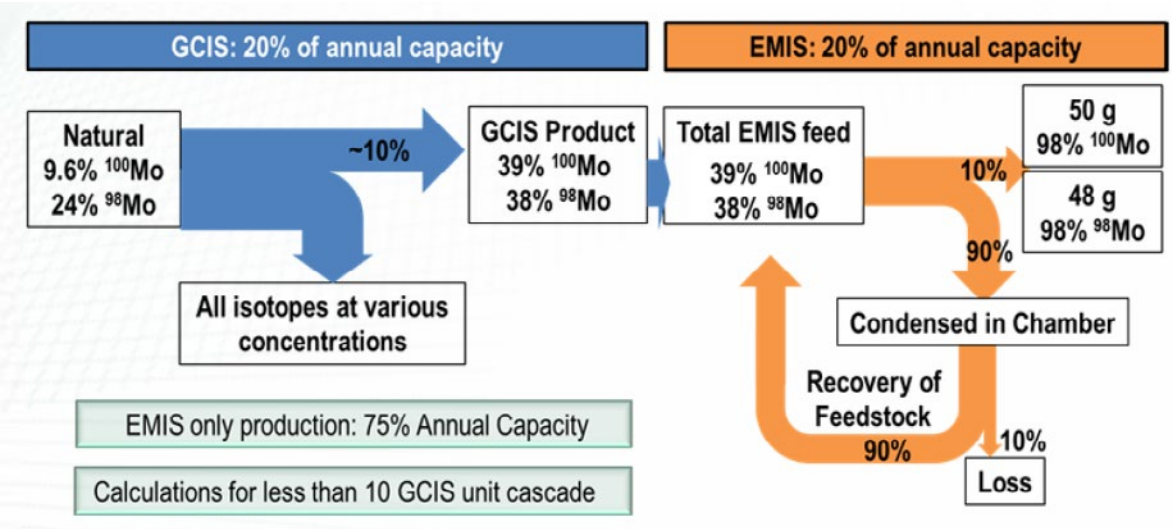


Figure 18: Production principle for enriched ^{98}Mo in ESIPP – Source Enriched Stable Isotope Pilot Plant ORNL/DOE

[32] "Meeting isotope needs and capturing opportunities for the future: the 2015 long range plan for the DOE-NP isotope program" – NSAC isotopes subcommittee – July 2015

Based on the ESIPP technology[33] that successfully produced ^{96}Ru in 2019, the US DOE recently launched[34] the future industrial Stable Isotope Production Facility (SIPF) project in ORNL. The SIPF's forecasted budget is 150-200 MUS$. This expansion of the ESIPP would include three production-class EMIS units and a less than 50-unit gas centrifuge cascade, or two EMIS units and a less than 100-unit gas centrifuge cascade.

Should this project be successful, it will establish a second sustainable worldwide player and mitigate the Russian monopoly.

In Europe, non-industrial scale mass separators exist, together with the necessary design and operation skills,[35] for instance:

- CERN: ISOLDE, MEDICIS
- Leuwen Isotope Separator
- SIDONIE (Orsay).

Future facilities are planned such as the SCK-CEN Proton Target Facility, GSI-FAIR (Germany) and ISOLPHARM (INFN, Italy). The PRISMAS-MAP[36] initiative proposal has been selected for funding in the Horizon 2020 programme, covering targets optimization, mass separation, ion source optimization, etc.

EU current status #4: A bright future is anticipated for NCA ^{177}Lu, as well as for other lanthanides, made credible by the large investments of Big Pharma (Novartis for example). The supply of its target material (enriched ^{176}Yb), already critical, would then be exacerbated, making recycling of the irradiated targets a must.

Russia is currently the main producer of ^{176}Yb for medical uses.
The USA has started to work towards a solution to the enriched isotopes issue with the ESIPP installation. But USDOE's EMIS output is currently very limited (~mg), far from the approximately 1 kg/year of ^{176}Yb produced by Russian players.

The potential future sourcing of enriched isotopes through the American SIPF industrial installation might be considered for a more diversified supply for the EU. But much work remains to provide a second source of supply of ^{176}Yb: no routine industrial supply by DOE is expected before 2030.

If more resilience is desired for the EU in the stable isotopes enrichment domain, an investment in an EMIS facility would be needed (see also §3.1.2.3).

[33] Enriched Stable Isotope Pilot Plant – ORNL brochure
[34] With key isotopes depleted, DOE plans production centre at ORNL – March 2020 – Oak Ridge Today
[35] 30 years ago, IBA designed an EM separator, EMIS250, never build.
[36] PRoduction of ISotopes from MAss Separation for Medical Application, including among others ARRONAX, CERN, GANIL, ILL, INFN SPES, KU Leuven IKS, PSI Radionuclide Development, SCK-CEN Proton Target Facility, TU Darmstadt, University of Greifswald

2.2.3. Irradiation installations targetry

Target systems are key components to any radionuclide production installation and must be optimized against various parameters: sustainability versus impinging particle beams or fluxes, physical integrity, production yield, recycling possibilities for costly target material reuse, expenditures and operational costs, minimization of waste volumes, safety and radiation protection, and other considerations.

Targets are machine-specific and source material-specific as well. In addition, their design, manufacturing, handling and processing directly impact the whole design of the installation (layout, supporting systems).

For maximizing production yields, designers continuously increase machine performances. Consequently, targets design becomes more and more difficult.

2.2.3.1. *Targets for accelerators - general*

Targets design optimization is an especially complex task for accelerators, with many important variables, among which:

- target nature (liquid, gas, solid),
- window material (separating the accelerator vacuum of the incoming beam from the target), strippers, etc.,
- target backing material, which must be as inert as possible in order not to generate impurities, but must be resistant enough to sustain the impinging beam,
- source material and its manufacturing/deposition techniques, which must ensure uniform spread on the target, stability under irradiation, appropriate thermal conductivity, and as high a density as possible in order to maximize the production yield,
- geometrical shapes (e. g. angle with incident beam, target form and dimensions),
- cooling system,
- handling system,
- radioprotection.

Developing cost-effective efficient targets requires finding the best balance among all these parameters through extensive testing. In an extreme installation such as the CERN, instant power on the targets may reach 1 GW. Targets are generally designed in a customized manner by each manufacturer of the commercial machines, or by the technology departments of the research centres operating large installations.

2.2.3.2. *Targets for small medical cyclotrons (SMCs)*

In cyclotrons, liquid or solid targets can be used. Their relative merits are summarized below.

	Solid targets	Liquid/gaseous targets
Target material nature	Solid targets are mostly used for medium/high atomic weight radionuclides (especially metals). Solid targets are currently used for ^{123}I, ^{89}Zr, ^{111}In, ^{64}Cu production (and ^{99}Mo, ^{177}Lu production in reactors, etc.)	Liquid targets are mainly used for low atomic weight target elements in their natural chemical form (^{18}O)
Production yields	Solid targets allow high-level production yields, compatible with industrial production, through high beam currents (up to hundreds of µA), with higher target material target densities.	Liquid and gaseous targets yields are more limited, due to lower density of target material and beam current limitations (<100-150µA).
Pre/Post irradiation specificities	Solid targets necessitate more complex operations/systems for the preparation of the backing support, the post-irradiation handling, transport and dissolution of the irradiated solid target and activated backing support, and recovery (if needed) of expensive enriched target material. Their use is reserved for industrial installations.	Most of existing hospital-based cyclotrons (SMCs) are equipped with liquid/gaseous targets for ^{18}F production. Production processes are largely automatized. Targets are generally rapidly and remotely transported and deliver the produced radionuclide in a more convenient chemical state.
Retrofitting	n.a.	Upgrade from liquid to solid targets is not feasible for most SMC production centres.

Table 13: Comparison table between solid and liquid/gaseous target specificities

In summary, unlike liquid targets, solid ones require more complex equipment and supporting systems leading to higher investment and operational costs, but they are best suited to industrial production owing to higher yields. As such, they are best suited to centralised cyclotron commercial networks, which can afford the necessary supporting systems.

Despite their inherently lower production yields, liquid targets allow for production of small radionuclides batches (mainly ^{18}F), automatized to a large extent, sufficient for local hospital or research needs, produced in small decentralised cyclotrons. Due to lack of space in the "self-shielded" cyclotrons layouts (the majority of SMCs), and costs of new investments, implementation of a solid target production line in SMCs currently equipped with liquid targets is often difficult, when not impossible.

EU current status #5: The type of targets used for radionuclide production in cyclotrons has a strong impact on yields and production costs. While solid targets are better suited to industrial production (higher yields), liquid ones present more interest in research and decentralized hospitals with limited sourcing possibilities, allowing for easier and less complex manufacturing, at the cost of lower yields.

As retrofitting of existing SMCs from liquid to solid target production may be very difficult when not impossible, the development of liquid target systems could foster radiometal production in small decentralised cyclotrons, but for productions limited to local hospital/university needs.

Such liquid targets necessitate R&D efforts, which are generally undertaken by the cyclotron manufacturers. (See for instance a development for ^{68}Ga production[37] - An example of ^{68}Ga direct production through liquid or solid target is detailed in Annex 3 – §A.3.2.)

2.2.3.3. *Targets for photonuclear reactions*

The photonuclear reaction is envisaged in the NorthStar, Niowave, and Lighthouse projects. It is also envisaged for ^{225}Ac production with ^{226}Ra targets.

The NorthStar project is detailed in the "Irradiation Installations", section 2.2.4.5 below.

If IBA's Rhodotron®, on which Northstar is based, is rather a mature technology, such is not the case for the targets needed in this installation. Its layout raises issues as well, due to radioprotection impacts of high gamma fluxes. Los Alamos and Argonne National Laboratory have strongly supported the development of the NorthStar concept in several domains illustrated below:

- Materials tests and selection for the converter and the targets;

- Targets detailed design;

[37] IBA's Radiopharma Solutions newsletter N°21- Spring 2019. Production of ^{68}Ga from a liquid target would enable radiopharmacies to produce the isotope locally. Process is similar to ^{18}F production allowing for [^{68}Ga]$GaCl_3$ ready for labelling with cold kits or in synthesis modules.

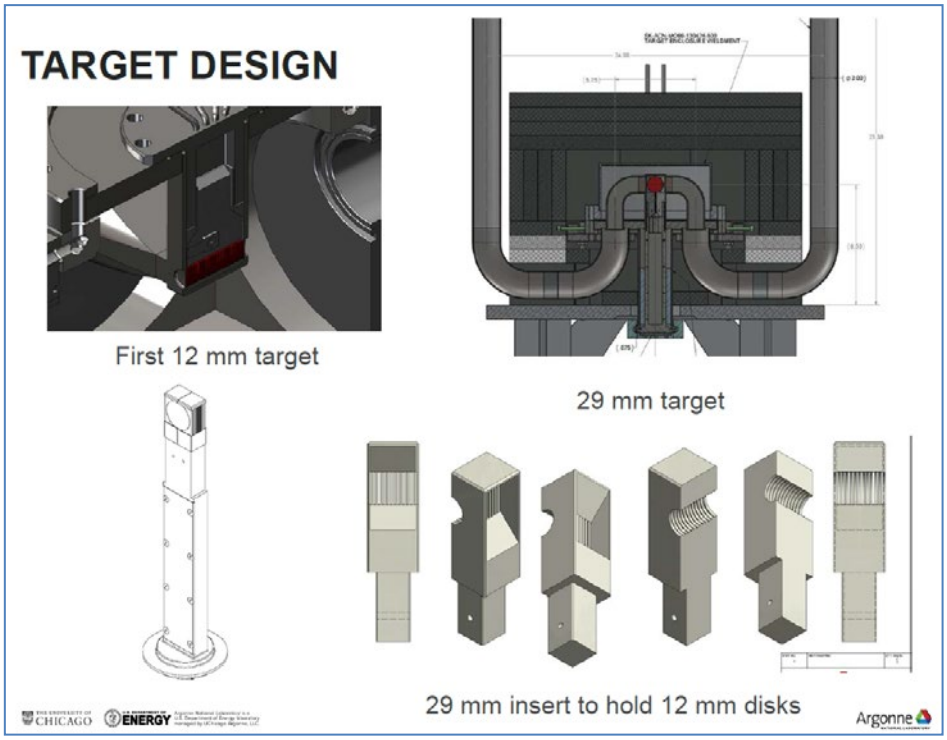


Figure 19: Target studies at Argonne[38] for the NorthStar installation

- Targets cooling system design: closed loop pressurized helium;

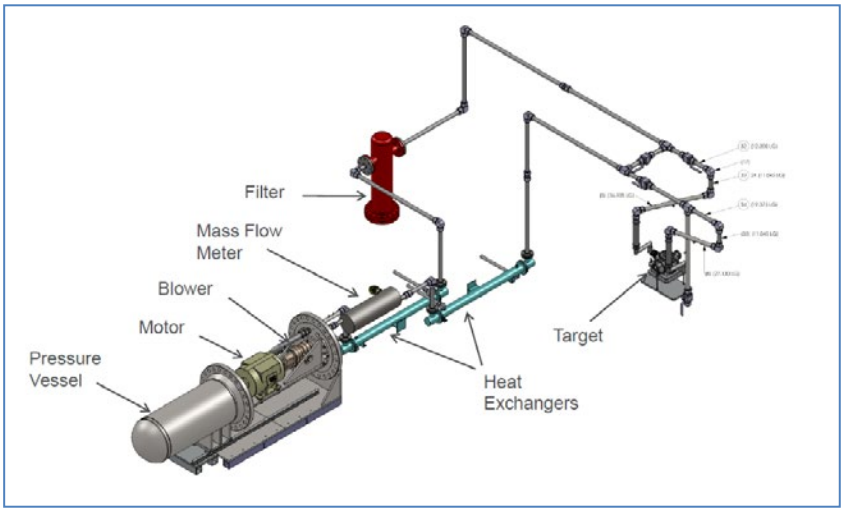


Figure 20: He cooling system for the NorthStar production cell

- Targets impurities content: the high-energy electron beam necessary for achieving appropriate production yields also leads to other photonuclear reactions creating undesirable impurities such as long-lived ^{95}Zr and ^{95}Nb among others. The level of impurities introduced during ^{100}Mo recycling is thus to be controlled;

[38] Accelerator-based production of Mo-99: photonuclear approach. Sergey Chemerisov et al. September 26, 2018, Knoxville, TN, Mo-99 Topical meeting

- Plant layout, as described in the "Irradiation Installations" section 2.2.4 below.

The NorthStar example illustrates that promising, laboratory-scale, production reactions raise delicate questions requiring extensive R&D efforts when it comes to industrialization and increase of production yields.

2.2.3.4. *^{226}Ra Targets for ^{225}Ac production*

^{225}Ac can be produced through ^{226}Ra(p,2n)^{225}Ac and ^{226}Ra(γ,n)^{225}Ra reactions, using ^{226}Ra targets. ^{226}Ra targets have the greatest potential for ^{225}Ac production per gram of target material, which justifies the interest of studying these routes.

However, ^{226}Ra raises significant challenges due to the availability of the material as well as safety hazards that complicate target manufacturing, irradiation, processing, and recycling: ^{226}Ra is highly radiotoxic, reactive with water and air, and decays to the alpha-emitting ^{222}Rn gas, through five alpha decays.

Accordingly, this production route would require infrastructures that are beyond what is typically used to make medical nuclide production targets.

Like the former example, this one shows that the industrialization of promising lab-scale reactions raises delicate problems, which often require costly solutions, and may impede the industrial development of a promising radionuclide, at least in decentralized, local, production schemes.

2.2.3.5. *Targets for research or accelerator-driven reactors*

Targets for research or accelerator-driven reactors (using mainly (n,γ) production reactions) are generally easier to design than ones for accelerators, because the incident power needed for a given production yield (kW/cm^2) is generally lower.

Mass production of fission products like ^{99}Mo currently uses LEU targets. For solid targets, their design is directly derived from the fuel design. These targets are mainly developed and manufactured by CERCA, a French company, which is the global leader. Their advantages and drawbacks (mass production vs. waste generation, HALEU availability) are discussed in section 2.2.4.3 below.

For other nuclides, targets can be in various forms. For instance, $^{176}Yb_2O_3$ powder is sealed into aluminium cans, which can be directly irradiated for ^{177}Lu NCA production in irradiation rigs handled manually by operators, or remotely operated owing to "rabbit" pneumatic systems. Other nuclides can be irradiated in polyethylene cans.

Targets can also be in a liquid form, as in the SHINE design, were uranium nuclei (uranyl sulfate solution) are submitted to a neutron flux stemming from an UO_2 neutron multiplier seed surrounding a fast neutron fusion source, triggered by a deuterons beam impinging a gaseous tritium target.

EU current status #6: Targets are a key element in any nuclide supply chain; they are nuclide- and machine-specific, and their design is a balance among many parameters. Targets directly impact production yields, the entire surrounding installation and finally the costs of goods produced.

Cost-effective availability of targets is a critical condition on the path to industrialization of any new nuclide.

Enough promising R&D results and promising commercial demand must exist for launching such target optimization development programs. These programs are generally undertaken by the machine manufacturers and/or the technology departments of research centres. Best-in-class manufacturers and research centres are available in Europe.

2.2.4. Irradiation installations

2.2.4.1. *Introduction*

Irradiation installations are designed for transmuting target nuclei into the desired radionuclides, by submitting targets to impinging beams or fluxes (α, electrons, neutrons, other charged particles) which trigger various fusion, fission, activation, spallation or photonuclear reactions. Thus irradiation installations are of various types, as illustrated in the following table, gathering examples of installations and technologies already operational along with projects under development.

Irradiation means	Examples	Beam(s) type and energy	Main radionuclides produced	Status
Small Medical Cyclotrons (SMC)	Hospitals, academic, industrial commercial network	proton (p) *up to 20MeV*	Light elements (^{18}F, ^{15}O…) and potential future production of ^{68}Ga, ^{64}Cu, ^{89}Zr; ^{99m}Tc…	Operating
Medium-Energy Cyclotrons (MEC)	Academic, industrial commercial installations	proton (p) *15-30MeV* deuteron (d) *8-15MeV* alpha (α) *30MeV*	^{68}Ge, ^{111}In, ^{123}I, ^{201}Tl, ^{211}At… in addition to SMC ones *(see figures 19-20)*	Operating
Large research cyclotrons (High-Energy Accelerators HEA)	Arronax (France)	proton (p) *30-70MeV* deuteron (d) *15-35MeV* alpha (α) *70MeV*	^{82}Sr, ^{64}Cu, ^{67}Cu, ^{211}At, ^{44}Sc…	Operating
	PSI (Germany) Injector-2 cyclotron	proton (p) *72MeV*		Operating
	SPES/Laramed + Isolpharm (Italy)	proton (p) *35-70MeV*	Similar to Arronax with also $^{52/51}$Mn	Project
Large linear accelerators (LINAC) (High-Energy Accelerators HEA)	MEDICIS-ISOLDE (Switzerland)	proton (p) *up to 1,4GeV*	1,000+ isotopes of 70+ chemical elements can be obtained (ISOL). Modest Production yields	Operating
	ISAC (Canada)	proton (p) *up to 480MeV*	No current focus on radionuclide production	Operating
	MINERVA (Myrrha Belgium)	proton (p) *up to 100MeV*		Project
	FAIR-GSI (Germany)	proton (p) *up to 70MeV*		Project
	ESS (Sweden)	proton (p) *up to 2GeV*		Project
	IFMIF	deuteron (d)		Project
Electron beam accelerators	CII (Canada) 2 LINAC	gamma (γ) *up to 40MeV*	Focused on ^{99}Mo production	Operating
	NorthStar (USA) 2 Rhodotrons	gamma (γ) *up to 40MeV*		Project (2021)
	Lighthouse/SMART	gamma (γ) *up to 70MeV*		Project (2028)
Research reactors	BR2, HFR, ILL, FRM-II, MURR, JHR, TRIGA, …	neutron (n)	^{99}Mo, ^{177}Lu, ^{60}Co, ^{125}I, ^{131}I… *(see figures 19-20)*	Operating
Power reactors	Candu	neutron (n)	^{60}Co and perhaps ^{99}Mo, ^{177}Lu in the future	Operating
LINAC with induced neutron production	SHINE	neutron (n) *fast fusion neutrons*	^{99}Mo and other fission products (see §2.2.3.5)	Project (2021)
	Sorgentina (NSFS)	neutron (n) *fast neutrons*	Focused on ^{99}Mo production	Project (lab scale)

Table 14: Different types of irradiation means and installations

Besides cyclotrons and research reactors, new projects dedicated to isotope production are ongoing, close to construction completion (e. g. NorthStar, Shine) or at an earlier stage. The first projects involving innovative technologies have been launched in the USA, as early as 10 years ago, for coping with the US's ^{99}Mo dependence on foreign production, aggravated by the perspective of the Canadian NRU reactor shutdown. As a result, these projects are currently mainly oriented towards ^{99}Mo production.

Side objectives were targeted as well by the USA: eliminate needs for HEU in research reactors, reduce waste, try to reach industrial scale production without the public subsidies on which research reactors CAPEX and OPEX are generally based (i.e. achieve "full cost recovery"). The US projects were/are nevertheless strongly supported by the Federal government (see appendix G).

For the time being, the mass-production workhorses are i) small medical cyclotrons, ii) medium-sized cyclotrons and iii) mass-producing research reactors, supplemented by iv) research installations generally supplying the rarer nuclides needed for R&D, and able to back up the other production installations to a limited extent.

However, not all these installations are able to produce all the necessary isotopes, as shown below, for imaging radionuclides (Figure 21) and therapeutic radionuclides (Figure 22).

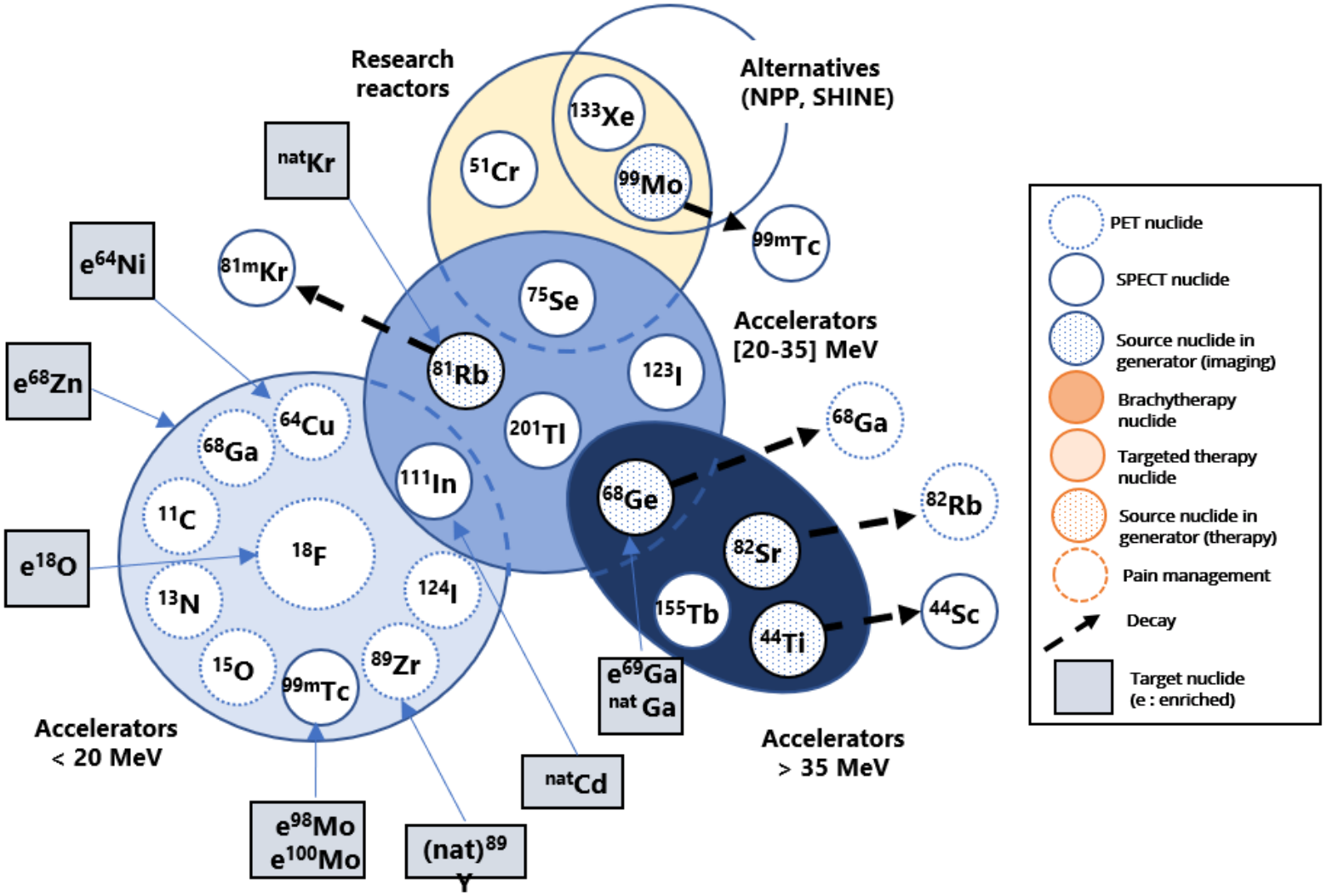


Figure 21: Summary of industrialized production routes for imaging radionuclides

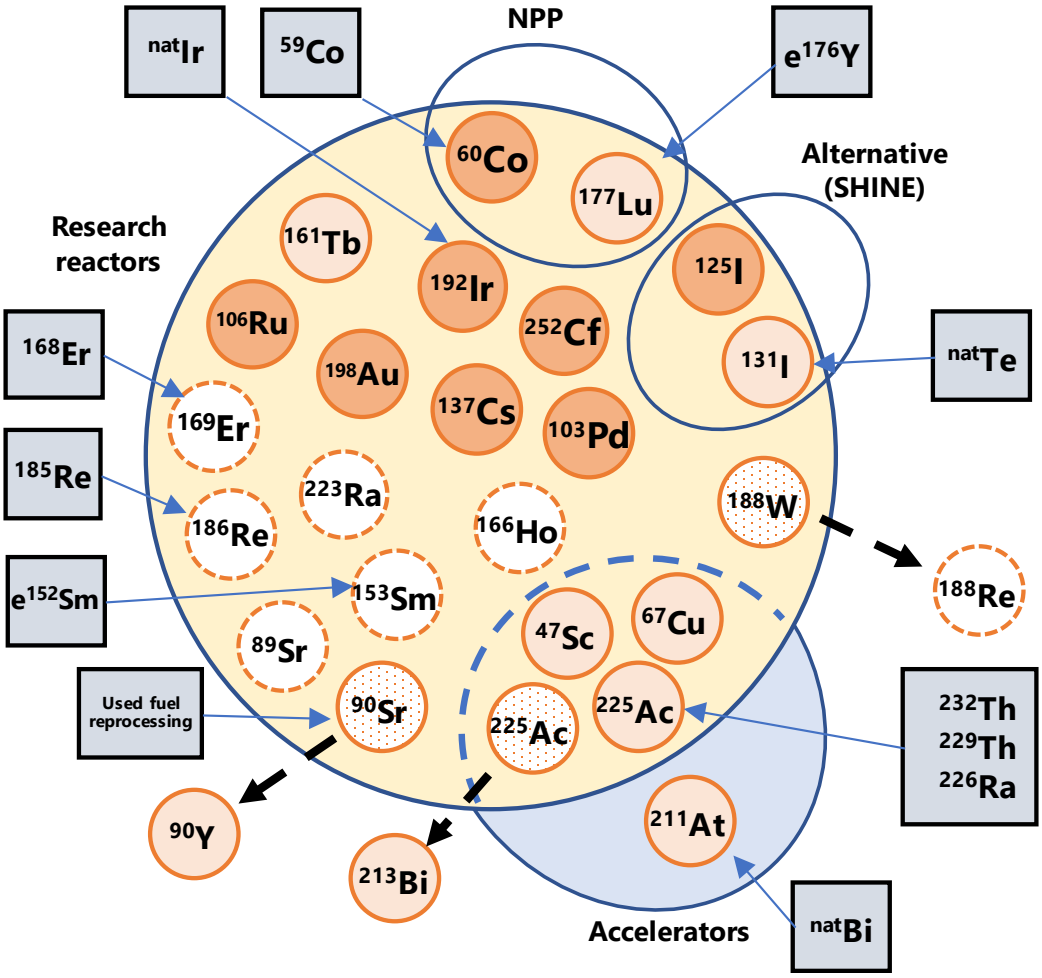


Figure 22: Summary of industrialized production routes for therapeutic radionuclides

The manufacturing routes, the irradiation technologies and the intrinsic characteristics of a radionuclide directly impact each RN accessible market: either local, regional or international/global.

From an EU perspective, keeping installations with local/regional outputs is mandatory for maintaining supply capacity of certain isotopes, whereas there is a risk/opportunity for installations with international export capacity to disappear from the EU if there is strong international competition. The next figure provides a summary of the existing supply chains that can already be found in the EU (upper part) for on-use RN, depending on the accessible market of the manufacturing route (local, regional or fully centralized). The lower part lists all the radionuclides without existing commercial manufacturing routes, for which developments are ongoing for setting up new radionuclide industrial production (^{64}Cu, ^{225}Ac, etc.) or replacing existing supply chains (direct production of ^{99m}Tc, ^{68}Ga, etc.)

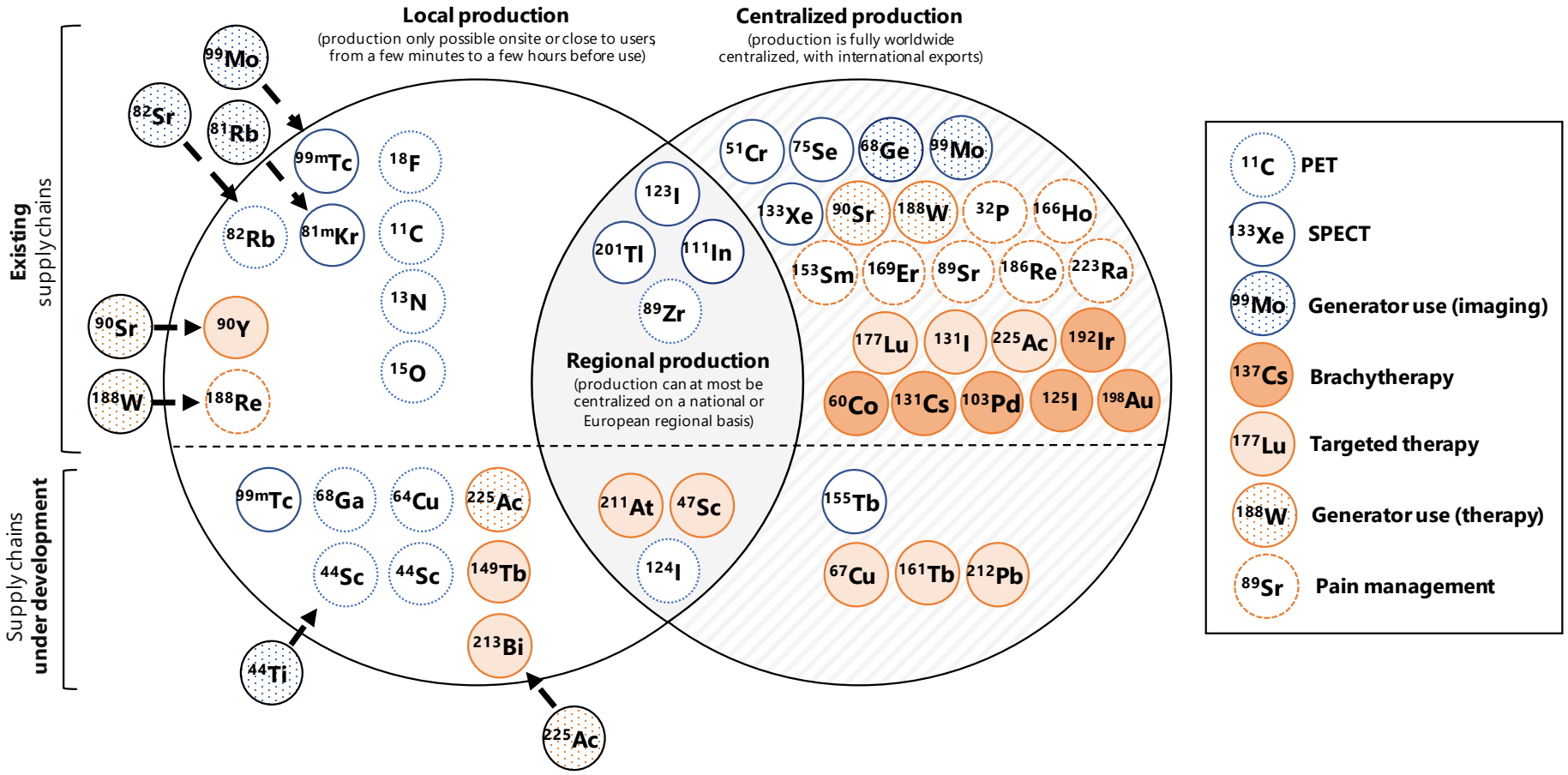


Figure 23: Summary of existing/future supply chains to be secured, according to their supply models: local, regional or centralized

EU current status #7: The current production capabilities of cyclotrons and research reactors are depicted in the figures 21 to 23. The two imaging workhorses, ^{18}F for PET and ^{99m}Tc for SPECT, are respectively produced in cyclotrons and reactors, whereas a majority of the therapeutics radionuclides are produced in reactors.

With regard to a diversified supply for all isotopes, the situation in Europe is currently very favourable, with adequate production capabilities for small and medium cyclotrons, large research accelerators and research reactors. Such balance of the installed production base is currently a guarantee of a sustainable medical radionuclides supply.

Advantages and drawbacks of the diverse irradiation installations – operating, under construction or planned –, as well as the future challenges they raise in Europe, are successively discussed in the following paragraphs:

- small medical cyclotrons and medium-energy ones
- research reactors
- alternative concepts under construction or planned.

2.2.4.2. *Small and Medium-Size Cyclotrons (SMC and MEC)*

Cyclotron applications and specificities for radionuclide production

Different kinds of cyclotrons are used for radionuclide production, as detailed in Figure 21, ranging from small medical cyclotrons (SMCs) for PET-nuclides production, to medium-energy cyclotrons (MEC) with higher energy (30 to 40 MeV) and much higher currents (1,000 µA as compared to a few hundred µA for SMCs). SMCs use liquid targets with limited yields, as compared to solid targets used by MECs, providing higher yields. The specificities and installed bases of both types are discussed hereafter.

Cyclotrons are industrial equipment with intrinsic technical and operational specificities limiting radionuclide production. For SMCs, irradiation parameters are generally optimized for a specific cyclotron baseload use (type of particles, beam energy, current (µA), etc.) and cannot be significantly changed without investments for revamping or renewal. This ultimately limits the versatility[39] of a given optimized machine. Side-production remains nevertheless achievable through various adaptations (e. g. filters for reducing beam energy, multiple beam lines).

SMCs are generally used in locally or in national or European clusters (see cyclotron installed base below), established close to main users, thus limiting decay losses for short half-life radionuclides, while MECs are more centralized.

Due to the short half-life of various PET radionuclides, cyclotron production facilities are generally established inside or in the periphery of large cities with high PET-camera density, allowing for a just-in-time delivery scheme. Doses are generally shipped at up to six hours' distribution distance. The existence of a dense cyclotron network has been, and remains, an important prerequisite to PET imaging development. Multiple cyclotron-based radionuclide production centres (generally including radiopharmaceutical production) are still needed to cover European needs. Despite a low unit cost per installation (up to a few tens of M€ per site for medium-energy cyclotrons), such deployment at the EU scale necessitated, and continues to necessitate large investments over multiple years.

As described in Figure 21, cyclotrons are largely used for the production of a wide range of radionuclides through proton excitation, with a strong focus on imaging ones.

- PET nuclides: almost all the positron emitters are usually produced via reactions involving accelerated protons at relatively low energies, below 15–20 MeV. This less demanding requirement significantly stimulated the

[39] Ability to produce at an industrial scale different radionuclides through a single equipment, ideally on a simultaneous basis like in research reactors

development of small compact cyclotrons dedicated to the production of ^{18}F, ^{11}C, ^{13}N and ^{15}O.

- SPECT nuclides used at an industrial scale, like ^{111}In, ^{123}I and ^{201}Tl: this production necessitates cyclotrons with beam energies higher than 20 MeV and up to 40 MeV. This would also be the case for producing adequately, through proton irradiation, ^{68}Ga (via $^{68}Ge/^{68}Ga$ generators) or ^{82}Rb (via $^{82}Sr/^{82}Rb$ generators).

- Cyclotrons are also well adapted for producing small-scale quantities for research purposes. For instance, products based on ^{225}Ac (via ^{226}Ra-route), or ^{44}Sc, ^{45}Ti, ^{47}Sc, ^{52}Mn, ^{52}Fe, ^{61}Cu, ^{55}Co, ^{67}Cu, ^{186}Re, ^{211}At can be studied, even if the appropriate targetry, processing/separation and R&D of pharmaceutical potential carriers are sometimes not yet at hand or incompletely developed. Indeed, in addition to widespread cyclotrons, few cyclotrons can also deliver higher beam energies or unusual beam particles (deuterium, alpha particles or even ^{3}He ions) for specific radionuclides production, such as ^{211}At, which requires 29 MeV alpha particles.

EU small and medium cyclotrons installed base

As of 2020, the latest estimates encompassed around 1,500 cyclotrons units[40] worldwide dedicated to the production of medical radionuclides. Cyclotrons are of all types, sizes and power levels: from small self-shielded compact solutions equipped with proton beam of a few MeV to larger research installations.

Inside the EU, there are currently ~240 cyclotrons in operation, the vast majority being small medical cyclotrons:

- small medical cyclotrons:
    - with power below 12 MeV: 60 units used for limited local PET radionuclide production;
    - with power between 12 to 20 MeV : ~160 units in EU, 2/3rd of the installed base;
- medium-energy ones (>20 MeV, around 20 units) are owned by industrial players for centralized production of less-used radionuclides (e. g. ^{123}I, ^{201}Tl).

[40] "Cyclotrons used in Nuclear Medicine Report & Directory, Edition 2020" - MEDraysintell to identify as many as 1,484 cyclotrons dedicated to the production of medical radionuclides installed worldwide. The global cyclotron market was valued at more than $180 million in 2019. The top three main suppliers of cyclotrons do share almost 70 percent of the world market installed base (in units), and some newcomers entered the market recently.

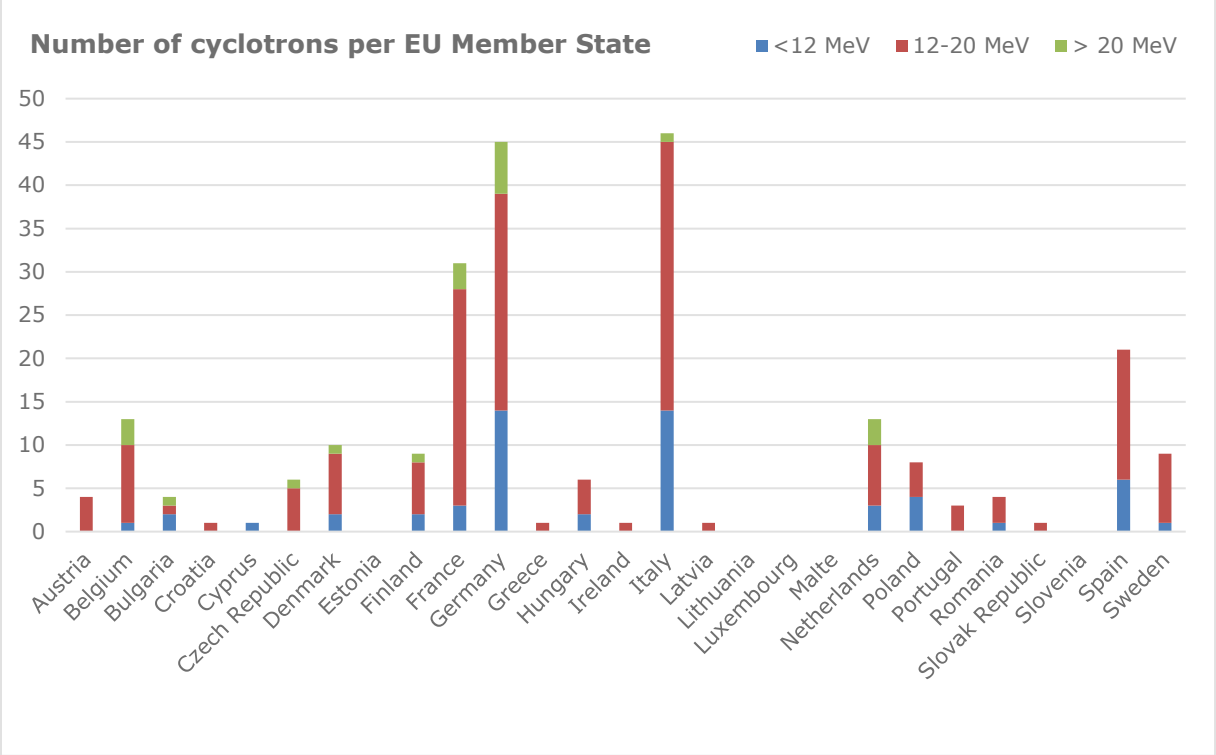


Figure 24: Cyclotron distribution over EU – Source IAEA[41]

The European cyclotron installed base is mature enough to cope with current PET and non-^{99}Mo SPECT radiopharmaceuticals needs (see §2.1). The market for new cyclotron facilities has been somewhat limited in Europe during recent years and has mainly been linked to proton therapy development.[42]

Aside from the standard industrial and medical constraints that directly impact the way cyclotrons are built and operated (proximity to the users, use of existing nuclear and cyclotron facilities, etc.), the European cyclotron network has been shaped according to multiple country specificities (national regulations for production and use of radiopharmaceuticals, national investment strategies for development of PET).

Accordingly, diverse MS-specific cyclotron ownership and operating structures can be observed in the EU, from fully centralized industrial production to onsite hospital production. Hospital-based production is most widely found in Northern Europe (Sweden, Finland, Denmark), Eastern Europe (Bulgaria, Hungary, Romania) and Germany. Industrial production is the standard in France, Spain, Netherlands, Austria, etc. Nevertheless, some countries tend towards a balanced situation (like Italy), with both industrial and hospital-based production. On rare occasions, public-private partnerships are implemented, with an industrial player in charge of hospital-based cyclotron operation (10-20 sites in the EU).

[41] Database of cyclotrons for radionuclide production – IAEA 2020
https://nucleus.iaea.org/sites/accelerators/Pages/Cyclotron.aspx
[42] https://www.ptcog.ch/index.php/facilities-in-operation

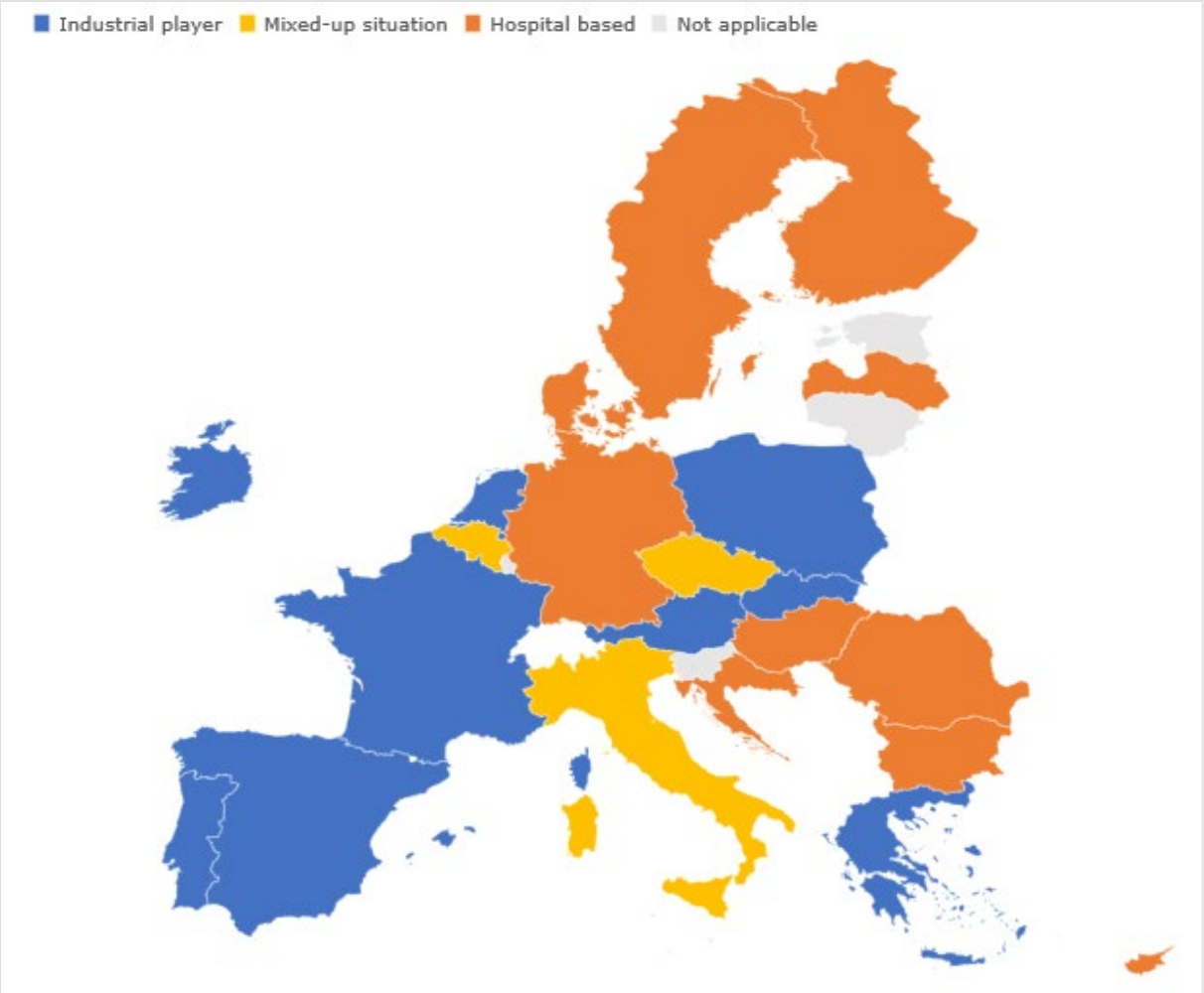


Figure 25: Structure of EU cyclotron network per Member State – Source NucAdvisor

Hospital-based cyclotrons (SMC)

With the rising interest for PET imaging, cyclotrons have been implemented inside hospitals, universities and research centres (~60% of EU cyclotrons, about 100 units). With more and more hospitals now being equipped with radionuclide production means (cyclotrons and associated processing facilities), the nuclear medicine departments in these MS have become self-sufficient for local production. Depending upon national regulation, these sites can also sometimes be licensed for offsite delivery or can directly deliver RP without restrictions to other radiopharmacies in their vicinity (e.g. German regulation).

Some cyclotrons have also been established in Universities or research centres and directly contribute to radionuclide production in addition to research applications. Roughly 50 such units exist in the EU.

Industrial cyclotrons (SMC and MEC)

Industry has played a large role in developing PET imaging in the EU, with investments in dedicated cyclotron installations generally located close to large cities and able to deliver RP doses to multiple radiopharmacies. More than one third of EU cyclotrons are owned by industrial players (~90 cyclotrons), the main ones relying on large networks such as Curium (26 sites across EU,[43] with locations in France, Spain, Italy and Finland) or AAA/Novartis (15 PET production centres across EU[44]); other players have more limited networks (e. g. Synektik, Monrol). National companies or small cyclotron networks (a few units) are tending to disappear, taken over by larger industrial groups.

Outputs of industrial installations are generally higher than hospital-based cyclotrons (more batches per day, higher yields per batch due to higher energy/current cyclotrons…) and produce the largest share of RPs in the EU. Out of the 240 cyclotrons in operation in the EU, ~100 of them are located in hospitals while the number of PET imaging centres in the EU can be estimated at more than 500.[45] Each of the 90 industrial cyclotrons thus supplies 3-4 radiopharmacies on average. Whereas three cyclotrons are installed in Portugal in two hospitals, they only produce 10% of FDG doses used in the country. Most of the production is done in Spain by a single private-owned cyclotron (~90% market share, delivering doses to 7 hospitals[46]).

[43] Press release - "Curium Acquires Finnish Radiopharmaceuticals Company MAP Medical Technologies Oy" (London and Paris – December 02, 2019)
[44] Press release - "Advanced Accelerator Applications and Blue Earth Diagnostics Announce European Manufacturing and Distribution Agreements for Axumin™ (Fluciclovine (18F)) for PET Imaging of Recurrent Prostate Cancer," 30th May 2017
[45] Based on Eurostat statistics, ~1,000 PET scanners can be numbered in EU, considering an average of 2 PET scanners per imaging centre or ~500 PET imaging centres
[46] Instituto Tecnologico PET website http://www.petmadrid.com/ingles/lab/cproduccion.html

Cyclotrons distribution over EU

Despite the fact that European cyclotron networks are able to cover Member States' overall current needs, discrepancies can be observed in the installed capacity. Northern and Western Europe equipment ratios PMP are larger than in Eastern Europe, in line with current nuclear medicine examinations statistics[47].

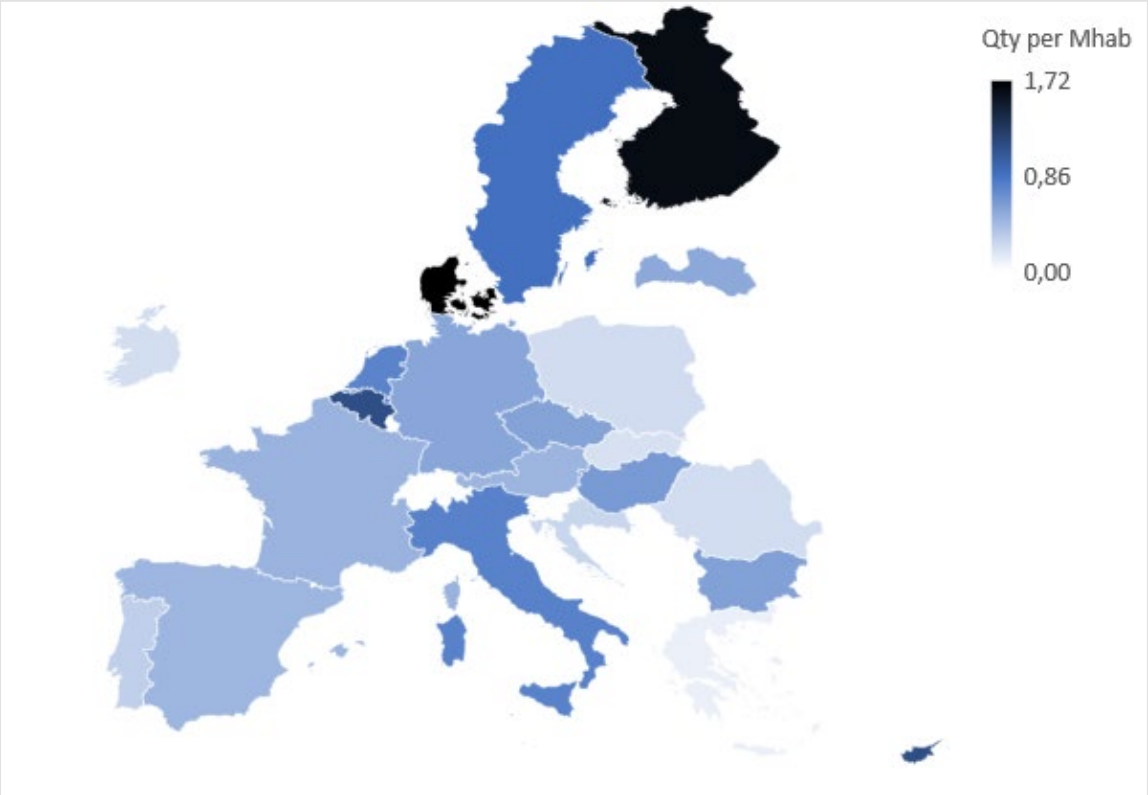


Figure 26: Cyclotron distribution in EU per million people - Source IAEA

The majority of the SMCs installed in Europe were manufactured by four companies: General Electric Healthcare (GE Healthcare), Ion Beam Applications (IBA), Siemens and Advanced Cyclotron Systems Incorporated (ACSI).

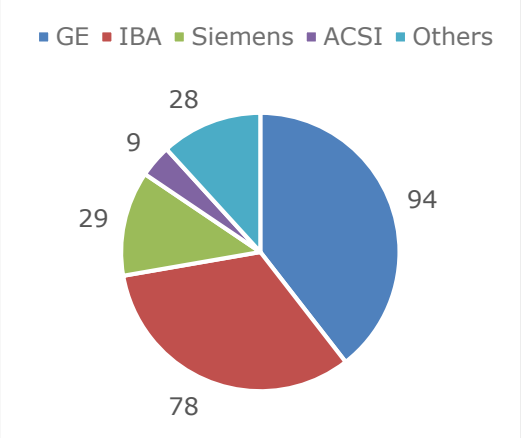


Figure 27: EU cyclotron breakdown (number of units) per manufacturer

[47] SAMIRA 2019 study: European Study on Medical, Industrial and Research Applications of Nuclear and Radiation Technology. Final Report. Contract ENER/17/NUCL/SI2.755660. MJ-03-19-070-EN-N

EU's cyclotrons fleet foreseeable evolution

While cyclotrons' current European fleet fulfils current European needs, cyclotron production is expected to grow in the future, due to:

- the continuous growth of ^{18}F use observed within the last decade, and the development of new ^{18}F-labelled radiopharmaceuticals;
- the recent promising development opportunities of several new cyclotron-produced radionuclides (positron emitters such as ^{64}Cu, ^{86}Y and ^{124}I, or some therapeutic radionuclides, at a local level);
- the potential development of alternative production routes based on cyclotrons (alternative to reactor-produced ^{99}Mo/^{99m}Tc generators via ^{100}Mo bombardment with protons or direct production of ^{68}Ga at a local level via proton irradiation of ^{68}Zn).

Different scenarios can be foreseen to cope with this increasing demand, from retrofitting a portion of existing medical cyclotrons to new investments, particularly in new MEC machines.

The direct ^{99m}Tc cyclotron-production, via the ^{100}Mo(p,2n)^{99m}Tc route promoted in Canada, is deemed inappropriate for covering European needs (see §2.2.4.5).

The need for a medium-energy cyclotron (MEC) network

A network of cyclotrons with higher beam energies and intensities, able also to provide other particles than protons, is needed to envisage a sustainable production in the EU of some very specific radionuclides.

Three examples are given illustrating the radionuclide production application of cyclotrons with medium/high energy beams and less common particle beams (alpha, deuterium, electron, etc.). An exhaustive view of MEC applications can be found in §2.1.

<u>30 MeV α-beam cyclotron for ^{211}At production</u>

^{211}At is produced in cyclotrons equipped with up to 30MeV α-beams (see Annex 15). ^{211}At is currently in its R&D phase, and the current production levels are sufficient for R&D needs, according to an overview[48] of the worldwide facilities equipped with such machines, dated early 2020.

[48] "Realizing Clinical Trials with Astatine-211: The Chemistry Infrastructure" – Cancer biotherapy and radiopharmaceuticals Volume 35, Number 2, 2020

The current European installations equipped with cyclotrons able to produce ^{211}At are described below.[49] In total, 12 sites in Europe could supply radionuclides for research needs in the next decade.

Location	Institute	Cyclotron Model
Copenhagen, Denmark	Copenhagen University Hospital	MC-32 Scanditronix
Oslo, Norway	University of Oslo	MC-35 Scanditronix
Nantes, France	Arronax	Cyclone 70, IBA
Orléans, France	CNRS—CEMHTI laboratory	THOMSON-CSF
Rez, Czech Republic	Czech Academy of Sciences	U-120M
Warsaw, Poland	University of Warsaw	U200-P *(planned)*
Cracow, Poland	IFJ-PAN Cyclotron Centre Bronowice	AIC-144
Groningen, The Netherlands	University of Groeningen	AGOR cyclotron
Birmingham, UK	University of Birmingham	MC-40 Scanditronix
Jyvaskyla, Finland	University of Jyväskylä	AVF K130
Brussels, Belgium	VUB	CGR-MeV model 560
Jülich, Germany	Forschungszentrum Jülich	Cyclone 30 XP, IBA

Table 15: Facilities with cyclotrons capable of producing ^{211}At

Among these installations only two produce ^{211}At on a regular basis: the Copenhagen University Hospital and Arronax in France. The situation is similar worldwide, with only two sites in the US, two in Russia and five in Japan. Hence, if ^{211}At reaches its industrial phase (beyond 2030, given the timeframe of a typical radiopharmaceutical development), the main issue regarding its cyclotron supply will be the availability of a cyclotron network able to deliver 28-29.5 MeV α-particles beams.

Electron beam accelerators for ^{99}Mo production

Concerning ^{99}Mo, IBA[50] and NorthStar (USA) recently announced that NorthStar has acquired its first two (out of 8) Rhodotron® TT300 HE (40 MeV electron machine) for manufacturing ^{99}Mo owing via photonuclear reaction on ^{100}Mo (see Annex 1, and §2.2.4.5).

Other nuclides:

Production of other radionuclides necessitating medium-energy machines is under investigation (e. g. ^{64}Cu, ^{67}Cu, ^{47}Sc, ^{225}Ac[51]).

EU current status #8:

It is likely that SMCs will continue to develop slowly, but complemented by larger, industrial installations.

[49] "Realizing Clinical Trials with Astatine-211: The Chemistry Infrastructure"– Cancer Biotherapy and Radiopharmaceuticals Volume 35, Number 2, 2020

[50] https://indico.cern.ch/event/699219/contributions/2929577/attachments/1655382/2649737/IBA_Presentation_Aries_Annual_Meeting.pdf and https://www.globenewswire.com/news-release/2019/03/29/1788112/0/fr/IBA-VEND-DEUX-PREMIERS-ACC%C3%89L%C3%89RATEURS-RHODOTRON-%C3%80-NORTHSTAR-MEDICAL-RADIOISOTOPES.html

[51] https://indico.cern.ch/event/699219/contributions/2929577/attachments/1655382/2649737/IBA_Presentation_Aries_Annual_Meeting.pdf

The development and spread of the cyclotron-based production of radiometals (^{68}Ga, ^{64}Cu, ^{89}Zr, etc.) beyond the laboratory scale is largely conditioned on investments in more powerful and versatile installations, to be made by the major commercial suppliers.

Indeed, the modern and efficient production of medical radionuclides will require reliance on accelerators with improved characteristics:

- more versatile machines, able to be tuned over a large energy range, toward higher energies (30 MeV), not limited to proton beams, to produce a wider range of nuclides;
- cost-effective equipment (initial investment and operating costs);
- capable of running at high currents for increasing production yields. This raises technical challenges, in particular the design of the targets.

While targetry questions are key in any irradiation installation, it is particularly the case for cyclotrons and accelerators in general. Targetry questions may limit or even prohibit upgrade possibilities for radiometals production in existing local SMCs. See §2.2.3 above.

Yet, the industrial landscape in the EU is served by adequate skills and means for facing these challenges. World-class European companies like Siemens (Germany) and IBA (Belgium) are marketing cyclotrons, and basic and technological research in this field is very active in Europe.

2.2.4.3. *Research reactors*

Research reactor applications and specificities for radionuclide production

The question of radionuclide production in EU research reactors has already been extensively studied,[52] especially through ^{99}Mo supply chain considerations.

The EU is currently the world leader for medical radionuclides produced in research reactors. The main mass-producing installations are HFR (Netherlands), BR2 (Belgium), Maria (Poland), and LVR-15 (Czech Republic).

These capacities are complemented with FRMII (Germany) and soon (2027), by RJH (France), near completion. ILL (the high-flux reactor in France) produces only occasionally. Smaller research reactors can also produce for local consumption, like TRIGA[53] reactors in Italy or Romania.

Production capabilities of reactors whose primary missions is research (e. g. FRMII, RJH, ILL) must be considered with precaution as research activities generally impact their load factor. The number of irradiation channels simultaneously available are also limited as compared to reactors dedicated more to nuclides production.

Indeed, owing to the possible simultaneous irradiation of various targets and source materials in different irradiation positions ("versatility"), mass-producing research reactors are particularly suited for filling a large part of imaging and therapeutic radionuclides needs (see figure 22). They are also served by proven global supply, processing and distribution chains, allowing them to reactively and cost-effectively fulfil medical needs, particularly the fast-developing needs for therapeutic radionuclides like NCA ^{177}Lu.

Research reactors' target technologies are simpler, either directly derived from the proven fuel technology (uranium targets for ^{99}Mo production), or under the form of simple cans (aluminium, quartz or polyethylene) filled with the target material (for instance $^{176}Yb_2O_3$ powder for NCA lutetium production). The targets can be easily positioned and retrieved in an individual manner while the reactor is operating, after their optimal exposure to the neutron beam, in manually handled irradiation rigs or via pneumatic ("rabbit") transfer systems.

Contrarily to decentralized installations, research reactors are generally equipped with all the necessary support systems (waste management, radioprotection

[52] See for instance many publications from the EC or OECD, and also the Samira Final Report MJ-03-19-070-EN-N: "European Study on Medical, Industrial and Research Applications of Nuclear and Radiation Technology"

[53] See "Oregon State Triga Reactor (OSTR/USA) and ICN Pitesti (Romania). Infrastructures for production of radioisotopes and progress in Mo-99 production from LEU targets." The 56thAnnual Meeting on Hot Laboratories and Remote Handling. 8-12 September, 2019, Mamallapuram, Tamil Nadu, India

systems, handling means, cooling systems, protection systems, physical protection, etc.) making it possible to focus all safety and operational constraints on a single mass-production installation. The need for a skilled and well-trained operation and maintenance staff is limited to the installation itself, contrarily to decentralised installations.

Intrinsic challenges of large nuclear installations apply to research reactors

Specific constraints for research reactor operation and radionuclide production are the counterparts of their advantages.

- Risk of shortage exists in case of unanticipated shutdowns of centralised production capacities, even though initiatives launched after the ^{99}Mo crisis mitigate this risk of global shortage owing to a close cooperation among world producers (Nuclear Medicine Europe, ex-AIPES), and the EU situation is closely surveyed by the European Observatory.

- Research reactors raise radioactive waste management challenges, essentially regarding their spent fuel, even if, when respective volumes are considered, the waste management issue of RRs' spent fuel is minor compared to the spent fuel question regarding nuclear power plants. Nevertheless, as long as there is no operational solution for reprocessing or disposal in Europe, interim storage has to be implemented for both RR fuel assemblies and uranium targets for ^{99}Mo production. Several countries are considering NPP fuel final disposal that will accept research-reactor wastes. Yet, whereas the EU Council[54] "*acknowledges that the non-energy uses of nuclear and radiological applications* [which generate the radioactive waste] *have a positive effect on the health of the society,*" it also "*highlights the importance of minimizing the amount and activity of radioactive waste, as reasonably practicable and in accordance with national policies and community law, and of developing and commissioning of new waste management technologies or facilities.*" Minimizing research reactor waste, particularly HLW, thus remains an objective.

- Research reactors are generally publicly supported worldwide.
    - In Europe, Member States like France,[55] Germany,[56] Belgium,[57] The Netherlands, Poland and the Czech Republic subsidize their installations with EU participation in some cases,[58] which is justified

[54] ATO 109/RECH 528/SAN 525. EU Council Conclusions. 19.12.2919.
[55] The CEA budget, owner and operator of the French research reactors among other activities, is funded by more than 70% public subsidies. Such ratio compares rather well with many other countries like the US, Australia, …which subsidize also heavily their installations.
[56] See for instance the German Research Reactors CAPEX and OPEX funding (2010). http://dipbt.bundestag.de/doc/btd/17/029/1702988.pdf
[57] See the Myrrha chapter below
[58] Namely for HFR (Petten)

by the multipurpose character (including research) of these installations.

  - In the US for instance, public support is also a key factor of success for centralized installations more dedicated to radionuclides production, like SHINE or NorthStar, as can be seen in Appendix G. Such support is justified by other considerations as well, like self-reliance objectives.
  - Implementing the FCR principle (i.e. "full cost recovery" for the irradiation services) and takeover of the installations by the private sector remains a goal to be pursued for the sake of efficiency, but it seems that public support will remain key for all centralized installations producing radionuclides, whether they are dedicated or not.

- Finally, the supply of the source material for the fuel of the research reactors (and for the uranium targets) raises the question of HALEU supply.

The HALEU (High-assay LEU) question

Research-reactor fuel and uranium-bearing targets are mainly produced in France by CERCA, the global leader. The necessary HEU and HALEU (uranium enriched at 19.75% in metallic form) source material is currently supplied only by the USA and alternatively, by Russia. The perspective of exhaustion of the US supply, foreseen somewhere between 2030 and 2040, as well as the US/Russian oligopoly, raises the EU self-reliance capability question acutely as, without fuel, no reactor production is possible at all. The question is particularly acute for the reactors (e. g. BR2, FRMII, ILL), which continue for the time being to use HEU fuel, essentially because using HALEU in their specific core design would degrade their performances. The conversion to HALEU of ^{99}Mo production processes using HEU targets has also raised problems, not yet fully solved for IRE. Thus, the HEU/HALEU supply concerns all existing reactors, including those already converted, especially if life extensions are considered.

Under the auspices of the Euratom Supply Agency, a report on "Securing the European Supply of 19,75% enriched Uranium Fuel" has been issued in 2016 and updated in 2019.[59] The necessary investment was evaluated and quoted with the support of Orano and Urenco. Recommendations made in this report are:

- mandating the European stakeholders to further define the conditions for having an enrichment and metallisation facility in Europe through a common project supported by the EU;

[59] "Securing the European Supply of 19.75% enriched Uranium Fuel, a revised assessment," Euratom Supply Agency (ESA), May 2019

- carefully following any changes in the available stockpile to avoid any breach in supplying the European operators;
- carefully following the development of high density HALEU fuel, which could impact the rate of consumption of the present stockpile;
- carefully following the development of new concepts of reactors (advanced reactors) and fuels, which could also impact consumption by drastically increasing the demand;
- exploring the possibility of having a dedicated working group at NEA to discuss this issue in an international context;
- envisaging R&D funding within Horizon 2020 (and the programme which will follow Horizon 2020) to update and further optimize the process for metal HALEU;
- making national regulators aware of the eventual erection of a metal HALEU fabrication facility;
- discussing with the US DOE overall (civilian) needs and ways to guarantee a safe, redundant, lasting and sustainable supply of metal to HALEU.

The ESA Advisory Committee's Working Group on European production of low-enriched (19.75%) uranium was re-instated in spring 2021 and mandated to continue the work based on the recommendations given in the 2019 report. The group will explore the necessary conditions for establishing European production capacity for HALEU to respond to the EU needs for the research reactors fuel and medical radioisotopes production.

EU current status #9:

Despite their drawbacks, reactors represent an essential European asset for research purposes and medical radionuclides production. Cyclotrons and reactors offer complementary radionuclide production means, generally not in competition. Cyclotron/accelerator-based alternatives exist for certain radionuclides produced in reactors such as ^{99}Mo (Canadian direct ^{99m}Tc production, SMART, etc.), but they are currently either not practicable for Europe (see §2.2.3.2), at project scale, or under construction (NorthStar, SHINE). For assessing in a compelling manner their chances to represent a relevant industrial alternative to research reactors, laboratory-scale successes are not sufficient, and experience feedback on their first industrial productions (CAPEX and OPEX, industrial production yields, reliability of the installations, etc.) must be available.

As expressed many times in EC documents, and re-stressed in recent draft conclusions,[60] the European Council *"underlines the important contribution of European nuclear research reactors and facilities when developing non-power*

[60] ATO 56, RECH 271, SAN 256 "Draft Council conclusions on non-power nuclear and radiological technologies and applications," May 2019

applications of nuclear and radiological technologies" while it "stresses that securing fuel supplies and implementing safe and sustainable solutions for the management of used fuels and radioactive waste from those reactors and facilities are important responsibilities of Member States and license holders" as well. Medical radionuclides production in research reactors should thus be maintained (see §3.1.2.2) and developed, namely for mitigating efficiently the drawbacks which come with their unrivalled advantages.

The HALEU supply for research-reactor fuels (and targets) remains a concern. The ESA Advisory Committee's Working Group on European production of low-enriched uranium will explore the necessary conditions for establishing European production capacity for HALEU to respond to the EU needs for the research reactors fuel and medical radioisotopes production.

2.2.4.4. *Large accelerators-based research installations*

Current and future applications to support medical radionuclide production

Aside from small/medium-energy cyclotrons and research reactors, Europe relies as well on a set of large accelerators-based research facilities such as CERN and PSI (Switzerland), GANIL and Arronax (France) and ESS (Sweden), among many others (see below). In addition to their main research functions, these installations play an increasing role in EU supply for radionuclides under development and/or non-standard productions.

Owing to their very high energy beams (tens to hundreds of MeV), these installations allow production of nuclides which can hardly be generated in commercial installations (cyclotrons or reactors) and provide additional opportunities for clinical research.

For example, ^{225}Ac supply in Europe was limited in the past to ^{229}Th extraction from JRC Karlsruhe stockpiles (see Annex 11), but large proton accelerators such as CERN can now produce it by means of the spallation reaction ^{232}Th(p,x)^{225}Ac with protons above 70 MeV. MEDICIS (CERN, see box below) is able to produce a few mCi per month of ^{225}Ac. With the potential proposed upgrades to MEDICIS, and perhaps other European facilities, the production could be enlarged and support research, pending availability of industrial manufacturing routes. [61] These installations are thus essential for fostering technological and scientific innovation, necessary for developing ever better performing products in nuclear medicine.

In addition to radionuclide production capacity, large accelerators are also used for developing the skills necessary for radionuclides R&D and industry in Europe. For instance, a noticeable initiative has been the Promed/Medicis ("MEDICIS-produced radioisotope beams for medicine") closed in 2019. Promed/Medicis has

[61] Development of 225Ac Radiopharmaceuticals: TRIUMF Perspectives and Experiences; Current Radiopharmaceuticals, 2018, 11, 156-172

been supported by a Marie Skłodowska-Curie innovative training network fellowship of the European Commission's Horizon 2020 program. 16 young researchers were trained on projects along the chain of non-conventional isotope production, related accelerator techniques and research in medicine.

The final conference of the Promed-Medicis program (30/4/2019) was the opportunity to launch a kick-off meeting to form a network of relevant "European Medical Isotope Production centres" for this incipient research community, as a European equivalent of the "National Isotopes Program" of US/DOE.[62]

Besides coordination on medical R&D nuclides production, the importance of mass separation installations and projects has also been highlighted.

CERN MEDICIS project

MEDICIS, started during the Promed/Medicis program, is based on dedicated infrastructures to both produce and separate (through mass separation) medical radionuclides, and on a network of collaborating institutes such as the high-flux reactor ILL, the high-power cyclotron Arronax, radiopharmaceutical/chemistry groups at NPL, PSI and IST, and hospitals of the Lemanic Arc among others.

A proton beam stemming from CERN's LINAC2 (50 MeV) is energized to 1.2GeV by the PS-Booster and passes through the ISOLDE system (used for basic scientific experiments, able to produce 1000+ isotopes of 70+ chemical elements) to the Medicis target system. For such installations with very high energy beams and/or high fluxes or currents, targetry requires innovative solutions. The targets must fulfil their duties (nuclei and beam interaction, isotope production confinement, heat dissipation, perform chemical reactions) while sustaining very severe operating conditions (high energy deposition, high temperatures, etc.) Desired radionuclides are separated owing to an off-line mass separator (ISOL) and purified in a chemical laboratory.

MEDICIS is dedicated to the production of non-conventional nuclides (e.g. to date Terbium isotopes produced by MEDICIS have been made available and are used for preclinical tests).

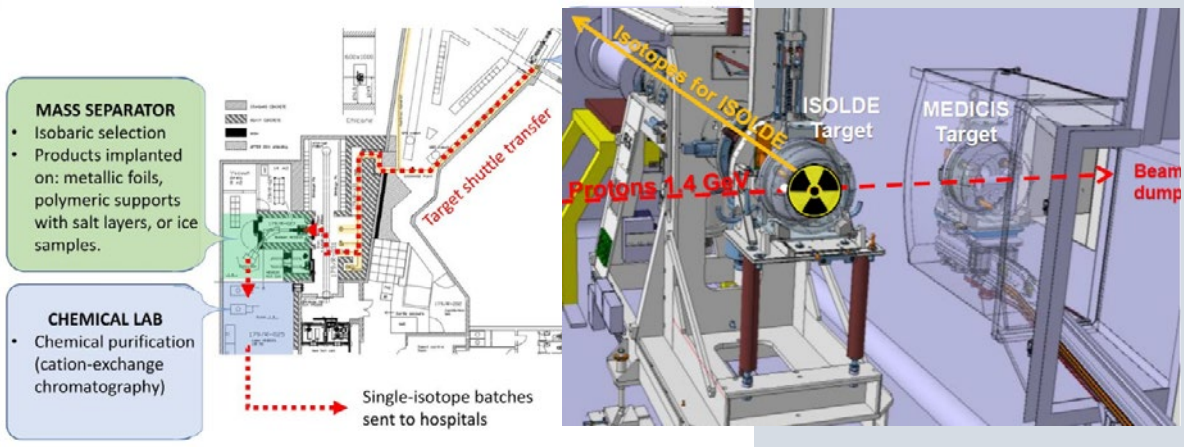


Figure 28: The MEDICIS main components (CERN)

[62] https://indico.cern.ch/event/782482/contributions/

Towards a European coordinated network of large accelerators?

The European PRISMAS-MAP [63] (PRoduction of ISotopes from MAss Separation for Medical APplication) initiative is currently assessing the feasibility of a unified network of accelerators, making it possible to provide a sustainable source of high-purity grade new radionuclides for medicine, involving from the onset upcoming major European infrastructures, and to provide a single entry point for all researchers active in this field including SMEs, global pharma, nuclear centres, hospitals, and universities, using standardised access procedures.

Installations that could be part of such an initiative are mapped in the figure on the next page and include various players, from key European intense neutron sources, isotope mass separation facilities and high-power accelerators and cyclotrons, to leading biomedical research institutes and hospitals active in the translation of the emerging radionuclides into medical diagnosis and treatment.

A financing request, as part of H2020 INFRAIA programmes (INFRA-2-2020) was validated by the EU in late 2020.[64]

[63] More information on PRISMAP initiative can be found on https://medicis.cern/prismap-european-medical-isotope-programme
[64] https://home.cern/news/news/cern/high-five-cern-european-union-projects

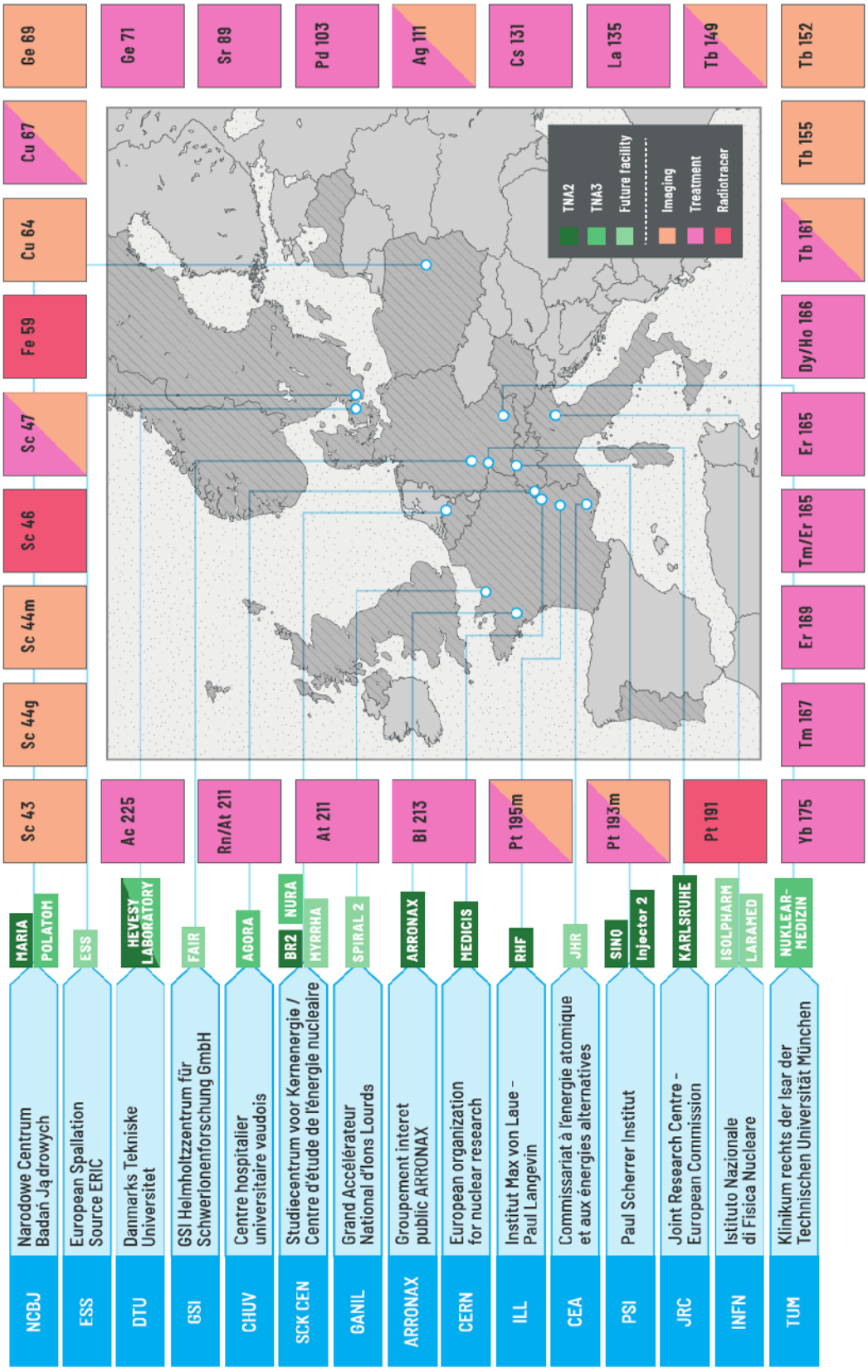


Figure 29: PRISMAP future network of installations for radionuclide production[65]

[65] Source: PRISMAP public information. https://medicis.cern/prismap-european-medical-isotope-programme

The Belgian Myrrha project

Although not being primarily aimed at isotopes production, the Myrrha project is depicted here due to its high innovation potential for the EU.

Started in 1998, pursuing an initiative of Nobel Prize winner Carlo Rubbia, the purpose of the MYRRHA programme was initially to demonstrate the ADS (accelerator-driven system) concept at pre-industrial scale, to evidence the nuclear waste transmutation efficiency of ADS. Other functions have been added, making currently Myrrha a flexible and multipurpose irradiation facility project, comprising fusion materials irradiation, R&D, and medical nuclides production.

Technology

The MYRRHA subcritical core, fuelled with highly enriched MOX fuel and cooled with a LBE (Lead-Bismuth Eutectic), would be triggered by a high-power superconducting linear accelerator delivering a proton beam of 600 MeV, 4 mA to a LBE spallation target.

Funding & organization

The project has been split into three phases, in order to i) reduce technical risk, ii) spread investment cost and iii) allow for a first R&D facility available in Mol at the end of 2026:

- Phase 1, called MINERVA, comprises a 100 MeV accelerator and target stations (protons and isotopic online separation -ISOL-, and fusion material testing facilities). MINERVA would be a fully modular infrastructure able to function autonomously as of 2026-2027, and generate scientific results and revenue;
- Phase 2 is the upgrade of the accelerator to 600 MeV;
- and Phase 3 is the nuclear reactor.

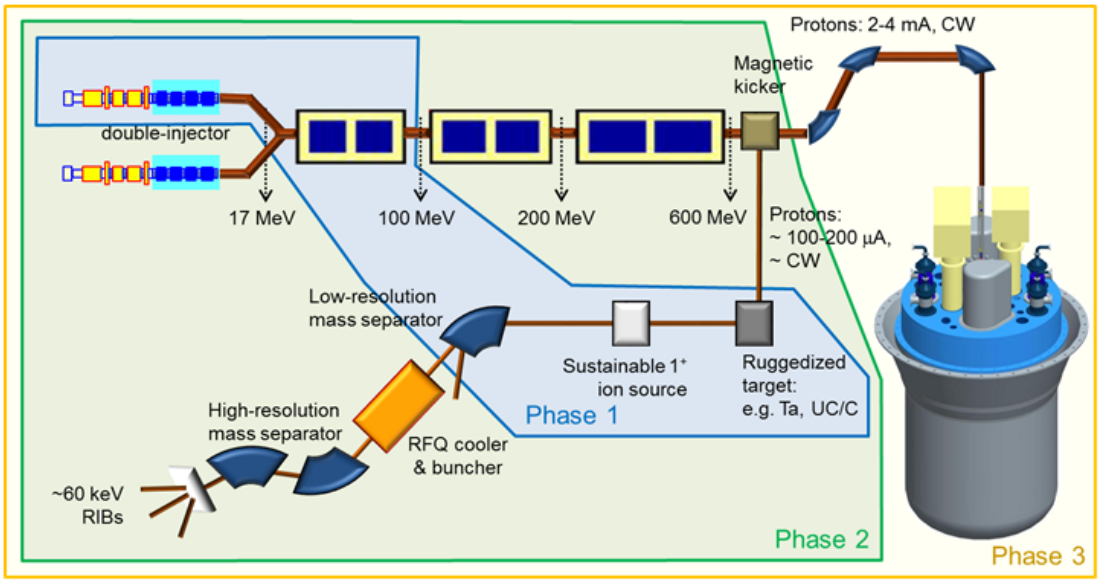


Figure 30: Myrrha project breakdown into 3 phases and installation principle

In September 2018, Belgium decided to fund around 40% of this €1.6 billion project, with 558 M€ for the period 2019-2038, comprising:

- 287 M€ over 2019-2026 for the CAPEX of MINERVA,
- 156 M€ for the 2027-2038 OPEX of MINERVA,
- 115 M€ over 2019-2026 for further design, R&D and licensing for Phases 2 & 3.

A stage-gate decision will be taken in 2026 whether to proceed with phases 2 and 3, either sequentially, or in parallel.

Belgium also established an international non-profit organization (AISBL/IVZW) aimed at welcoming the international partners and gathering the necessary complementary funding.

As of October 2020, Myrrha was selected by the European investment bank (EIB) as a potential project for EIB financing, with procedure ongoing, as well as being on the candidate project list for financing by the European Fund for Strategic Investment (EFSI).

Medical nuclides production

Of particular interest to the present study are the nuclides-production capabilities of the Myrrha project. As a (p, x) installation, the Phase 1 MINERVA installation will allow production of R&D quantities of advanced isotopes (see Table 9, Chapter 2.1).

Even if they have different detailed characteristics in terms of energy, current or coupling with an ISOL station, the (p, x) capabilities of installations like TRIUMF

(Canada), Arronax (France) (see Table 16 below), or PSI (Switzerland) and CERN give an idea of the nuclides that could pertain to the MINERVA production program.

TRIUMF PRODUCED ISOTOPES					
Nuclides	Targets	Reaction	Installation	Use	EOB Yield
^{44}Sc		^{44}Ca(p,n)^{44}Sc	TR13 cyclotron with adapted liquid target system	PET	5,6 MBq
^{68}Ga		^{68}Zn(p,n)^{68}Ga			445 MBq
^{86}Y		^{86}Sr(p,n)^{86}Y			6,6 MBq
^{89}Zr		^{89}Y(p,n)^{89}Zr			110 MBq
^{99m}Tc	^{100}Mo		TR30, beam energy degraded to 24 MeV	SPECT	1 TBq
Other nuclides produced : ^{18}F, ^{13}N, ^{11}C, ^{94m}Tc, ^{61}Cu, ^{64}Cu, ^{52}Mn, ^{55}Co, ^{192}Ir					

Isotopes of interest studied at ARRONAX				
Nuclides	Targets	Reaction	Installation	Use
^{82}Sr	^{nat}Rb	^{nat}Rb(p,xn)	Arronax (IBA) Cyclotron @ 70 MeV	
^{211}At	^{nat}Bi	^{209}Bi(a,2n)	Arronax (IBA) Cyclotron @ 28 MeV	Therapy
^{64}Cu	^{64}Ni	^{64}Ni(d,2n)	Arronax (IBA) Cyclotron @ 16 MeV	immuno-PET
^{68}Ge	^{nat}Ga	^{69}Ga(p,2n)	Arronax (IBA) Cyclotron @ 30 MeV	Generator for ^{68}Ga (PET)
^{44}Sc	$^{44}CaCo_3$	^{44}Ca(d,2n)	Arronax (IBA) Cyclotron @ 16 MeV	Theranostics with ^{47}Sc
^{67}Cu	^{68}Zn	^{68}Zn(p,2p)	Arronax (IBA) Cyclotron @ 70 MeV	Therapy
^{47}Sc	^{nat}Ti	^{48}Ti(p,2p)	Arronax (IBA) Cyclotron @ 70 MeV	Therapy

Table 16: Examples of nuclides produced in TRIUMF and ARRONAX

For the nuclear reactor part of Myrrha (Phase 3, 2038), decision has been taken to remove the fission isotopes production from the scope of the installation. However, thermal neutron activation positions for activation isotopes as well as fast neutron-based isotopes production capabilities are maintained. Production capacity is not yet defined.

Even if isotope production is not its sole purpose, Myrrha should play a great role in the coordinated production of R&D isotopes (PRISMAS-MAP, etc.).

EU current status #10:

The European large research installations could play a strategic role in the medical radionuclides supply chain:

- for the production of the nuclides needed for R&D, up to at least the clinical trials, before commercial organizations take over;
- for diversifying the production as a backup for the industrial installations;
- for development of the scientific and technical skills guaranteeing sustainable innovation in all aspects of the medical radionuclide supply chain and for fundamental research on radionuclide production (cross-sections, yields, etc.).

With the EU financing the PRISMAP initiative, Europe could in the future rely on a large network of installations offering radionuclide production capacity for medical/industrial/fundamental research on the model of the US National Isotopes Development Program (NIDC).

2.2.4.5. *Alternative industrial installations*

A series of "alternative technologies" projects, aimed at creating large, more or less dedicated radionuclide production, have been depicted in the literature[66] and are ongoing.

In the present chapter, information about the most advanced projects is updated: direct production of ^{99m}Tc in cyclotrons (Canada), SHINE (USA), NorthStar (USA), CANDU radionuclide production (Canada), SMART (ex-Lighthouse, Belgium).
A comparison of some of these installations is summarized in §3.3.

Is direct production of ^{99m}Tc in cyclotrons (Canadian-promoted option) a viable solution for Europe?

According to Triumf, *"a new cyclotron-based approach to producing this critical diagnostic tool has received Health Canada approval end of 2020, greenlighting the made-in-Canada technology for national implementation and opening the door to a greener, more reliable way to make technetium-99m."*[67] In the SAMIRA study[68] cited above, this solution had already been deemed impracticable for Europe.

This production route implements the ^{100}Mo(p,2n)^{99m}Tc reaction in around 20 MeV cyclotrons. As the short half-life of ^{99m}Tc limits this production to users geographically close to the accelerator, its generalization at a country level would require a large network of cyclotrons of around 20 MeV and several hundred μA.

According to Triumf,[69] the network of 28 existing Canadian cyclotrons, of which 18 deliver around 20 MeV protons or above, operated 1 x 6 hr runs/d, 240 d/yr is able to cover the needs of the 35M (as of 2012) Canadian citizens.

Given that:

- the total EU cyclotrons fleet is currently about 240 units, already largely loaded, of which only 20 are >20MeV,
- most of the cyclotrons are not equipped for handling solid targets,
- the cyclotrons are unevenly spread over EU,

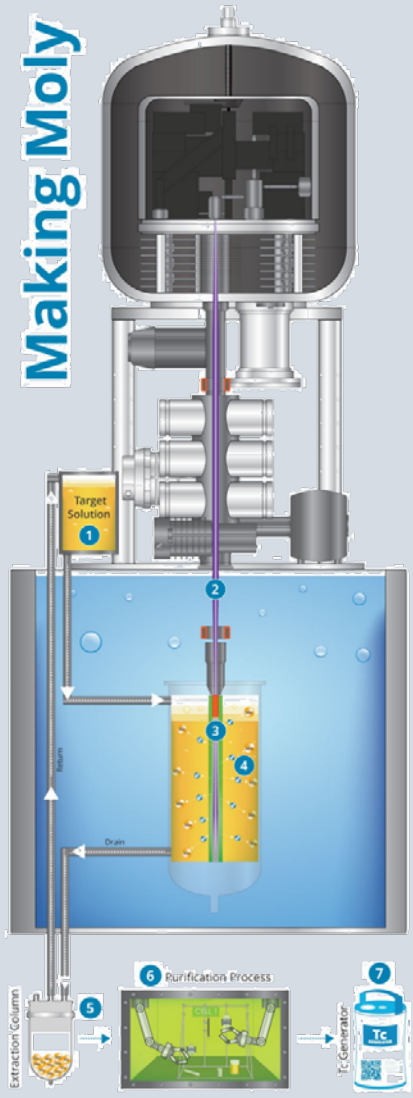
a simple rule of three shows that this would require a fleet of more than 100 new cyclotrons, fully dedicated to ^{99m}Tc, operated in an industrial manner, with 2 runs per day (producing during the afternoon is not efficient due to the 6h half-life of

[66] See Samira final report MJ-03-19-070-EN-N: "European Study on Medical, Industrial and Research Applications of Nuclear and Radiation Technology," Appendix A14 and §13.10
[67] https://www.triumf.ca/headlines/cyclotron-produced-technetium-99m-approved-health-canada
[68] SAMIRA 2019 study: European Study on Medical, Industrial and Research Applications of Nuclear and Radiation Technology. Final Report. Contract ENER/17/NUCL/SI2.755660. MJ-03-19-070-EN-N
[69] Technical Summary and Preliminary Cost Analysis for the Direct Production of 99mTc. NNSA Mo-99 Workshop, Washington, DC

^{99m}Tc). Even if cyclotron's unit cost is relatively low (see §3.3.2.3), such an investment would be prohibitive.

SHINE

An alternative to ^{235}U fission in research reactors is developed by SHINE Medical (USA). Its principle is depicted below.



1. Target Solution: Low-enriched uranium (SHINE receives LEU from the US Government, and dissolves it, creating a uranyl sulphate mixture①. This mixture is pumped into a target solution vessel (TSV, ④).

2. Accelerator: Electrons are stripped from deuterium using microwave energy. The resulting positively-charged deuterium ions are shaped into a beam and accelerated (300 keV) ②

3. Fusion Chamber: The deuterium ions are accelerated into a gas target made of tritium resulting in fusion reactions that generate up to 1,5 10^{14} neutrons/s ③.

4. High energy fusion neutrons (14,1 MeV) enter a neutron multiplier ③ surrounding the target (natural U metal, encapsulated within an aluminium jacket) where fission, (n,2n) and (n,3n) reactions take place. Neutrons then pass into the TSV.

5. Fission Target: The neutrons cause the fission of uranium nuclei in the target solution. Fission power is ~ 125 kW per Irradiation Unit (8 devices), ^{99}Mo production rate per device is > 500 6-day Ci/ wk.

6. Moly, Iodine and Xenon (gas) Extraction: The target solution is irradiated for approximately 5,5 days, then pumped through extraction columns. Moly and Iodine stick to the columns and the rest of the target solution is purified and returned for re-use. A separate solution is then pumped through the extraction columns to take the moly and iodine to purification.

7. Purification: A chemical process purifies the moly-99 and iodine to meet pharmaceutical standards and customer specifications.

One irradiation unit of the SHINE installation (8 units are foreseen) is illustrated below. The accelerator is connected with the tritium target, inserted in the target solution vessel (not represented). Tritium laboratory is pictured on the left. Other auxiliary systems are not shown. Accelerator + target vessel height is about 8 meters.

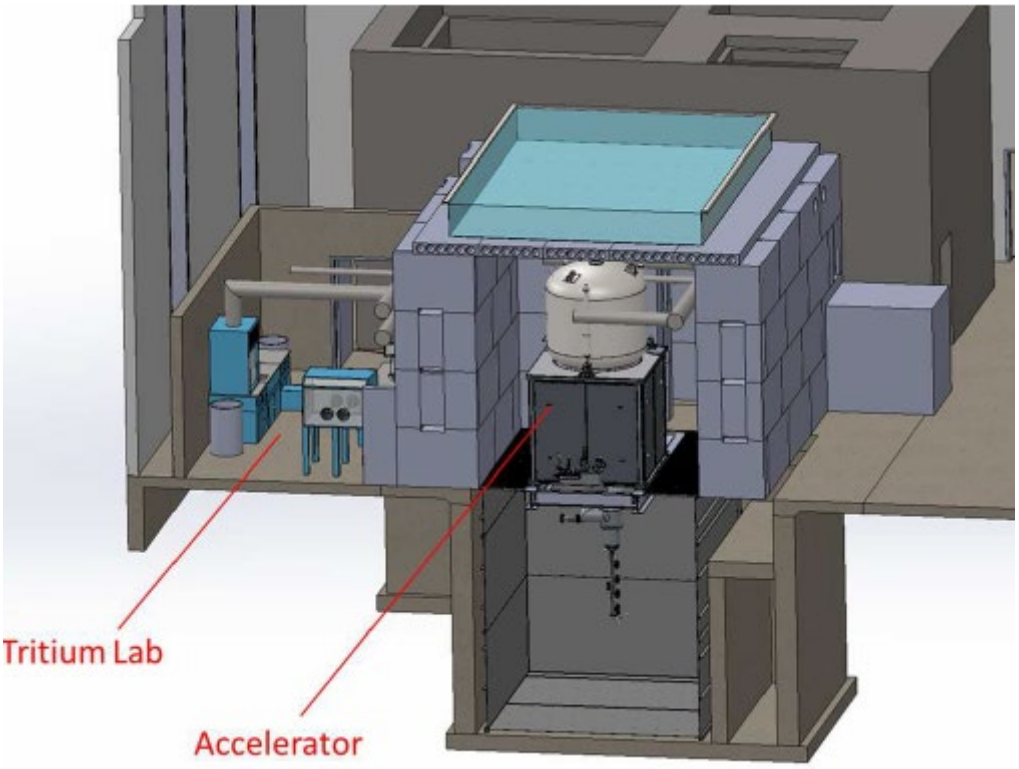


Figure 31: An artistic view of a SHINE production unit

The SHINE production process differs greatly from the current one in reactors and is based on innovative technologies, combining in an integrated manner nuclear (fission & fusion), reprocessing and chemical processes that have been generally validated separately and still necessitate demonstration at full industrial scale.

Previous steps

The Construction Permit was filed at the Nuclear Regulatory Commission (NRC) in 2013 and was granted in February 2016, with a series of 120^{+} conditions (see corresponding USNRC Safety Evaluation Report), and pending fulfilment of USDOE-funded R&D programmes: for instance, at ORNL, for irradiation and corrosion testing to study mechanical performance of materials; at Argonne, for characterizing behaviour of uranyl sulphate in the target solution and for developing reprocessing processes (see appendix G). As a result, important modifications have been made to the process.

"Building One" (built in 2018) was intended to house the so-called SHINE Demonstration Unit, on which SHINE planned to conduct a series of short-duration tests within an accelerator-driven subcritical operating assembly. Unlike the future commercial irradiation units, the demonstration unit would not require engineered safety features or a physical protection system, which remain to be finalised and approved by the NRC. Outcomes of such demonstration tests were not published but have been satisfactory according to SHINE.

The construction of the industrial facility started in September 2019. The Operating License application files were submitted to the NRC (with a public version of the FSAR[70]) in July 2019.

Situation as of mid-2021

The FSAR is currently being reviewed by the US NRC. During the process, RAI (requests for additional information) are normally raised by the NRC, and answered by the applicant, before NRC can issue a SER (safety evaluation report) and eventually grant the Operating License.

As per the FSAR, SHINE's licence would cover ^{99}Mo, ^{131}I and ^{133}Xe production. Despite the target vessel having a provision for two irradiation positions, similar to research reactors, theoretically allowing for neutron-activation reactions on solid targets, their effective use is currently not submitted for NRC approval (i.e. not mentioned in the FSAR). Feasibility and capabilities of production of neutron-activated isotopes thus remain to be proven.[71]

SHINE is currently anticipating the start of ^{99}Mo production in late 2021, to be followed by FDA review and approval for beginning of sales in 2022. ^{131}I and ^{133}Xe production will follow. The company has prepared a responsible scale-up process with the NRC. This scale-up process will take approximately one year.

The standard pharmaceutical licensing process will be implemented: i) production batches for industrial testing to assess radiochemistry, product purity, etc.; ii) production batches for health and validation, where ^{99}Mo quality will be tested for ^{99m}Tc imaging to assess potential discrepancies; and iii) FDA review and market authorization for generators based on SHINE's ^{99}Mo.

SHINE funding

Regarding project financing, SHINE secured more than $450 million received or committed to date (March 2021)[72]; in addition, the company has received $50 million of government funding (US DOE/NNSA, without accounting for DOE support to US Laboratories, see appendix G). Estimation of total budget at completion has not been disclosed.

SHINE is also moving towards the construction of a similar installation in Europe, and a site in the province of Groningen (Netherlands) was selected in May 2021.

Sorgentina Project

Like SHINE, the Sorgentina project (ENEA, Italia) relies on a fast neutron source; but these fast neutrons are directly used for producing ^{99}Mo via the

[70] https://www.nrc.gov/docs/ML1921/ML19211C143.html
[71] "*corresponding manufacturing routes are not developed or not disclosed* " as we were told by a SHINE Executive.
[72] FAQ, SHINEMED site

^{100}Mo(n,2n)^{99}Mo reaction. ENEA deems that such a concept would be easier to build than a research reactor and is currently searching to set up a lab scale installation. Project is in very early development phase. In parallel, ENEA is planning to revamp its TRIGA reactor in order to increase its ^{99}Mo production capability for local/regional consumption.

NorthStar / Photonuclear production

^{99m}Tc can theoretically be produced in two ways in accelerators:

- direct production with a proton beam: ^{100}Mo(p,2n)^{99m}Tc, ^{99m}Tc being directly produced as seen above for the Canadian option;
- indirect production through an electron beam generating γ rays, inducing the photonuclear reaction ^{100}Mo(γ, n)^{99}Mo; ^{99}Mo is then used in a specific ^{99}Mo/^{99m}Tc generator.

Both routes use enriched ^{100}Mo as a source material for reaching acceptable production yields and impurity levels.

The photonuclear reaction is envisaged in the NorthStar, Niowave, and Lighthouse (now SMART) projects. It is also envisaged for ^{225}Ac production with ^{226}Ra targets.

<u>Photonuclear reactions</u>

The photonuclear production route raises additional complications as compared to the (n, γ) production routes implemented in research or accelerator-driven fission reactors. Indeed, due to their lack of charge, slow neutrons do not have to hurdle the Coulomb potential of atomic electrons and can relatively easily reach the nucleus. Once close to the nucleus, they are captured, and the nucleus becomes excited.

For producing photonuclear reactions, an accelerator directs an electron beam on a target, basically composed of:

- a converter, in which the primary beam electrons lose energy and change direction due to inelastic scattering. Some of the lost energy is converted to x-rays which have a range of energies, from zero up to the energy of the electrons of the primary beam. First, photons are absorbed, and the converter's nucleus becomes excited. Then, the excitation energy is released – in the form of a photon, neutron, or a charged particle (proton, alpha particle, etc.) The resulting high-energy photons can cause many photonuclear reactions;
- the source material, in which the released particles generate the desired radionuclide.

In order to maximize the yield of the nuclides produced by the photoneutron or photoproton methods, the electron beam current needs to be maximized.

However, higher energy can also lead to other reactions, such as (γ,2n) and (γ,np), which often produce unwanted by-products and complicate the separation process. Careful analysis is thus necessary to find the optimum irradiation parameters for each target material. Also, converter design will affect the flux. An optimum thickness exists for each material and electron energy. Typical bremsstrahlung converter materials have high atomic number and density, and include for instance tungsten, tantalum, platinum, lead, and gold, or compounds like lead-bismuth eutectic (LBE) in the Niowave project.

Finding the optimum converter thickness and material to maximize the photon/neutron flux and the nuclide production rate is a challenge and requires extensive R&D programs.

The planned NorthStar ^{99}Mo production plant is based on eight IBA Rhodotrons® accelerating electrons up to 40 MeV. The low specific activity ^{99}Mo generated will be used with the Radiogenix® generators. The plant comprises a ^{100}Mo targets reprocessing unit. Each production unit of the NorthStar project involves two Rhodotrons®, both beams being directed towards solid ^{100}Mo disk-targets in a two-side way in order to maximize the production yield.

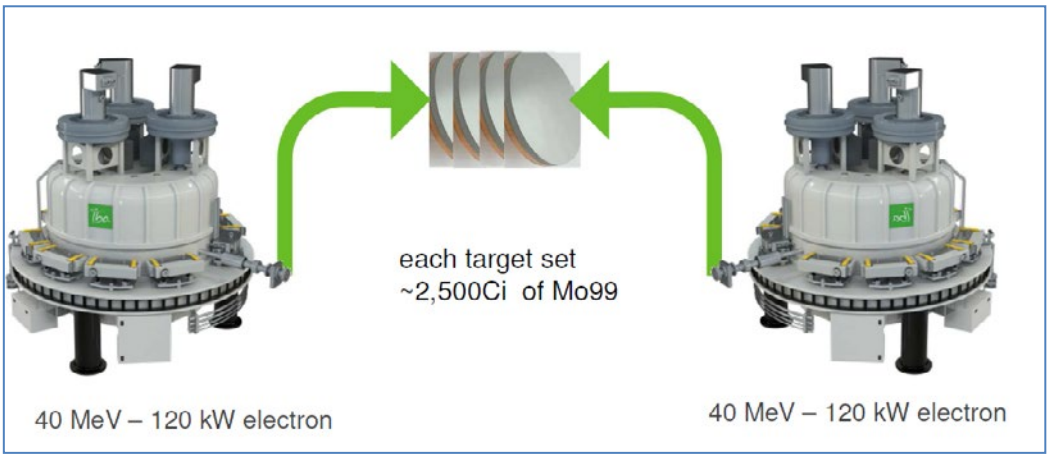


Figure 32: Two-sided irradiation with Rhodotrons®

The claimed interests of producing ^{99}Mo by means of photonuclear reactions, in comparison to ^{235}U(n,γ) production (reactors, SHINE) are:

- the absence of proliferation risks,
- the use of an innovative accelerator system (Rhodotron®),
- the negligible waste generated by the target processing.

However, enriched ^{100}Mo targets are needed, that may become an issue in the case of large production through this manufacturing route.

Industrializing this production route raises many questions as well, namely the targets and their cooling-system design, target handling and radioprotection problems, due to high gamma fluxes, which impact the layout of the installation. These aspects have been particularly studied by ANL and LANL national labs, which support the NorthStar project (see §2.2.3.3).

A typical NorthStar production unit is sketched below, showing the two Rhodotrons®, their bent electron beams, the target room, the hot cell necessary for handling the targets and their Helium cooling system. Three to six such cells are foreseen in the NorthStar plant. Rhodotron® diameter is about 3.5 m. The twin-Rhodotron® cell dimension is typically 15m x17m. Note the size of the concrete shields necessary for protecting workers.

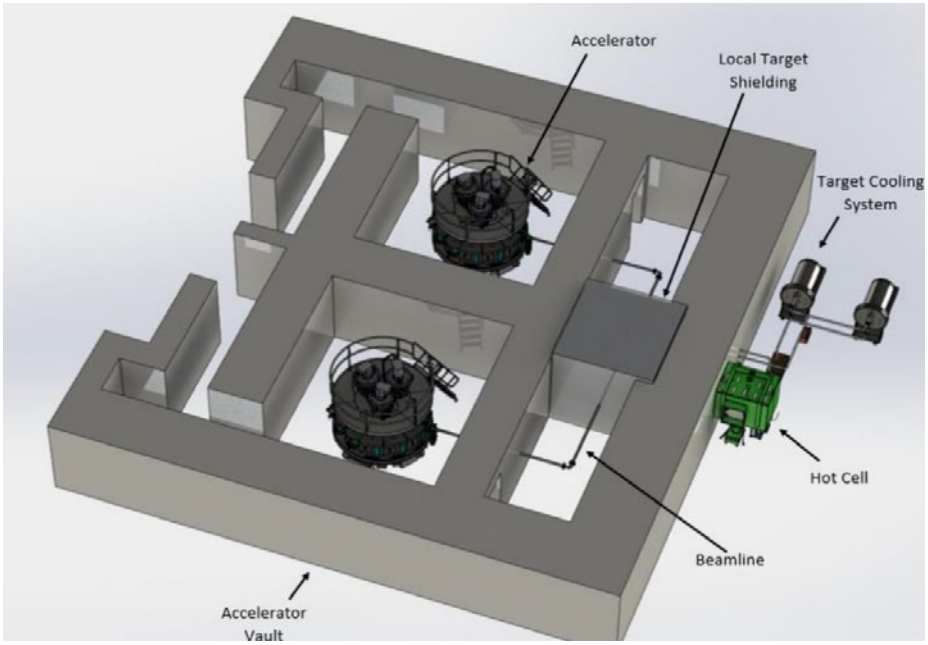


Figure 33: A twin-Rhodotron® production cell of the NorthStar projected plant[73]

This example shows that industrialization of promising lab-scale processes always raises delicate technical problems, which complicates the design and increases costs.

The NorthStar plant is under construction. The first two Rhodotrons® are currently installed for first production runs announced by 2021. Like SHINE and other US projects, NorthStar benefited from:

- NNSA "cooperative agreements," for a cumulative total of 65 M$ (as of 2019) covering its two projects (the one with MURR and the present one);
- extensive US national labs support (see Appendix G).

[73] "NorthStar: The new producer and distributor of Mo-99." 2019 Mo-99 Stakeholders Meeting. Chicago, IL. September 12, 2019

Production in CANDU Reactors

The idea of benefiting from "free" neutrons in excess in Nuclear Power Plants for producing nuclides is tempting. It is already implemented in the US Watts Bar PWR for producing tritium for military purposes, and overall, in Canadian CANDU reactors for mass production of ^{60}Co (See Annex 22).

CANDU reactors offer two irradiation possibilities:

- either introducing targets vertically in a flux detector guide tube (see figure below) or in the so-called adjustment rods positions (typically for two years as is the case for ^{60}Co);
- or horizontally, in lieu and place of fuel bundles in fuel channels.

In both cases, irradiation durations can be adapted as in research reactors. In the latter case the channels containing the targets are subject to specific fuel management.

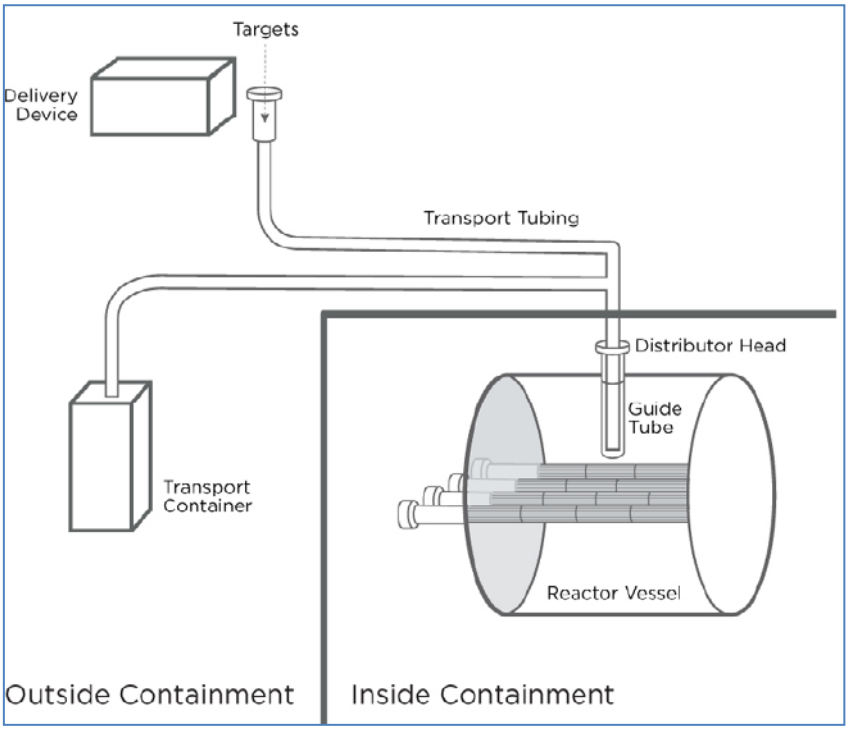


Figure 34: Principle (simplified) of ^{177}Lu production in Bruce Unit 7 through vertical guide tube

Both approaches require modifications on existing licensed reactors, with new equipment to be installed and safety/licensing files to be submitted. Two projects are currently underway in Canada for RN production in CANDU and are more detailed hereafter:

- OPG/BWXT project for ^{99}Mo production,
- Bruce Power and Framatome/Kinectrics (ISOGEN) project for ^{177}Lu production.

OPG/BWXT project for ^{99}Mo production

The production of ^{99}Mo in reactors is achievable through the reaction ^{98}Mo(n,γ)^{99}Mo. This manufacturing route is currently in use in the MURR Reactor for NorthStar. BWXT (Canada) is working on adapting this process for production in CANDU reactors (Darlington). In the BWXT project, the lower specific activity of produced ^{99}Mo would be counterbalanced by a specific generator technology.[74]

Ontario Power Generation (OPG) subsidiary Laurentis Energy Partners, BWXT ITG Canada Inc. and its affiliates announced they are making "significant progress" towards the production of ^{99}Mo at OPG's Darlington nuclear station.[75] The formal request to the FDA for generator approval shall be submitted in 2021 (based on ^{99}Mo produced in MURR). Production perspectives in OPG's CANDU reactors have not been disclosed.

Bruce Power/Framatome/Kinectrics project for ^{99}Mo, ^{177}Lu and ^{192}Ir production

Bruce Power signed an agreement in 2017 with Framatome and Kinectrics (grouped into ISOGEN) to design and supply equipment, to be installed in Bruce's CANDU units, to allow for online production at commercial scale of a wide range of nuclides including short half-life nuclides such as ^{99}Mo, ^{177}Lu and ^{192}Ir.

In addition, Bruce Power and ITM/ITG signed a Memorandum of Understanding in June 2018 to explore the production of NCA ^{177}Lu at Bruce and claimed that they have the ability to meet global supply needs until 2064.

Going a step further, ITM Medical Isotopes GmbH and ISOGEN signed a formal supply arrangement in October 2020 to provide a reliable supply of ^{177}Lu for the next 15 years. The partnership would aim to meet the medical community's growing demand for the radionuclide. Development, processing, and global distribution of ^{177}Lu would be managed by ITG.[76]

According to the Licensing file submitted by Bruce Power to the Canadian Nuclear Safety Commission (CNSC)[77], Bruce Power initially plans to produce ^{177}Lu in Unit 7 only:

- *"Production of nuclear substances is to be limited to Cobalt-60 (Bruce B) and Lutetium-177." "However, the proposed amendment is intended to address production of various nuclear substances in all eight Bruce site*

[74] https://www.bwxt.com/what-we-do/medical-isotopes/medical-isotopes-1
[75] https://www.neimagazine.com/news/newsdarlington-takes-step-towards-producing-mo-99-8150475.
[76] https://www.world-nuclear-news.org/RS-Bruce-Power-and-ITM-to-supply-cancer-therapy-isotope-2906187.html
[77] Public hearings foreseen from January 2021 up to end May 2021

units. As the isotope production business expands, Bruce Power will request appropriate revisions to the LCH,[78] subject to acceptance by CNSC staff."

- *"Bruce Power plans to install an isotope production system to permit in-core neutron irradiations. A target finger tube assembly is to be installed via a vacant vertical flux detector guide tube assembly. Targets are to be contained within protective carriers (Aluminium) and are to be inserted and retrieved by a pneumatic system (Helium). The carrier gas vent lines will be connected to contaminated exhaust stack. Irradiated targets are to be discharged to Type B(U) transport containers. Initially, the isotope production system is to be installed in Unit 7 for the production of Lutetium-177 from Ytterbium-176 powder. Target quartz ampules are inserted into a target carrier, which is designed to maintain the integrity of the ampules during insertion and retrieval. An operator will load one or more target carriers into the IPS. The same (or very similar) isotope production system may be installed in other units. Additional isotopes or non-medical irradiation may be considered in the future, subject to global health demands and innovation, and as consistent with the safety case."*
- *"Installation of the isotope production system (IPS) in Unit 7 is currently planned to begin in 2021 Q4, with production beginning in 2022 Q1. Decisions with respect to other units will be made at a future time, subject to safety, feasibility, and global health demands."*

Focus on NCA ^{177}Lu production capability in CANDU

NCA lutetium production yields depend upon the local neutron fluxes and the targets management scheme (irradiation duration and number of targets irradiated per week).

Production yields expected for Bruce Unit 7 have not been publicly disclosed. Even if average fluxes in a CANDU (typically 10^{13} to 10^{14} n/cm^2/s) are lower than in a research reactor (typically above 2 10^{14} n/cm^2/s in the core), the flux at the Bruce Unit 7 core position accessible with the IPS may be far higher than the average. These points as well as the number of CANDU reactors in Bruce's fleet which can be potentially used in the future make this production route a serious one to be considered (see Chapter 3).

The impact of neutron flux on irradiation yields is detailed in the following figure.

[78] Licence Conditions Handbook

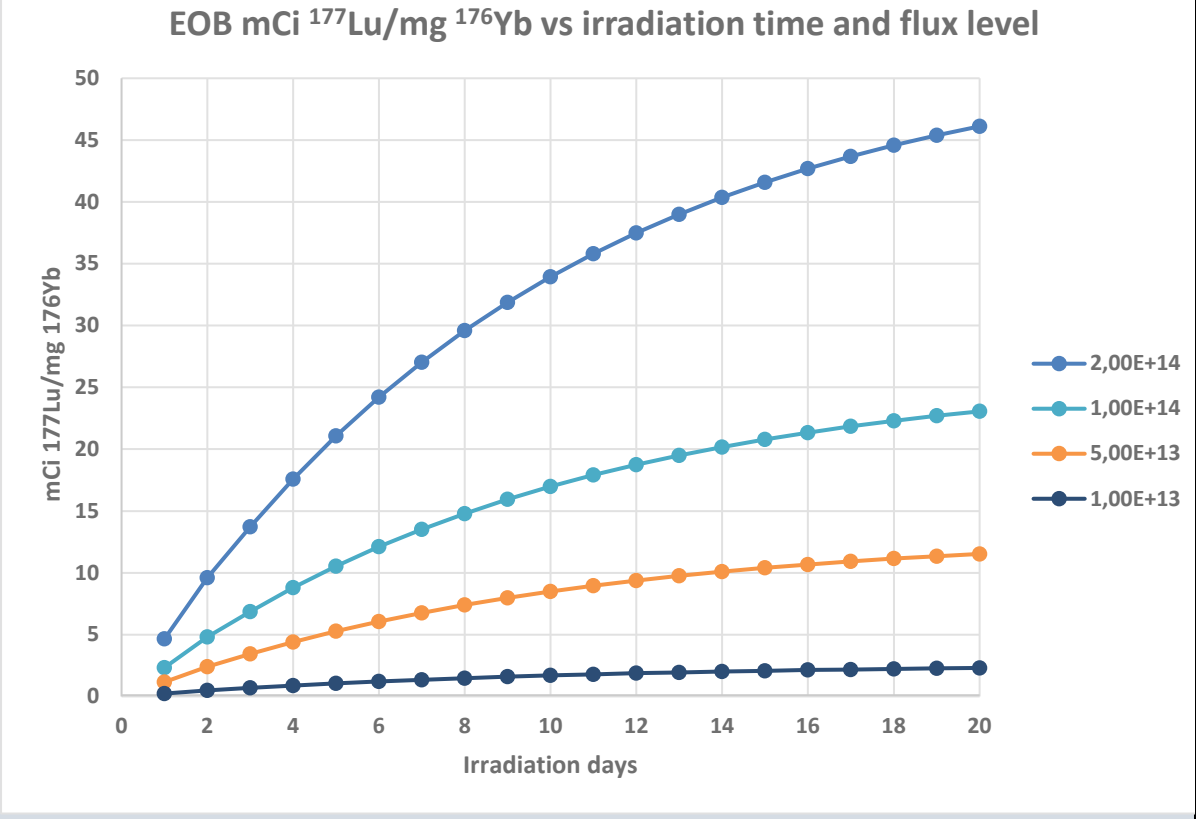


Figure 35: ^{177}Lu production rate in enriched ^{176}Yb targets (NucAdvisor simplified estimate)

NCA Lu/Yb mass ratio in the irradiated targets is generally very low (100 ^{177}Lu mCi/mg ^{176}Yb represent only 0.9 μg of ^{177}Lu per mg of ^{176}Yb). Diluted quantities are notoriously difficult to separate and necessitate complex processing steps, explaining why several 10^{14} n/cm2/s fluxes are necessary for producing NCA ^{177}Lu with acceptable yields.

CANDU production in Europe?

Only two heavy-water reactors exist in the EU – Cernavoda 1 & 2 in Romania. According to Nuclearelectrica, their isotopes production projects include only ^{60}Co. As their priority is producing electricity, they do not want to take the risks of perturbing this baseload production with possible malfunctions of isotopes targets or their handling devices.

SMART (ex-Lighthouse) project

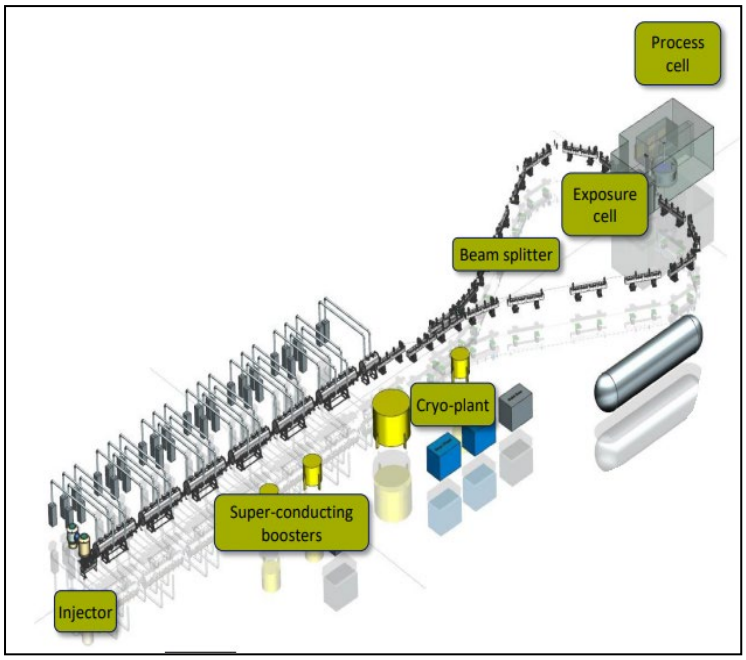


Figure 36: Lighthouse principle

In the EU, a photonuclear-based project had been launched by ASML, a Dutch leader in semiconductor lithography machines. The project is based on a FEL (free electron laser) machine similar to those ASML has developed for producing EUV light for lithography applications.

In free electron lasers, an electron beam is accelerated in a LINAC, and passes through undulators to generate radiation. Such machines are typically 60 meters long. The intense γ rays generated can be used for ^{99}Mo production through the ^{100}Mo(γ,n)^{99}Mo reaction.

The Belgian company IRE has joined ASML in the project, now renamed SMART,[79] whose schedule as of mid-2019 is shown below.

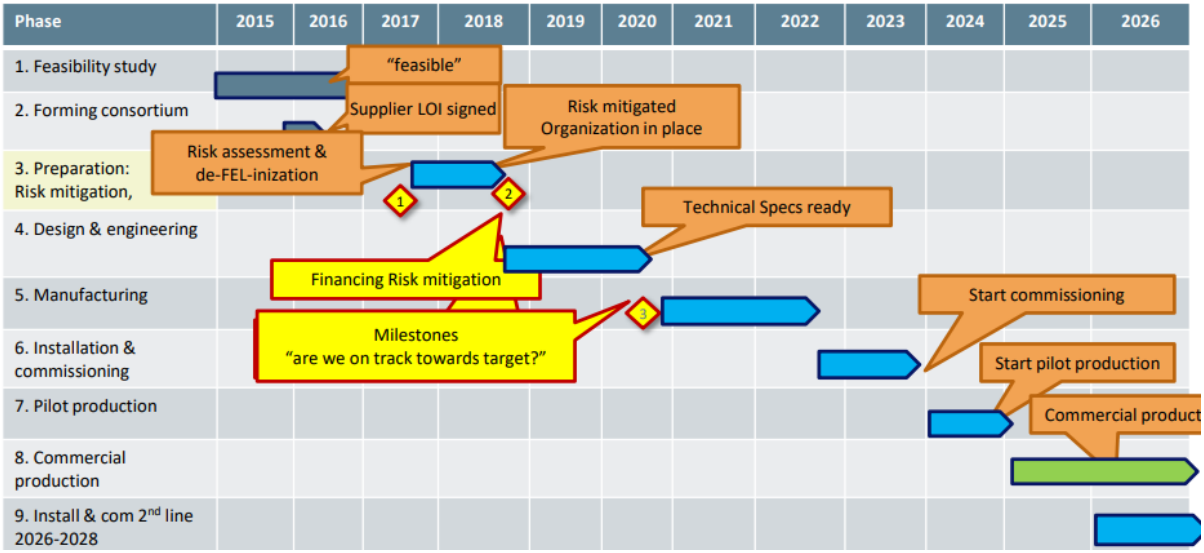


Figure 37: Lighthouse project planning as of mid-2019

2021 update:

IRE's objective is to reach higher production yields per target than comparable photonuclear installations, in order to remain compatible with the current supply

[79] https://ec.europa.eu/energy/sites/ener/files/documents/s1-3_ekollegger_ire.pdf

chain, namely with only minor adaptations of the $^{99}Mo/^{99m}Tc$ generators. The targeted performances of the accelerator have been set to 70 MeV and 40 mA.

Schedule:

The risks associated with the SMART concept are being carefully identified by IRE. The preparation and risk mitigation phase takes thus more time than anticipated in the schedule above. IRE plans now to complete the Design & Engineering phase by the end of 2022. At this date, risk (technical, market, etc.) assessment of the project will be finalized, allowing for a go/no go decision to be taken for launching construction. Production would start in 2028.

The targeted output of the installation is typically 150 000 6d-EOP Ci/year, and the investment is evaluated at between 200 and 300 M€.

Current status #11: The innovative industrial systems depicted above are under construction or in early project phases. They are often based on promising extrapolations of lab-scale experiments or validations at their individual components level.

Assessing whether one or another of these concepts will be competitive in terms of costs, production yields, reliability, quality of the goods produced, etc. with the current proven installations (cyclotrons and reactors) would require that experience feedback of their first full scale industrial system is available.

This should be the case in the coming decade, when NorthStar (2021), SHINE (2022), SMART (2027), and CANDU irradiation (2022?) will have started.

2.2.5. Processing

After their irradiation, processing the targets is necessary to extract the desired radionuclide, under a form suitable for further labelling. At the end of this phase, the radionuclide is called a "radiopharmaceutical precursor," or a "radiochemical," ready for further labelling with pharmaceuticals.

2.2.5.1. *Processing technologies*

The processing technologies encompass four main steps:

- target dissolution (in the case of solid targets),
- phase extraction of the radionuclide (separation),
- purification/filtration,
- conditioning for further use:
    - either radionuclides packages to be labelled with cold kits (generators, vials) in radiopharmacies
    - or radiopharmaceutical doses ready-to-use.

A particularly critical step of the process is the separation/purification of the desired nuclide from the irradiated targets with two purposes: isolating the desired radionuclide in carrier-free form as far as possible, and in some cases recovering the enriched target material for reuse.

Aside from the ISOL isotopic separation process, used in large research installations, based on a mass separator (see section 2.2.4.4 above), analytical chemistry techniques are used for separation:

- precipitation: the oldest, most well-established chemical separation technique. It is however generally restricted to laboratory procedures, with reduced commercial application;
- solvent extraction (liquid-liquid extraction): a well-known example[80] of this technique is the PUREX process, using tri-butyl phosphate (TBP), for separation of uranium and plutonium in the fuel reprocessing industry. Such techniques are also used for separating ^{90}Sr (^{90}Y precursor) and ^{137}Cs from spent fuel. A variant of the similar UREX process has been developed by Argonne for SHINE;
- ion exchange: this technique is one of the most popular radiochemical separation techniques due to its high selectivity and the ability to perform separations rapidly. In this technique, a solution containing the ions to be separated is brought into contact with a synthetic organic resin containing specific functional groups that selectively bind desired ions. In a later step

[80] La Hague spent nuclear fuel reprocessing plant

the ions of interest can be removed from the resin by elution with another suitable solution that differs from the initial solution;

- extraction chromatography: a form of solvent extraction where one of the liquid phases is made stationary by adsorption on a solid support.

Many of the above techniques may take hours to perform, and accelerating the processes is a goal for industrial use. One of the most rapid techniques is gas chromatography (f.i. thermochromatography). Another quick technique is separation by volatilization, but it is adapted only to elements forming volatile hydrides like As, Se, Sn, Sb and Te.

Even if the above techniques are largely used in analytical chemistry, they must be adapted to the specificities of radiochemistry:

- due to the medical destination of the product, purity is essential in order to get to the largest extent possible a carrier-free product;
- very small amounts of material are involved;
- high separation factors may be needed;
- presence of radioactivity implies certain regulatory and safety concerns;
- depending on the case, short-lived nuclides are dealt with;
- unique sensitivity is necessary (see box below).

ITM GmbH produces EndolucinBeta®, in the form of vials containing NCA $^{177}Lu^{3+}$ diluted in 0.04 M HCl (hydrochloric acid aqueous solution). The capacity of the vials produced is 2 mL or 10 mL. They contain between 0.075 mL and 3.75 mL of Lu solution of about 40 GBq/mL, diluted in HCl in order to reach the desired final GBq content, between 3 and 80 GBq (2 mL vials) and 8 and 150 GBq (10 mL vials). A typical therapeutic dose is about 800 mCi (7.2 μg of Lu), dispensed to the patient in 4 intravenous injections of 200 mCi each (1.8 μg) over a few weeks. The biggest 150 GBq vial allows for about 20 injections, i.e. 5 patients. This vial contains about 36 μg of ^{177}Lu. The sum of impurities (Fe, Zn, Cu, Pb, ^{176}Yb) must be less than 0.5 μg/GBq, with strict limitations for each impurity. These figures give an idea of the unique sensitivity associated with radioanalytical methods, which is necessary for the radiopharmaceutical's precursors production. Different analytical techniques such as ICP-OES, ICP-MS, ICP-AES, etc. are typically necessary to determine the chemical purity of the final product, served by skilled scientists and technicians.

2.2.5.2. *Processing industry*

The European industrial processing landscape is very diverse, from small radiochemistry laboratories developing new products to industrial players, mixing tens of private companies (Curium, AAA, ITM, Eckert & Ziegler, etc.) and public institutions or public-owned companies (Polatom, IRE, Izotop, CEN/SCK, NRG, Medical Universities, etc.).

Their products portfolios are diverse as well, for in-vitro or in-vivo use:

- generators or vials and cold kits for further labelling in radiopharmacies
- or radiopharmaceuticals doses ready-to-use, in liquid or solid forms.

The associated logistics are diverse as well, from processing online (cyclotrons and fluorine-radiopharmaceuticals, directly shipped to end users) to offsite processing (molybdenum, lutetium, iodine, yttrium production facilities receiving irradiated targets, involving an intermediate transportation before processing and shipping to the end-user).

Development and industrializing of suitable processes requires extensive R&D for achieving the optimal quality together with the appropriate throughputs, while taking safety and radioprotection into account at each step.

Processing being closely isotope-dependent, associated industrial installations are isotope-specific as well. They have to allow for reliable reproducibility at an industrial scale of the desired product characteristics, for each of the radionuclides that are candidates for industrial use, and require the corresponding investment.

CAPEX for these installations is commensurate with the radioactivity handled, their degree of automation and the nature of their product. Installations generally operate in conformity with cGMP[81]: a market authorization is generally mandatory for the radionuclides, as radiopharmaceutical precursors,[82] in each member state where the product is to be used.

A lutetium production laboratory costs a few M€ (see illustration below), whereas large industrial installations like a new molybdenum production facility with two production lines, with 4/5 hot cells each, may cost up to 100 M€.

Europe can rely upon equipment suppliers like Comecer,[83] Van Gahlen or Lemer Pax for the hot laboratories, Wälischmiller for the telemanipulators, and Siemens or Trasis for the radiosynthesizers, in the case where synthesis of the radiopharmaceutical is performed online with the radionuclide production.

[81] Current (constantly evolving) Good manufacturing practices: specifying premises and equipment, quality control, personnel qualification and documentation. See for example EudraLex. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines to Good Manufacturing Practice. Medicinal Products for Human and Veterinary Use
[82] Directive 2001/83 CE
[83] Now owned by ATS Automation (Canada)

Figure 38: NCA ^{177}Lu "plant" (Comecer brochure)

2.2.5.3. *Challenges associated with processing*

Processing is a key element in the radiochemicals value chain. Even if radiochemistry R&D installations are relatively easily affordable, developing appropriate processes is lengthy, which explains why public institutions are particularly active in this field. As subsequent industrial investments may be high, existence or reliable perspectives of an efficient irradiation + processing isotope-specific set for each new candidate is one of the prerequisites for big pharmaceuticals companies to invest in clinical Phase III studies. This is why new products, even promising at a laboratory scale, generally experience difficulties in ousting incumbent ones.

EU current status #12: Europe seems well equipped with laboratories and industrial players in radiochemistry. Except for the long-term threat on skills availability, treated further in this report, no specific challenge has been identified for the processing step of radionuclides supply.

2.2.6. Regulations applicable to the medical radionuclides supply chain

2.2.6.1. *Safety / radioprotection / waste regulations*

Medical applications of radionuclides are obviously associated with radioactive waste management, safety and radioprotection challenges that have already been extensively studied.[84] They also have to obey other stringent regulations.

Among the many regulations applicable, three European Directives governing safety, radioprotection and waste aspects of medical radionuclides supply chains are of particular importance:

- COUNCIL DIRECTIVE 2014/87/EURATOM of 8 July 2014 amending Directive 2009/71/Euratom establishing a Community framework for the nuclear safety of nuclear installations;
- COUNCIL DIRECTIVE 2013/59/EURATOM of 5 December 2013, laying down basic safety standards for protection against the dangers arising from exposure to ionizing radiation;
- COUNCIL DIRECTIVE 2011/70/EURATOM of 19 July 2011, establishing a Community framework for the responsible and safe management of spent fuel and radioactive waste.

Member States had to transpose these directives into their laws, regulations and administrative provisions by, respectively, 15 August 2017, 6 February 2018 and 23 August 2013, while being free to reinforce certain measures of these Directives.

EU current status #13: The EU Directives concerning waste, safety and radioprotection are among the most demanding at the international level and guarantee EU citizens suitable protection against the risks induced by ionizing radiations in general. Thus, licensing of new installations can be challenging in the EU, and corresponding cost and schedule consequences must be taken into account in the new projects.

2.2.6.2. *Pharmaceuticals regulations applicable to radiochemicals*

The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and Volume 5 of the EudraLex publication "The rules governing medicinal products in the European Union."

Good manufacturing practices, specifying premises and equipment, quality control, personnel qualification and documentation are dealt with in Volume 4.

Quality standards are subject of the European Pharmacopoeia, and EMA market authorizations are mandatory for radiochemicals.

[84] MJ-03-19-070-EN-N already cited. Chapters 8 and 9

As for nuclear regulations, Member States can sometimes adapt the EU Directives.

EU current status #14: The EU regulations relative to medicinal products are among the most demanding at the international level and guarantee EU citizens suitable protection against the risks induced by the use of pharmaceuticals. Thus, licensing of new installations can be challenging in the EU, and corresponding cost and schedule consequences must be taken into account in the new projects.

2.2.6.3. *Transport regulations*

As for safety, radioprotection and waste, transportation regulations are particularly demanding, and guarantee the safety of transport in Europe. They are applied all along the diverse radionuclide supply chains, from source material to shipping of the radiochemical end-product.

Transportation of radioactive goods in Europe are mainly governed by:

- Directive CE-2008-68 (Transport of Hazardous Material), which refers to:
  - ADR (Accord for Dangerous goods by Road),
  - RID for rail transport,
  - ADN for river transport (generally not used in the medical radionuclides supply chain).

  ADR, RID and ADN establish limitations on radioactivity levels, together with prescriptions on transport packages, among many other measures (tagging, surveillance, etc.); radioactive transports are specifically detailed in Class VII of these regulations.
- Euratom transport regulation 1493/93[85];
- transport aspects of the Euratom regulation 2013/59 (BSS Directive)[86];
- ICAO that regulates air transport;[87]
- IMDG (International Maritime Dangerous Goods) that regulates sea transport (not used in the radionuclides supply chain).

[85] This Regulation shall apply to shipments, between Member States, of sealed sources and other relevant sources, whenever the quantities and concentrations exceed the levels laid down in Article 4 (a) and (b) of Directive 80/836/Euratom. It shall also apply to shipments of radioactive waste, between Member States, as covered by Directive 92/3/Euratom. Practically, a holder of sealed sources or radioactive waste who intends to carry out a shipment of such sources or waste must obtain a written declaration of the consignee that the latter complies with Directive 83/836 (art. 3) and relevant regulations of its country.

[86] Where transportation is essentially treated from the radioprotection protection standpoint

[87] International Civil Aviation Organization (ICAO) is a specialized agency of the United Nations. ICAO is distinct from other international air transport organizations, particularly because it alone is vested with international authority (among signatory states): other organizations include the International Air Transport Association (IATA), a trade association representing airlines.

Of particular importance for avoiding any spread of radioactivity in case of a transport accident are the packages/containers. They are to be chosen according to the limitations prescribed by the regulations, by order of increasing activity transported:

- type A, used for instance for transporting $^{99}Mo/^{99m}Tc$ generators,
- type B, for larger radioactivity amounts,
- type C, for air transport.

Each package type obeys specific requirements relative to the robustness of the package. To be used, the packages must obtain a (temporary) licence from each of the concerned Safety Authority.

Each MS is responsible for implementing the European regulations regarding transport and can even go beyond the EU regulations. This represents a major burden for the producers and the carriers, especially for international shipping. For air transport, airlines and airports are free to refuse radioactive freight. For trucks and their drivers, local rules may apply, as in the different Länder of Germany for instance[88].

EU current status #15: Due to the just-in-time characteristics of the medical radionuclides supply chain, transport represents a major obstacle to the development of medical radionuclides supply, particularly for centralized production installations serving the international market.

[88] https://www.lfu.bayern.de/strahlung/transport/begriffsbestimmung/index.htm
https://www.lfu.bayern.de/strahlung/transport/index.htm (in German)

2.2.7. Skills development & communication

The large spread of nuclear medicine products over the EU and the production of novel radionuclides for innovative radiopharmaceuticals require multidisciplinary collaboration between nuclear physicists, material scientists, radiochemists, engineers, radio pharmacists, immunologists, structural biologists, health physicists, coordination chemists, nuclear medicine practitioners, etc. For maintaining and developing the entire medical nuclides supply chain at an EU level, for developing products and equipment, constructing and operating the installations, for bringing safe products on the market, the availability of skills is key.

A major threat to this availability is the disaffection among European students for nuclear and radiochemical engineering, sciences and technologies. The EU Council is aware of this situation;[89] it *"invites the Commission in cooperation with Member States to communicate on the benefits and risks of various non-power applications of nuclear and radiological technologies"* and "*underlines the importance of further strengthening the capacity building of Member States, particularly through interregional, regional and national training courses and other activities in areas of non-power nuclear and radiological science, technology and applications*."

The EU Member States which are the most active in the radiochemical industry and research are also the countries which have a long nuclear-energy record: Germany, France, Belgium, Netherlands, Sweden, Czech Republic, Slovakia, Italy, Romania, etc. In these countries, professional bodies and networks devoted to the different skills involved in the radionuclides industry and research may be very active. For instance, for radiochemistry, the "Fachgruppe Nuklearchemie" (radiochemistry specialized group) of the "Gesellschaft Deutscher Chemiker" (German Chemistry Society), relying also on a historically strong chemical industry, brings together an active network of universities, research installations and industrial sites, linked with hospitals, which might partly explain the success of Germany in developing new radiochemicals and pharmaceuticals.

[89] "Council Conclusions. Non-power nuclear and radiological technologies and applications." 24/5/2019. ATO 56/RECH 271/SAN 256

EU current status #16: Given the successes and promises of European nuclear medicine, communicating on the medical radionuclides industry and the importance of research should be a top priority action in the Europe Beating Cancer Plan[90], in complement with the actions of the national medical and pharmaceutical professional bodies concerned.

Many tools exist for promoting entry of young students in the careers linked with the radionuclides supply chain, like for instance Marie Skłodowska-Curie actions, as implemented in the Promed-Medicis programme. However, large-scale communication should be envisaged in Europe in order to restore the image of nuclear applications in the younger generation and increase the attractiveness of nuclear careers, particularly those related to Nuclear Medicine.

2.2.8. General conclusion of the step-by-step analysis

Each step of the radionuclides supply chains (source material, enrichment, irradiation, processing, etc.) raises specific questions which make the path to industrialization and medical success of new nuclides an obstacle course, even for ones that are promising at the lab scale.

That fact necessitates long-term multidisciplinary R&D efforts, even before the interest of investors (specialized laboratories, large pharmaceuticals companies, etc.) able to take over from the clinical trials phases is stimulated. That process may take 20 years or more as shown by the ^{177}Lu example.

Public support in such long-distance hurdle races remains mandatory, as shown by the US (Appendix G) or Russian examples, not to mention China and India, even if commercial interests must take over at a certain step of the development.

[90] COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL Europe's Beating Cancer Plan COM(2021) 44 final {SWD(2021) 13 final}

3. How to foster a sustainable supply of radionuclides in the European Union?

In this chapter, future European radionuclide demand is first quantified (§3.1.1).

The question of whether existing installations, taking into account their possible life extensions, would be able to cover EU needs in the next two decades is then assessed (§3.1.2).

The most delicate steps of the supply chains for securing European needs are identified and translated into several scenarios for European supply (§3.2).

The scenarios are then subjected to a multi-criteria analysis (§3.3) and conclusions are proposed.

3.1. EU current supply chains capability to cope with future RN demand

Securing Europe's radionuclide demand may require taking initiatives in Europe to renew or build new facilities along the supply chain (*from enrichment to processing facilities)* and support Research & Development activities. In order to build relevant scenarios, two questions are first answered:

- What are the variations expected on EU radionuclide demand in the next two decades, nuclide per nuclide? (Chapter 3.1.1),
- To what extent can the current European supply chains contribute to secure RN supply up to 2040? (Chapter 3.1.2).

Many different technologies and manufacturing routes, European and foreign projects could be competing in the near future, resulting in large uncertainties when trying to imagine future supply chains.

With these elements and the issues and the options identified in the preceding chapter along the different supply chains, diverse scenarios can be defined, each having advantages and drawbacks for European security of supply.

As it is not practicable to individualize each combination of all the possibilities, the conservative approach chosen in this report is to develop typical bounding scenarios, allowing identification of the associated risks and benefits for security and sustainability of radionuclide supply in the EU (Chapter 3.2).

3.1.1. What are the demand trends for radionuclides in the next two decades?

Quantifying future demand is a difficult task, especially for developing therapeutic radionuclides considering the lack of a reliable and homogeneous EU-wide database and the technical and market specificities (radioactive decay and time for shipping to users, different production routes, calibration standards, etc.).

However, given the lengthy time delay necessary for getting market approval of new pharmaceuticals, the number of ongoing clinical studies[91] for each RN is a pertinent indicator for validating the trends.

For the radionuclides of interest in this study, an overall assessment of current and future European demand is summarized in the following table (see Annex for more details).

[91] https://clinicaltrials.gov/ct2/home. 219 countries covered. Stats made on the presence of various forms of the RN's name in the title and content of the studies. Only indicative trends.

RN	Use	Ongoing clinical studies	Current EU demand (nb of procedures)	Current & expected trend	Future EU demand (nb of procedures)
^{99m}Tc	SPECT	~500	~10 M	↗	~11 M
^{123}I	SPECT	~40	10 – 50 k	↗	50 – 100 k
^{18}F	PET	~1000	~1 M	↗	1,2 – 1,5 M
^{68}Ga	PET	~250	20 -30 k	↗↗	0,5 – 1 M
^{64}Cu	PET/Therapy	~25	< 1 k	↗↗	50 – 100 k
^{89}Zr	PET	~40	< 1 k	↗	10 – 50 k
^{124}I	PET	~20	< 1 k	↗	10 – 50 k
^{177}Lu	Therapy	~90	5 – 10 k	↗↗	Up to 100 k per RP
^{90}Y	Therapy	~80	10 – 50 k (RSV) > 10 k (TRNT)	→	10 – 50 k (RSV) > 10 k (TRNT)
^{131}I	Therapy	~60	10 – 50 k	→	10 – 50 k
^{223}Ra	Therapy	~50	20 – 40 k	→	20 – 40 k
^{225}Ac	Therapy	~15	*Limited to research & clinical trials*	*Demand correlated to clinical trials successes/failures*	
^{211}At	Therapy	***Few Ones (<10)***			
^{188}Re	Therapy				
^{166}Ho	Therapy				
^{67}Cu	Therapy				
^{212}Pb	Therapy				
Tb *isotopes*	Theranostics pairs				
Sc *isotopes*	Theranostics pairs				

Legend	Trend
→	Steady
↗	Limited growth (1-2%/yr)
↗↗	High growth (>5%/yr)

Table 17: Quantification of future RN demand in 2040

For radionuclides currently in the R&D phase, (^{124}I, ^{89}Zr, ^{67}Cu, ^{212}Pb, ^{166}Ho, ^{188}Re, $^{149\text{-}152\text{-}155\text{-}161}$Tb, $^{44\text{-}47}$Sc, ^{211}At…), with no global supply chain established to date, future demand will be correlated with the success of RP clinical trials and radiopharmaceutical industry support.

It is assumed that for most of these radionuclides, demand shall remain limited to R&D at least until 2030, with limited volumes of doses needed per year. Nevertheless, for the sake of conservativeness, it is assumed that by 2040, the supply chain should at least be sufficient to produce up to 10,000 doses for therapeutic RNs (e. g. ^{212}Pb, ^{188}Re, ^{47}Sc), while the demand for imaging RNs is capped at 100,000 doses per year for EU needs.

Radionuclides market dynamics are summarized in the following table:

RN	Period		
	2020	2020-2030	2030-2040
Large-scale commercial production	^{99m}Tc ^{18}F ^{131}I, ^{123}I ^{223}Ra, ^{90}Y	^{99m}Tc ^{18}F ^{131}I, ^{123}I ^{223}Ra, ^{90}Y ^{68}Ga ^{177}Lu	^{99m}Tc ^{18}F ^{131}I, ^{123}I ^{223}Ra, ^{90}Y ^{68}Ga ^{177}Lu ^{64}Cu
Limited commercial production	^{68}Ga ^{177}Lu ^{64}Cu	^{64}Cu	**Unknown**
Production for R&D and clinical trials	^{225}Ac ^{124}I, ^{89}Zr, ^{67}Cu ^{212}Pb, ^{166}Ho, ^{188}Re Tb, $^{44-47}$Sc, ^{211}At	^{225}Ac ^{124}I, ^{89}Zr, ^{67}Cu ^{212}Pb, ^{166}Ho, ^{188}Re Tb, $^{44-47}$Sc, ^{211}At	**Unknown**

Table 18: Demand dynamics for radionuclides, per type of use (plain line: likely evolution / dotted line: uncertain evolution based on expert judgment) – Source: NucAdvisor

3.1.2. To what extent could EU current supply chain installations contribute to secure supply up to 2040?

European industry is currently the leading exporter of various RNs (e. g. ^{99}Mo, ^{177}Lu, ^{68}Ga), which puts it in a favourable position on the international market. This industry relies on dozens of industrial and public players, located throughout the EU, at all steps of the supply chain, for industrial production as well as for research. Such diversity ultimately guarantees privileged access to most radionuclides for EU citizens.

As seen in Chapter 2, three elements of European supply chains appear to be particularly critical when considering the future security of supply in Europe:

- the accelerators/cyclotron fleet, for accompanying the development of PET isotopes and α-therapeutic isotopes;
- the fission/neutron activation irradiation installations, due to the planned definitive shutdowns of several research reactors within the next two decades, for producing the most-used therapeutics (e. g. NCA ^{177}Lu, ^{131}I, and ^{90}Y) as well as ^{99}Mo;
- the source material supply, for both stable isotopes and metallic HALEU, due to the limits of current EU production means.

The ability of current European equipment to meet future European needs is assessed in the next three sections.

3.1.2.1. Irradiation installations self-reliance: SMC and MEC accelerators

It has been shown in §2.2.4.2 that:

- the expected growth of ^{18}F should be fully covered by the existing production network of SMCs (from ~1M procedures in 2020 to 1.2-1.5 M in 2040) and corresponding periodic renewals;
- the direct route for producing ^{99m}Tc with cyclotrons (promoted in Canada) is not practicable for Europe;
- a limiting factor for the current network is the inability to expand significantly the production spectrum by producing and delivering additional RPs over the day. Installations planning are generally optimized for 5-10 RN/RP per day, and it is often impossible to add new production cycles during the day;
- accordingly, if no new cyclotrons are built, or current ones not replaced by more efficient machines, the EU network will not be able to satisfy demand for new RPs or RNs:
    - radionuclides that can only be locally produced in accelerators (short half-life and no generator possibility) and for which supply chains are not yet industrialized in Europe (e.g. ^{123}I, ^{124}I, ^{89}Zr, ^{211}At, ^{64}Cu) might face supply difficulties, if and when corresponding RPs develop at an industrial scale;
    - that is the case for ^{68}Ga as well, if cyclotron-direct production is preferred to the Ge-generator route;
    - an exception is ^{225}Ac; its longer half-life (9.9 days) could allow centralized installations like (γ,n)[92] or $(p,2n)$[93] cyclotrons, or Myrrha to supply Europe.

However, development of a MEC cyclotron commercial network remains essentially in the hands of private companies, which will perform investment decisions only once demand is secured and established.

Europe cannot base its long-term self-reliance on the existing cyclotron installed base and investments are necessary because:

- existing PET centres already have optimized production planning and expanding the production spectrum over the day is not feasible for most players;
- many cyclotron production routes are not yet industrialized in EU and will necessitate investments in case of increasing demand from the medical sector (e.g. ^{123}I, ^{124}I, ^{89}Zr, ^{211}At, ^{64}Cu, ^{68}Ga).

[92] See JRC Karlsruhe's research, for example
[93] As proposed by Alfarim for instance

3.1.2.2. Irradiation installations self-reliance: large centralized installations

The current mass-producing EU reactors and their life extension possibilities are illustrated below, showing that only FRMII and RJH remain operational after 2040.

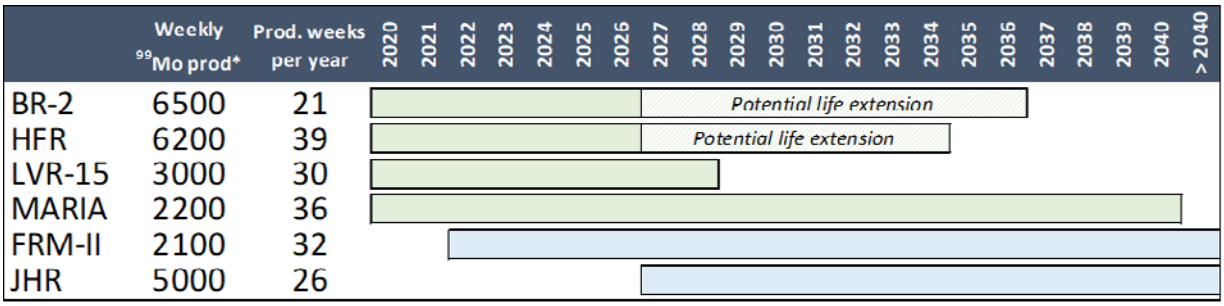


Figure 39: Lifetime of the existing European Research reactors (source OECD)

Weekly ^{99}Mo production capabilities and production weeks per year are those currently announced by the operators.[94] Potential life extensions are those envisaged by the operators, as given in the OECD report, but not yet endorsed by the regulators.

New projections have been announced by the operators at the 17th Plenary Meeting of the EU Observatory for the Supply of Medical Radioisotopes (29 June 2021):

- LVR-15: > 2030, unlimited license,
- start of ^{99}Mo production in FRMII: 2023/2024.

They have not been taken into account in this paragraph, but they do not change fundamentally what follows.

According to the OECD, *"In the HLG-MR policy principles, it was proposed that a processor should hold a level of paid ORC sufficient to replace the largest supplier of irradiated targets in their supply chain. Likewise, participants further down the supply chain should hold similar levels of ORC. This is the so-called (n-1) criterion, that is, the level of ORC required by a customer to ensure that no supply disruption occurs when their largest individual supplier has an unplanned problem. There have been occasions over the last few years when, for some participants, the (n-2) criterion (e.g. the ability to replace their two largest suppliers) may have been a more appropriate measure for ensuring secure supply."* The n-1 criterion is all the more appropriate as the number of installations is reduced: losing one supplier out of two is more severe than losing one out of 4 or 5.

With the n-1 criterion, it is possible to assess the probability that the EU reactor fleet can meet European industrial needs, week after week all year long, during

[94] High-Level Group on the Security of Supply of Medical Radioisotopes, "The Supply of Medical Radioisotopes. Medical Isotope Demand and Capacity Projection for the 2019-2024 Period" NEA/SEN/HLGMR(2019). JHR data have been updated by the CEA.

the next two decades. The EU's ^{99}Mo needs are evaluated at 30% of the global demand.

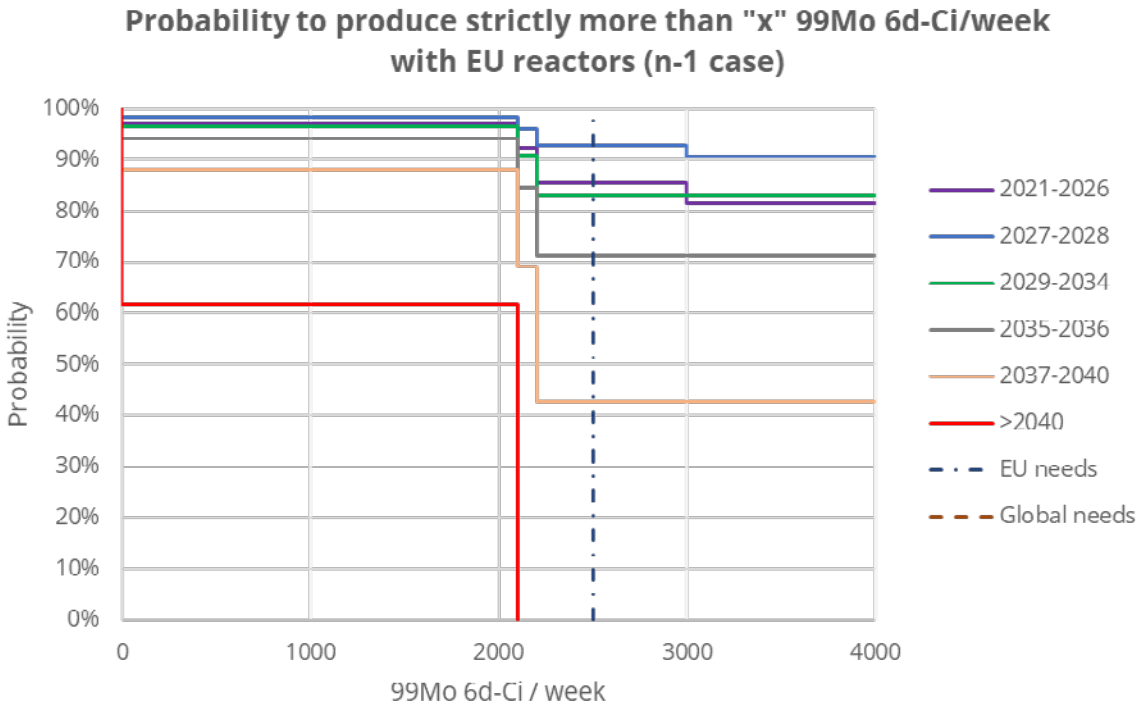


Figure 40: ^{99}Mo production capacities of existing reactors as compared to EU needs

This figure shows that the probability of meeting ^{99}Mo European needs with European means degrades with time, and that the two reactors remaining after 2040 are unable to entirely cover EU needs (n-1 case).

The above figure concerns only ^{99}Mo production. The case is even worse when considering the needs for NCA ^{177}Lu. Indeed, more than half a dozen high-flux irradiation positions in a dedicated reactor would typically be needed to produce the 100 000 Ci of ^{177}Lu necessary for around 120 000 treatments in Europe. 100 000 Ci is just sufficient for one single ^{177}Lu labelled radiopharmaceutical reaching a large market in Europe and is far below what is anticipated in 2040 (see projections Table 17). This is without accounting for the simultaneous needs for other (n,γ)-produced nuclides than ^{99}Mo and NCA ^{177}Lu. Such capacities are beyond the capacities and missions of FRMII and RJH for the reasons given in §2.2.4.3.

	Future EU weekly demand	Weekly irradiation capacity	
		FRM-II *Up to 65% availability*	**JHR** *Up to 55% availability*
^{99}Mo	2200-2800 6d Ci EOP	Up to 2100 6d Ci EOP	Up to 5000 6d Ci EOP
^{177}Lu	~1500 Ci EOI	Up to 155 (NCA) Ci EOI	*Undisclosed*

Table 19: FRMII and RJH production capabilities for ^{99}Mo and NCA ^{177}Lu

In the perspective of EU self-reliance, new large installations are thus mandatory for Europe. Such position is shared by the European industry, which recently highlighted the need for additional installations to satisfy European demand. Their position being the following[95]:

> *"It is necessary to anticipate the shutdown of several irradiating reactors in the next decades. To maintain redundancy and enough capacity, it is necessary to build at least one new reactor that is (at least partly) dedicated to target irradiations in the next decade and that has a significant number of normal operating days/year and a significant production capacity for ^{99}Mo production. […] One or two new (at least partly) dedicated irradiation reactors will be necessary in the next decade to replace the reactors expected to shut down."*

However, new large installations other than research reactors can be considered:

- a (n,γ) production installation like a European SHINE;
- large (p,x) production installations, like a centralized cyclotron installation or Myrrha;
- photonuclear-based installations like SMART or a "European NorthStar" (no known project for the time being).

Their performances are compared more in depth in §3.3.2.2, but each of these installations has its specific capacity in terms of RN production range and volume.

[95] From European Research Reactor Position Paper by CEA, NCBJ, PALLAS, NRG, SCK-CEN, TUM, RCR – published on the 15th of June 2018

	Cyclotrons	SMART	SHINE	Research reactor	CANDU (Canada)
Additional scope of RN production (versatility adaptability)	PET imaging isotopes + ^{225}Ac, ^{67}Cu, ^{64}Cu, ^{47}Sc to be proven	^{99}Mo (low activity) and theoretically ^{225}Ac, ^{67}Cu, ^{64}Cu, ^{47}Sc to be proven	Fission RN (^{99}Mo, ^{131}I, ^{133}Xe) Scope extension theoretically possible to be proven	Simultaneous production of all fission and neutron activation RN, comprising industrial ones	^{60}Co ^{177}Lu (Bruce 7) ^{99}Mo (project)

Figure 41: Isotope production scopes of industrial installation options

Whereas production capabilities and levels are well known for research reactors, they are more uncertain for the other, emerging production routes.

For R&D purposes, Europe is well equipped with large research installations. This supply deserves to be better coordinated, as proposed in the PRISMAS-MAP initiative.

For the large irradiation installations it appears that, if EU self-reliance is targeted for all necessary isotopes, new large industrial installations are necessary, as well as better coordination of large research R&D installations, complementing the adaptation of the cyclotron fleet.

The relative merits of the different options for large industrial installations are further discussed in Chapter 3.3.

3.1.2.3. *EU enrichment and fuel manufacturing capability self-reliance*

HALEU case

HALEU is used for ^{235}U targets (^{99}Mo production in research reactors, 15-20 kg/yr for EU needs) and overall, for their fuel. The HALEU needed is in metallic form and is procured mainly from the USA (Y12 installation, down-blending weapon-grade HEU) and possibly from Russia. It is transformed into fuel and targets, essentially in the CERCA premises in Romans, France.

No HALEU enrichment capability exists in Europe, and no installation exists for producing metallic uranium.

Tensions can be anticipated on this market from 2030 onwards, especially if new small reactor designs using HALEU reach the market.

This situation is a threat to EU security of supply, as HALEU supply is mandatory for decades:

- for the current mass-producing reactor fleet[96]: up to 2040 for BR2, HFR, LVR15, MARIA and far beyond for FRM-II and RJH;
- in the case of new fission-installations (research reactor(s) or EU-SHINE), or even new HALEU-fuelled power reactors (SMRs).

[96] Some of them (e. g. BR2, FRMII) have not yet even completed their transition from HEU to HALEU.

As seen in §2.2.4.3, the challenge of sustainable HALEU supply for the EU is being closely overseen by the ESA (European Supply Agency). The ESA Advisory Committee's Working Group on European production of low-enriched (19.75%) uranium was re-instated in spring 2021 and mandated to continue the work based on the recommendations given in the 2019 report.[97] The group will explore the necessary conditions for establishing European production capacity for HALEU to respond to the EU needs for the research reactors fuel and medical radioisotopes production.

Stable isotopes enrichment capabilities

For gaseous centrifugation, there is a single[98] EU player with stable isotopes enrichment capability (Urenco), whose product portfolio currently allows part of the EU's source materials demand for targets to be satisfied. Though Urenco is expected to expand its capacity and product portfolio over the next few years, and though ORANO has announced ambitions in this domain, it is possible that import of enriched isotopes will remain a necessity (Iron, Tin, Osmium, Lead, and Sulphur isotopes).

Other forms of enrichment technologies (distillation, EM enrichment) are not industrially available in the EU.

- Despite the fact that engineering skills exist in Europe, European electro-magnetic enrichment capabilities are limited to laboratory scale. An industrial electro-magnetic isotopes separation installation (EMIS) might be necessary.
    - ^{176}Yb (for NCA ^{177}Lu production) is industrially produced through EMS and fully imported from Russia. The Russian company EKP, with a production capacity of about 700g per year, is currently the largest supplier. That production capacity is to be compared to future estimated demand: the ^{176}Yb needed for the treatment of 100,000 patients (4 doses per patient) with NCA ^{177}Lu per year is roughly 3 kg/year (4 times higher than current worldwide production capacity), and would represent a 48 MUS$ yearly market (^{176}Yb is valued around 16,000 US$/g). ^{176}Yb irradiated target recycling would obviously reduce demand, but recycling limitations may exist (impurities, costs, etc.).
    - An EM facility could be combined with gaseous centrifugation (as in the ESIPP facility, see Chapter 2, Figure 18) for easier production of

[97] "Securing the European Supply of 19.75% enriched Uranium Fuel" – May 2019 https://ec.europa.eu/euratom/docs/ESA_HALEU_report_2019.pdf
[98] ORANO's enrichment capability is focused towards ^{235}U for NPP use.

^{98}Mo for ^{99}Mo (n,γ) production, and also ^{100}Mo necessary for direct production of ^{99m}Tc in large accelerators.

- A European EMIS installation would have additional benefits beyond the production of medical radionuclides and would be welcomed by other applications and sciences (see §3.3.2.4). Hence, whilst an EU EMIS industrial facility would represent a significant investment (>100M€), its use would go beyond the sole enrichment of ^{176}Yb, and could justify building a centralized, shared installation in Europe.

- ^{18}O for ^{18}F production in cyclotrons is produced by distillation. As seen in §2.2.2, a diversified international market exists for ^{18}O supply. The necessary amount for 1,000,000 exams per year (European needs) is about 300 kg/yr, representing a value of less than 10 M€/yr. It is likely that, given the market price, the global capacity (6 times Europe's consumption), as well as the number of global suppliers, investing in an enriched ^{18}O water EU-installation would not be considered by strictly private interests.

The quantitative European needs for enriched stable isotopes are summarized on the next table.

Source material for targets	Enrichment technology	Rationale on expected European needs up to 2040	Current EU supply	Supply increase needed[99]
^{98}Mo	Centrif.	Demand for ^{98}Mo shall remain limited to potential non-EU CANDU production of ^{99}Mo. No EU project at this stage to launch production in EU CANDU reactors (Romania).	Limited quantities supplied (Urenco)	+
^{100}Mo	Centrif.	Demand for ^{100}Mo will depend on production volumes and success of recycling used targets. Target characteristics currently unknown for EU/US projects (SMART/NorthStar). An order of magnitude of 1-5 kg of ^{100}Mo per year for a large industrial player.	Limited quantities supplied (Urenco)	+
^{18}O	Distill.	The EU demand is currently equivalent to roughly 300kg per year of ^{18}O (2-4mL needed per batch allowing for 15-25 exams)	None	+++
^{68}Zn	Centrif.	Demand for ^{68}Zn is currently limited, in the absence of industrial ^{68}Ga direct production. A mass of 100-300mg per solid target could be considered, in the case of 100 cyclotrons equipped with solid target and producing on a daily basis, up to roughly 2-3kg or ^{68}Zn could be needed per year.	Limited quantities supplied (Urenco)	+
^{176}Yb	EMS	Demand of ^{176}Yb is expected to rise drastically in the next decade. Target need depends on reactor flux and expected Ci at shipment (process duration): With a production in high flux reactors (2 10^{14} n/cm^2/s), this could lead to a yearly demand of ~3 kg ^{176}Yb per year to supply 100,000 Ci	None	+++

[99] Assessment of the supply increase needed in European production capacity to reach self-reliance. From limited to large increase (+ to ++) to setting production capacity from scratch (+++). Such increase will be linked to success/failures of new projects and new RP developments.

Source material for targets	Enrichment technology	Rationale on expected European needs up to 2040	Current EU supply	Supply increase needed[99]
^{152}Gd ^{155}Gd ^{160}Gd	EMS	Demand for Gd isotopes would depend on the development pace of Terbium radionuclides.	None	+++
^{130}Te	Centrif.	Demand for ^{130}Te is assessed in the case where no more production from ^{99}Mo fission route is available. Enriched ^{130}Te is only used for high specific activity needs. If 25% need of high SA is assumed, considering a total demand of 50k doses of 100mCi at end of irradiation and a yield of 0.83Ci/g of ^{130}Te, the corresponding yearly need for enriched ^{130}Te is 1.5 kg/year and ~15 kg/year of ^{nat}Te	Limited quantities supplied (Urenco)	+

Table 20: Estimate of stable isotopes needed to support EU demand

EU HALEU and stable isotopes enrichment capabilities – conclusions

The HALEU manufacturing capabilities for the current irradiation production workhorses as well as the enriched source material for isotope production are both respectively inexistent or insufficient, making EU currently strongly dependent upon imports.

Such a situation is of concern as recent history has shown that disruption of international trade / air transport in case of pandemics (e. g. Covid-19), natural disasters (e. g. volcanic eruption) major acts of terrorism (e. g. 9/11) or political sanctions / embargoes are not only theoretical possibilities.

If priorities are to be considered:

- investing in an installation for HALEU enrichment and metallization seems a priority 1, given the threats on US supply, for guaranteeing the supply for existing and future installations;
- with regard to the current Russian monopoly, EM enrichment capability seems the next priority, given the predicted importance of ^{177}Lu in future cancer therapies, and despite the market entry of the US SIPF installation beyond 2030;
- reinforcing European (URENCO, ORANO) centrifugation enrichment of stable isotopes, possibly combined with EM enrichment could be proposed at the same level of priority, before investing in a distillation installation, taking into account the associated breadth of global ^{18}O sourcing possibilities.

3.1.3. European self-reliance: general conclusion

Recent history has evidenced the weaknesses of the European radioisotopes supply chain. The supply of metallic uranium from the US's Y12 plant is more and more problematic;[100] ^{176}Yb supply is in the sole hands of Russia; China masters most of the raw materials and international tensions can no longer be excluded. The eruption of the Eyjafjallajökull in 2010 had already disturbed air transport. At the date of this report, due to the COVID pandemic, many airlines are no longer operating, and border closures are also affecting the distribution of radioisotopes.[101] According to IAEA,[102] many hospitals have delayed diagnosis applications, and hospitals in some countries have been forced to reschedule interventions as they are no longer receiving the necessary isotopes. In this context, the issue of European self-reliance on the different supply chains becomes particularly acute.

Besides the considerations expressed above about the necessary additional enrichment and HALEU supply capabilities in Europe, the elements supplied in §3.1.2.1 and §3.1.2.2 suggest that, if the EU wants to secure its supply with its own means, current accelerators/cyclotrons and fission/neutron activation production installations would not be sufficient for ensuring EU self-reliance in the long term, without new European installations.

In order to meet European demand with own European irradiation production means, a mix of the new irradiation installations presented in the next table would be needed. Different manufacturing routes or irradiation installations are sometimes possible (e.g. ^{99m}Tc: direct production or via 99Mo; or ^{68}Ga: direct production or via Ge generator).

[100] https://www.nrc.gov/docs/ML1924/ML19241A501.pdf
[101] https://s3.amazonaws.com/rdcms-snmmi/files/production/public/images/Carousel_Generic/NMEu%20COMMUNICATION%2030%20MARCH.pdf
[102] https://world-nuclear-news.org/Articles/Medical-isotope-supply-chain-faces-challenges-from

RN	$T_{1/2}$ (G) generator	Existing installations remaining beyond 2040	Additional irradiation installations necessary for EU self-reliance beyond 2040				
			SMC	MEC	HEA	Others	Research reactor
nca ^{177}Lu	6,7 d	2 (n,γ)					at least 1
^{90}Y	64,6 h						
^{131}I	8 d					1 SHINE	
^{166}Ho	26,8 h						
^{188}Re	17 h						
^{223}Ra	11,4 d				Annex 10		
^{99m}Tc (^{99}Mo) or	66 h (G)					1 SHINE or (*)	
^{99m}Tc (direct)	6 h	-	> 100				
^{18}F	109,8 min	> 200 SMC					
^{68}Ga (direct)	67,7 min	few installations in EU	> 200				
or ^{68}Ga (G)	271 d (G)			1-3			
^{123}I	13,2 h			1-5			
^{124}I	4,2 d			1-5			
^{211}At	7,2 h			>10		(*)	
^{64}Cu	12,7 h			~50			
^{89}Zr	3,3 d			1			
^{225}Ac	9,92 d			1-5	1-5	(*)	
^{67}Cu	2,58 d			depends on RPs development		(*)	Fast neutrons
^{44}Sc	4 h	large research installations	To be defined after R&D phase				
^{47}Sc	3,3 d						
^{149}Tb	4,1 h						
^{152}Tb	17,5 h						
^{155}Tb	5,3 d						
^{161}Tb	6,9 d						

Note: (*) production via electron accelerators routes, e.g. with Rhodotrons or SMART IRE project

Table 21: New irradiations installations needs per radionuclide to achieve EU self-reliance

Assessing in detail which combination of these installations would be the optimum for Europe from all points of view (self-reliance, investment needs, equal access, waste minimization, cost of medicines, TRL, etc.) is not yet possible, due to many uncertainties impacting:

- demand at the EU level, by radiopharmaceutical, by isotope taking into account that these demands are correlated, geographically spread, and depend upon the time to market of the possible future RP labelled with these isotopes;
- combined probabilities of each production route for each isotope to reach the industrial market, depending upon:
    - the achievable industrial production yields (and their time-to-market), isotope per isotope, particularly uncertain for breakthrough developing options;

- the willingness of the industry to invest (into MEC cyclotrons, for instance), which will in turn depend upon detailed market demand isotope by isotope and which is closely dependent upon external influences like those of the international markets;
- the possible life extensions, the ability to upgrade existing installations and the possibilities for co-production of several isotopes in a given installation.

More information about the costs of the different options are given in §3.3.2.3.

The figures in the previous table are to be taken as evaluations which will become more substantiated as more details are available about the demand and supply parameters. Since the number of combinations to be considered and the still significant associated uncertainties prevent the implementation of an analytical approach to all possible scenarios, a reduced number of typical scenarios is defined in the next chapter and is subjected to a multi-criteria analysis, of which the level of investments necessary.

3.2. Definition of scenarios for long-term European supply

3.2.1. Definition rationale

Six findings conditioning security of supply have been substantiated in this study.

1. Accelerators/cyclotrons and fission/neutron-activation large installations are complementary, in the long-term, as covering different isotopes-scopes.
2. If reduction of EU reliance on foreign supply is targeted, new investments are necessary in both domains, as existing installations cannot fill EU needs in the long term.
3. The production scopes of the different large industrial installations options are not equivalent.
4. Other critical points from a security of supply point of view are HALEU supply and enrichment of stable isotopes.
5. The coordination between large European research installations is key for supplying R&D isotopes and promoting new production routes.
6. Life extension and revamping of existing installations is to be considered whenever possible.

Starting from these issues, many scenarios can be imagined for securing European supply. Four typical scenarios have been defined and are subjected to a multi-criteria analysis for assessing their relative merits.

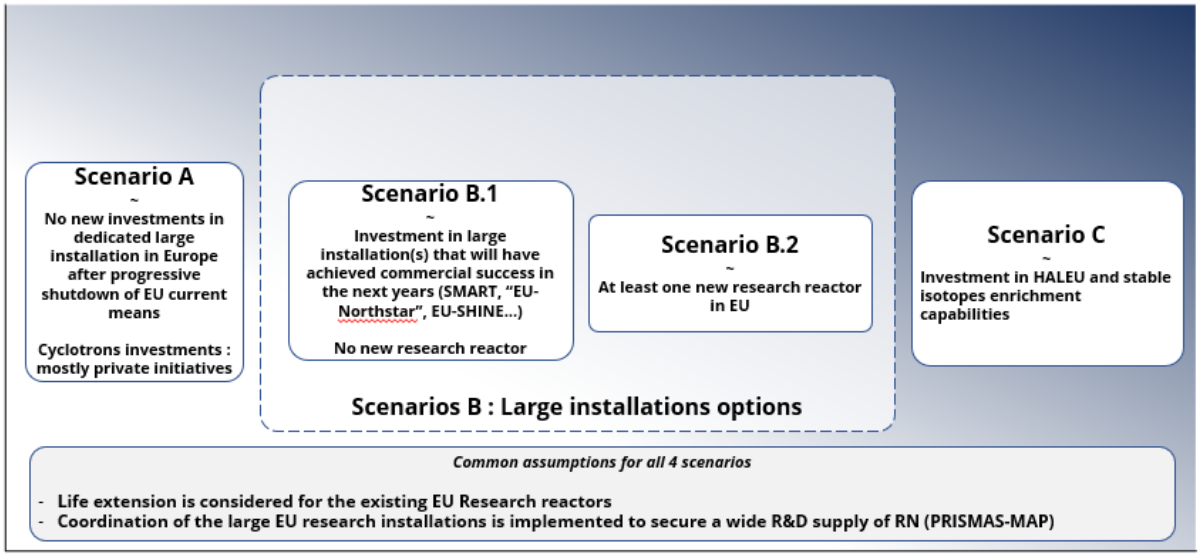


Figure 42: Scenarios considered

According to findings 1, 2 and 3, scenarios A, B and C are not exclusive one from the other and should be taken as cumulative. According to finding 3, a discussion can take place for optimizing the irradiation means in variants B.1 and B.2.

According to findings 5 and 6, underpinning all four scenarios:

- a coordination effort between the large European research installations is assumed, following the PRISMA-MAP initiatives, on the US NIDC model, for the supply of R&D isotopes and the backup of industrial installations;
- life extension of existing installations is to be considered whenever possible.

3.2.2. Scenario narratives

Scenario A **EU supply is based on new accelerators/cyclotrons investments. New large industrial installation projects in Europe are supposed unsuccessful.**

In such a scenario, European RN production is ensured through different major manufacturing routes:

- local production in existing cyclotron network (^{18}F);
- new cyclotrons for ^{68}Ga, ^{225}Ac, ^{89}Zr, ^{211}At, ^{64}Cu etc., or international import (^{225}Ac, ^{68}Ge, etc.);
- centralized radionuclide production (^{99}Mo, NCA ^{177}Lu, etc.) is ensured by current EU research reactors, life-extended until FRM-II & JHR remain alone, progressively completed by international imports as required.

EU enrichment capacity remains unchanged; EU continues to rely on Russian supply of stable isotopes, with risks of tension in the case of high demand for products such as ^{176}Yb, and on US supply of enriched U metal (HALEU or HEU) for fuelling the European reactors.

The long-term import perspectives at the global market level are closely dependent upon the outcomes of the current North American projects.

- If they are successful:
    - owing to SHINE, NorthStar and Canadian CANDU projects, supplying the US market in priority, ^{99}Mo global supply is less tense and imports perspectives remain favourable;
    - owing to SHINE, ^{131}I and ^{133}Xe supply is eased as well. For other neutron-activation isotopes, feasibility and production yields in SHINE remain to be proven;
    - owing to Bruce Power's CANDU project success, global NCA ^{177}Lu supply could be ensured too;

  - owing to NorthStar, in addition to ^{99}Mo, other long-lived photonuclear-produced isotopes might be exported.

- If North American projects are not at the expected performance level, shortages risks would appear on the most-used isotopes market: ^{99}Mo and therapeutic neutron-activation produced ones.

From the point of view of European investments, as accelerator/ cyclotron unit costs are relatively low, initiatives could generally be let to private players. They would invest according to the market demand, which may raise non-timely investment risks. For delicate investments (for instance, cyclotrons producing ^{225}Ac via ^{226}Ra target routes), EU centralized installations could be imagined for coping with the burden of safe ^{226}Ra management.

In this Scenario A, long-term EU supply:

- relies mainly upon the success of the accelerator-production routes;
- will become more and more dependent upon the global market, and particularly on the North American one for the therapeutic neutron-activation isotopes.

Scenario B **EU self-reliance is targeted for irradiation/processing means allowing production of all types of RN needed in EU, while stable isotopes supply continues to partially rely on imports.**

As in Scenario A, industry manages the development of local/regional radionuclide production means (SMC, MEC), under public authorities' supervision.

In addition, acknowledging the importance of an EU supply of radionuclides, industry and public authorities work towards new large irradiation projects to cope with dependency and limited supply risks inherent in Scenario A, and complementary investments are made in Europe for achieving or improving EU irradiation/processing self-reliance.

Scenario A cyclotron/accelerator investment strategies are then subjected to a cost-benefit analysis taking into account the production capacities of the large installations.

Concerning the large industrial production installations, CAPEX needs are yet uncertain. It cannot be excluded that, due to the known difficulty of reaching full cost recovery, public support is needed.

HALEU and stable isotopes enrichment capabilities are not considered in Scenario B.

Two different variants are considered, B.1 and B.2, for taking into account the different production capabilities of the diverse large industrial installations technologies.

Variant B.1 - No new research reactor is secured in EU after possible life extension and shutdown of existing mass-producing ones; EU focuses on alternatives.

Private industry, with support of the Member States, if applicable, secures a part of the missing supply capacity through establishment in the EU of alternative technologies projects that could achieve commercial success in the coming years: SMART, NorthStar, CANDU or ADS-based fission technology (e. g. SHINE).

In all cases, EU self-reliance would be ensured for ^{99}Mo.

However, for NCA ^{177}Lu or other therapeutic nuclear-activation isotopes:

- SMART or NorthStar are unable to produce them;
- except for ^{131}I, feasibility and capabilities of production in a European SHINE remain to be proven;
- no production project in CANDU exists currently in Europe (except for ^{60}Co).[103]

Hence, after shutdown of EU's main production capabilities, long-term EU supply would rely more and more on global market, as in Scenario A, except for ^{99}Mo (and ^{131}I if SHINE technology is chosen).

Variant B.2 – At least one new research reactor is secured in EU, possibly along with EU non-fission alternatives.

As compared with variant B.1, industry and EU public authorities decide without delay to proceed with a new Research reactor project. Opportunity of combining such project with a SMART project or an EU-SHINE and a renewed fleet of cyclotrons is assessed with the objective of allowing for the best coverage of EU needs (RN production scope and RN quantities).

As such project(s) are successful, the EU relies on a diversified network of large irradiation installations combined with cyclotrons, and EU reliance on foreign sources for isotope supply is reduced to a minimum.

[103] as confirmed by Nuclearelectrica

Scenario C **EU self-reliance is targeted also for stable isotopes enrichment and HALEU fuel and targets manufacturing installations.**

Full EU self-reliance for radionuclide supply chains (from stable isotopes enrichment to processing) is achieved through additional investments in missing enrichment and fuel fabrication capacities (electro-magnetic, gaseous centrifugation, HALEU enrichment and metallisation, etc.). Irradiation means are those of scenarios A, B.1 or B.2.

From an EU perspective, supporting the development of European stable isotopes enrichment capacities is justified by:

- the willingness to secure an EU industrial sector that is currently highly dependent on imports, despite the existence of a world-class European player (Urenco) for gaseous centrifugation enrichment;
- the expanding needs for enriched isotopes, particularly for cyclotron-production routes.

In this scenario, together with enhanced effort on targets recycling, the EU develops its own EM enrichment capability, while continuously improving existing gaseous centrifugation capability[104]. Distillation is not considered as a priority (see §3.1.2.3).

In this scenario, pursuing the ESA 2019 recommendations, and the future outcomes of the ESA Advisory Committee's Working Group on European production of low-enriched (19.75%) uranium, re-instated in 2021, it is decided to go a step farther in supporting investment in uranium enrichment and metallization facilities. Necessity of HALEU may nevertheless be influenced by technological option chosen.

The four scenarios A, B.1, B.2 and C have diverse merits, with regard to many parameters, considering:

- the security of supply: coverage of EU needs and import perspectives,
- technical aspects like technological readiness level, radioprotection, safety, waste, regulations and transport,
- economical aspects: investments,
- social benefits aspects.

These relative merits are assessed in the next chapter.

[104] Orano has recently announced its ambitions in this domain as well.

3.3. Multi-criteria analysis

3.3.1. Criteria for the analysis

The following list of criteria shall be considered as a reference analysis approach to compare scenarios and technology options in the field of radionuclides production.

Criterion #1: Security of supply	1.1	Dependency	Dependence relations of the supply chain on EU and non-EU stakeholders and associated risk & opportunities
	1.2	European needs coverage	To what extent European needs in terms of isotopes and their quantities are covered
	1.3	Redundancy	Intrinsic economic and technical complexity of setting "production margins" and redundant capacities to cope with possible gaps
	1.4	Versatility	Identify the radionuclide production spectrum of the technology, along with the capacity to simultaneously produce different radionuclides
Criterion #2: Economic & time constraints	2.1	Investment needs	Investments needed to develop or maintain supply chains to cope with demand for radionuclides beyond 2030
	2.2	Private investment vs public support	Private investment vs. public support
	2.3	Integration	Assess the capacity of the technology to be implemented in the EU and integrated among existing supply chains
	2.4	Production cost	Evaluate and compare production costs among manufacturing routes and the parameters affecting it (yields, centralized production, etc.)
	2.5	Maturity & Time-to-market	Risks & opportunities related to technology's maturity and its capacity to produce radionuclides with sufficient quality (GMP, pharmaceutical grade, etc.)
Criterion #3: Radioprotection, Safety, waste, regulations, transports	3.1	Radiation protection	Identify any specificity complexifying radiation protection management for workers and citizens exposed to radionuclides
	3.2	Safety	Identify safety limitations, risks and challenges associated with radionuclide production along the supply chain
	3.3	Radioactive waste	Identify challenges linked to radionuclide production waste management and availability of waste management options
	3.4	Regulations	Identify the regulations in force in the supply chain and whether they are appropriate or how they could help to the development of sustainable supply chains
	3.5	Transports	Identify to what extent transportation raises problems in the supply chains and how to solve them, depending on the case
Criterion #4: Social benefits	4.1	Social benefit	Identify technology side-impacts that provide additional added value for EU citizens and foster research and innovation
	4.2	Equal access	Identify challenges and threats leading to supply discrepancies among Member States, and the ease of providing radionuclides to all European citizens
	4.3	Public acceptance	Identify any public acceptance-related threats when establishing supply chain, along with public acceptance of RN-related applications
	4.4	Resources & skills	Identify the technology supporting resources (equipment, human skills, etc.) and any lack within the EU that should be mitigated

Table 22: Criteria used in the multi-criteria analysis

3.3.2. Multi-criteria analysis

3.3.2.1. *"Security of supply" criterion*

The question of the dependence upon imports for covering European needs is on top of the criteria list and is closely related to versatility of the installations (i.e. their capability to produce various types of nuclides simultaneously).

The table below summarizes the European future situation in the four scenarios, from two aspects: EU self-reliance and EU imports perspectives. The analysis further differentiates between two technology options for scenario B.1, based on either the photonuclear or the fission production route as provided respectively by the SMART and the EU-SHINE projects, as their production scopes are different.

RN		EU self-reliance perspectives beyond 2030	EU import perspectives : depending on North-american (NA) projects performances	
			Worst case : unsufficient	Best case: success
Scenario A Accelerators/ cyclotrons (ess. p,x)	Imaging	Limited to imaging accelerators-isotopes, except ^{99m}Tc	Global ^{99}Mo shortage	EU dependence on foreign supply
	Therapy	Self-reliance for accelerators-produced: ^{225}Ac, ^{67}Cu, ^{211}At,… but not for neutron-activated therapeutic RN	Global therapeutic neutron-activated RN shortage	
Scenario B.1 Cyclotrons + SMART Accelerator (photonuclear)	Imaging	All most used imaging isotopes		
	Therapy	Self-reliance for accelerators-produced: ^{225}Ac, ^{67}Cu, ^{211}At,… but not for neutron-activated therapeutic RN	Global therapeutic neutron-activated RN shortage	EU dependence on foreign supply
Scenario B.1 Cyclotrons + EU-SHINE	Imaging	All most used imaging isotopes		
	Therapy	Self-reliance for accelerators-produced: ^{225}Ac, ^{67}Cu, ^{211}At,… and ^{131}I, but not for other neutron-activated therapeutic RN	Global therapeutic neutron-activated RN shortage	EU dependence on foreign supply
Scenario B.2 Cyclotrons + Research Reactor	Imaging	All most used imaging isotopes	Export perspectives for EU	
	Therapy	Self-reliance for most of therapeutic RN comprising accelerators-produced: ^{225}Ac, ^{67}Cu, ^{211}At		
Legend		Minimal reliance on foreign supply EU supply security depending on imports Global shortages risks		

Table 23: European dependence upon imports in the 3 scenarios A, B.1 and B.2

As already depicted in §3.2.2, only scenario B.2 (with at least one new research reactor added to cyclotron investments, and perhaps added to a more ^{99}Mo-dedicated installation as well) makes it possible, in a proven manner as it is currently the case, to minimize EU reliance on foreign supply and foreign policies/inputs concerning all nuclides, as well as to open export perspectives.

Adding HALEU and stable isotopes enrichment capabilities in the EU (Scenario C) would further reduce reliance on foreign supply.

3.3.2.2. *"Technical and regulatory aspects" criterion*

Besides the isotopes production scope, aspects considered here are technological readiness level, status of technical references, waste production, and regulatory aspects.

This technical comparison concerns the different irradiation installation options characterizing each scenario (cyclotrons, SMART, SHINE and a research reactor). CANDU is added for comparison even if there is currently no project in Europe. It is recalled that scenarios A and B (B.1 and/or B.2) are basically cumulative.

	Scenario A	Scenario B.1 (2 technology options)		Scenario B.2	
	Cyclotrons	SMART	SHINE	Research reactor	CANDU (Canada)
Additional scope of RN production (versatility adaptability)	PET imaging isotopes + ^{225}Ac, ^{67}Cu, ^{64}Cu, ^{47}Sc to be proven	^{99}Mo (low activity) and theoretically ^{225}Ac, ^{67}Cu, ^{64}Cu, ^{47}Sc to be proven	Fission RN (^{99}Mo, ^{131}I, ^{133}Xe) Scope extension theoretically possible to be proven	Simultaneous production of all fission and neutron activation RN, comprising industrial ones	^{60}Co ^{177}Lu (Bruce 7) ^{99}Mo (project)
Technological Readiness level	depends upon isotope & production route considered	TRL 4-6	TRL 6 full-scale industrial demo 2022	TRL 9	TRL 7-8
Status/references	depends upon isotope & production route considered	SMART: go/no go 2022 US-NorthStar: construction underway, no known similar EU project	US-SHINE: being constructed. Design & Operating license (FSAR) under review by US NRC (2022)	1 new project in Europe (PALLAS)	No EU project
Nuclear regulations	Relatively simple in general, but spread over Europe	Relatively simplified	To be adapted to homogeneous reactor as in the US ?	as usual	as usual
Yearly waste production	depends upon isotope & prod. route considered	Reduced	LLW (US regulations): 590 m^3	SF: 4m^3 (reprocessing) ILW: < 1m^3 (+8 m^3 IPF) LLW: 20m^3 (+12m^3 IPF)	RN-induced waste negligible vs power production-induced waste
Lifecycle	20 years +	Unknown	30 years (FSAR) + to be proven	> 50 years	> 50 years

Table 24: Comparison of irradiation installations in Scenarios A, B.1, B.2

Concerning the production scope, it must be stressed that low-specific activity ^{99}Mo would require deep changes in the current downstream supply chain, as current generators would be inappropriate.

The technological reference level (TRL) is an important parameter for any investor, as it characterizes the risk associated with a project:

- for cyclotrons, TRLs depend upon the isotope and the production route considered, but are generally low, except for the few already industrialized isotopes. However, as the unit investment is generally low as well, risks taken by the investor(s) are small;
- for large installations, and for emerging routes (photonuclear like SMART and NorthStar, or SHINE), TRLs remain relatively low for the time being, until the industrial feedback of ongoing projects (namely in the US) is available in the coming years;
- for research reactors, given the many references available, the TRL is quoted as 9, as industrial feedback exists and the project risks are well known.

From a nuclear regulations point of view:

- cyclotrons do not raise specific regulatory problems. The main regulations applicable are related to radiation protection and waste management. For large photonuclear based installations (SMART, NorthStar), it should be the same, despite the fact that the radioprotection risks (and the shielding requirements) are higher due to strong γ fluxes and parasitic nuclear reactions. For these large installations, special attention is nevertheless to be brought to the question of target cooling system safety;
- although SHINE is accelerator-driven, it is also a fission reactor. As it is not a power reactor, NUREG-1537 (1996) has been defined as the regulatory basis by the US-NRC, augmented by an Interim Staff Guidance (2012) to take into account specificities of homogeneous reactors. This raises the question of which regulations would be applied to an EU-SHINE;
- the regulations applicable to research reactors are well defined, taking into account the post-Fukushima consequences;
- intra-European transborder transports raise specific problems as many local rules apply (see §2.2.6.3). In this perspective, as it relies more largely on decentralized cyclotrons, Scenario A could appear favourable. However, it implies imports of non-cyclotron-produced isotopes, particularly by air that raise other problems (see COVID or Eyjafjallajökull eruption impacts on air transports). Such situation reinforces the interest of having a variety of

production means available, both decentralized and centralized, for coping with any supply disruption.

The yearly waste generated is also an important parameter to be considered:

- whereas a large experience feedback exists concerning research reactors' yearly waste production;[105]
- such is not yet the case for cyclotrons and large photonuclear installations. Even if no transuranics are created by these installations, industrial experience is scarce relatively to the waste resulting from target processing and recycling. Waste should be minimum for cyclotrons, but a more precise assessment will need to be made when the first industrial experience feedback is available;
- SHINE expects a yearly waste amount[106] of about 600 m^3, classified as LLW according to US regulations despite the presence of plutonium isotopes. Such an amount seems high, even when compared to the LILW waste generated by a large nuclear power plant;[107]
- end-of-life decommissioning is fully mastered for research reactors; for emerging installations, it might raise original problems, either due to the number of installations concerned (decentralized cyclotrons) or due to the original features of large installations options:
    - activation of structures and components by parasitic nuclear reactions in photonuclear installations
    - or by energetic fusion neutrons and contamination of the many radioactive fluid systems in SHINE.

Finally, the lifecycle of the installations is also a parameter to consider, as it impacts the return on investment for a given CAPEX:

- the lifecycle of research reactors largely exceeds largely 50 years as attested by many examples;
- the lifecycles of emerging large production installations (SMART, NorthStar or SHINE) are as yet unknown. For SHINE, a lifecycle of 30 years has been justified by calculations in the FSAR and could be extended when experience feedback is available. A parameter influencing the lifecycle (and the reliability) of these new installations is the maintainability[108] of their

[105] "Long term Management of Australia's Radioactive Waste" (Jacobs SKM for the Australian Government, 2014) is the source of the data indicated in the comparison table.
[106] https://www.nrc.gov/docs/ML1921/ML19211C143.html Chapter 11, Table 11.2-1
[107] https://www.oecd-nea.org/rwm/profiles/Netherlands_report_web.pdf
[108] Access, in-service-inspection (ISI) possibilities, etc.

structures, systems and components, which will necessitate an experience feedback as well, especially for the most original ones.

Hence, in addition to isotope production capabilities, and before comparing investment needs (next paragraph), technical aspects like waste production aspects, design impact of European regulations, technical capabilities, time-to-market and lifecycle, etc. must be investigated carefully, as well as the side impacts of each installation on the whole associated supply chain (e.g. necessity of special generators). This is all the more difficult for the solutions that are still in their development stage, without experience feedback from industrial operation available.

3.3.2.3. *"Economic aspects and time constraints" criterion*

For defining the level of investment necessary in the four scenarios, an assessment of the number and type of installations has been made in Chapter 3.1.3 (Table 21).

The typical unit costs of each installation are given below.

	Installations	Typical CAPEX range (M€)
Accelerators/ cyclotrons ESS (p,x)	Small medical cyclotrons (currently 220 units < 20 MeV in EU)	10 M€ x number of new or revamped (if possible) SMC cyclotrons
	Medium Energy Cyclotrons (currently 20 units > 20 MeV in EU)	20-30 M€ x number of new Medium Energy cyclotrons
Large installations	Existing RRs life extension	50 M€ / operation (BR2 2016)
	Large research installations coordination	Limited investments
	SMART	200-300 M€
	EU-SHINE	unknown
	Research Reactor	> 1000 M€
Supporting installations	HALEU installations	?
	EMIS installation	150 M€

Table 25: Unit costs of the various installations considered

As a result, indicative investment levels that should be made in each case can be derived.

RN	$T_{1/2}$ (G) generator	Existing installations remaining beyond 2040	Additional irradiation installations necessary for EU self-reliance beyond 2040					Typical Investment (M€)
			Scenario A			Scenario B.1	Scenario B.2	
			SMC	MEC	HEA	Others	Research reactor	
Unit cost (M€)			10	30	>> 100	SHINE : unknown SMART : 200-300	> 1000	
nca ^{177}Lu	6,7 d	2 (n,γ)					at least 1	> 1000
^{90}Y	64,6 h							
^{131}I	8 d					1 SHINE		
^{166}Ho	26,8 h							
^{188}Re	17 h							
^{223}Ra	11,4 d				Annex 10			
^{99m}Tc (^{99}Mo) or ^{99m}Tc (direct)	66 h (G)					1 SHINE or (*)		
	6 h	-	> 100					> 1000
^{18}F	109,8 min	> 200 SMC						progressive renewal
^{68}Ga (direct)	67,7 min	few installations in EU	> 200					> 1000
or ^{68}Ga (G)	271 d (G)			1-3				or 30-100
^{123}I	13,2 h			1-5				30-150
^{124}I	4,2 d			1-5				30-150
^{211}At	7,2 h			>10		(*)		> 300
^{64}Cu	12,7 h			~50				500
^{89}Zr	3,3 d			1				50
^{225}Ac	9,92 d			1-5	1-5	(*)		TBD
^{67}Cu	2,58 d			depends on RPs development		(*)	Fast neutrons	100
^{44}Sc	4 h	large research installations	To be defined after R&D phase					
^{47}Sc	3,3 d							
^{149}Tb	4,1 h							
^{152}Tb	17,5 h							
^{155}Tb	5,3 d							
^{161}Tb	6,9 d							

Note: (*) production via electron accelerators routes, e.g. with Rhodotrons or SMART IRE project

Table 26: CAPEX levels associated with each irradiation installation option

As stated in Chapter 3.1.3, and as the scenarios are cumulative, assessing in detail which combination of these installations would be the optimum for Europe from all points of view (self-reliance, investment needs, equal access, waste minimization, cost of medicines, TRL, ability to produce isotopes simultaneously and in a flexible manner, etc.) is not yet possible, due to the many uncertainties affecting demand, production and CAPEX, especially for emerging production installations. The CAPEX evaluations above must then be considered only as an order of magnitude and will need to be revisited when more information is available.

Qualitative elements may nevertheless be highlighted.

Despite unit costs being relatively low, Scenario A, based on cyclotrons, may induce high investments due to the number of installations needed, especially in the case of short-half-life isotopes, preventing long-distance shipping. This is particularly the case for direct production of ^{99m}Tc, ^{211}At or even ^{64}Cu. Due to the short half-life of ^{99m}Tc, covering the whole of EU needs with cyclotrons would

require many dedicated machines and a rather high investment, making scenario B.1 or B.2 more economical. ^{64}Cu requires special cyclotrons with very high currents for achieving an acceptable production yield. On the other hand, Scenario A investments can be graded and optimized according to the needs, the development of the production routes and the opportunities for co-producing several isotopes in a single installation.

Scenario B.1, encompassing either an EU-SHINE installation and/or a photo-nuclear one (e. g. SMART) in addition to cyclotrons, is first optimized for ^{99}Mo production. An EU-SHINE installation is also theoretically able to produce other (n,γ) isotopes, but feasibility and yields remain to be proven. In the case of SMART, the installation is theoretically able to produce α-therapy isotopes (e. g. ^{225}Ac, ^{211}At) or ^{67}Cu in addition to ^{99}Mo.

Scenario B.2, comprising at least one Research Reactor added to cyclotrons, requires that the investment is roughly doubled. Capabilities for producing all the fission/activation isotopes simultaneously are nevertheless proven in that case. Interest of investing in a scenario B.1 installation (SMART or SHINE) is then to be assessed.

Reflections about investment triggering

Recommendations about how to foster investments are beyond the scope of this study. It must be noted, however, that all scenarios require investments with, most often, uncertain ROI due to the known difficulty of implementing a full cost recovery (FCR) principle, especially in the global context where competitors are all more or less publicly supported (USA, Russia, Australia, South Africa, tomorrow India and China, etc.).

For graded investments in cyclotrons, private initiatives might be relied upon. However, prerequisite for such initiatives is the existence of a market. For large installations, fully private initiatives might not be practicable at all.

Due to the many players involved in the investment decisions, the risk is high that investments will not be made in a timely manner. Coping with such a situation may thus require a mix of public incentives and private initiatives. The US ^{99}Mo-domestic production program, launched in 2009 and not yet completed, gives a good example of such an approach and the amount of time that its implementation requires.

Accordingly, with regard to the strategic importance of a secured EU supply of radionuclides, European authorities (EU and MS) might consider going beyond the usual policy of creating/enhancing a level playing field, and increase their support, for instance in the form of:

- technology-neutral public support program / incentives, through Horizon Europe programs for example, as is the case in the US, where national laboratories and federal authorities significantly support private projects (see Appendix G);
- mechanisms for guaranteeing (at least temporarily) volumes and selling prices to investors for selected projects (for instance, non-HEU FCR add-ons as in the US);
- or even CAPEX and/or OPEX direct public support of projects, not precluding their takeover (for instance, through concession contracts) by private operators at a certain moment of development.

This direct support could envisage innovative organization and financing tools such as:

- public-private partnerships;
- international non-profit organizations, aimed at welcoming international partners and gathering the necessary complementary funding, as considered for instance in Belgium[109] for the Myrrha project;
- implementation of European investment bank (EIB) financing;
- partial financing by the European Fund for Strategic Investment (EFSI);
- the Euratom Treaty tools (Joint undertakings, commercial or emergency stocks -Article 72-);
- financing of relevant projects by the Recovery and Resilience Facility[110] (RRF) instruments.

[109] AISBL (in French, "Association internationale sans but lucratif" – International Non-Profit Association), or "IVZW" ("Internationale Vereniging Zonder Winstoogmerk") in Flemish.
[110] https://ec.europa.eu/info/business-economy-euro/recovery-coronavirus/recovery-and-resilience-facility_en

3.3.2.4. *"Social benefits" criterion*

Besides Health benefits, technical differences and investment levels, social benefits differentiate the four scenarios as well. Two of them seem particularly important:

- maintaining European innovation capability and momentum
- education.

It is recalled that the scenarios are basically cumulative.

<u>European innovation momentum</u>

Maintaining innovation momentum is particularly important in the current knowledge economy era. Each scenario triggers innovations, which are listed below.

	Installation	**Support to innovation and research in EU**
Scenario-independent	Large research installations coordination	Besides fundamental and applied sciences, medical nuclides R&D
Scenario A	Accelerators in general	Accelerators science, technology and industry (see APPLICATIONS OF PARTICLE ACCELERATORS IN EUROPE, EUCARD2, 2017) Targets technologies
Scenario B.1	SMART	
	EU-SHINE	D-T accelerators, Tritium, homogeneous reactors Reprocessing technologies
Scenario B.2	Research Reactor	Neutron science and technologies (see ESFRI "Neutron scattering facilities in Europe", 2016) RN-based research and applications Industrial isotopes
Scenario C	HALEU installation	New power reactors New fuels
	EMIS installation	Fundamental sciences (nuclear and particle physics) Tracers for environmental research

Table 27: Innovation sectors supported in each scenario

In addition to innovation in the medical RN domain, support to innovation is ensured in Scenario A and scenario B.1 (SMART or photonuclear option, as well as SHINE) for accelerator science and technology. As emphasized in the 2017

EUCARD2 report, Europe benefits[111] in this promising domain from advanced skills, labs and industry where applications largely exceed medical ones alone.

The capabilities of research reactors to foster innovation in neutron sciences and technologies are well known. Despite the European Spallation Source perspective, the neutron landscape group of ESFRI warned in 2016 about the threat of "beam-time" shortage in the future. A new reactor in Europe could allow better balancing of the load between the remaining reactors beyond 2040 after shutdown of the existing installations. The 2020-2023 TOURR[112] Euratom action outcomes will be instructive in this perspective.

In scenario C, HALEU installations would allow Europe to guarantee an own potential for developing new fuels (e. g. accident-tolerant) and new reactors (e. g. Small and Medium power reactors). A stable isotopes electro-magnetic enrichment installation would reinforce European influence in other sciences as well (see box below).

Enriched stable isotopes are also required in many other disciplines. They serve e.g. as ion source feedstock to produce heavy ion beams of specific isotopes. Examples are beams of ^{48}Ca or ^{50}Ti to produce superheavy elements and exotic isotopes of other elements at GSI/FAIR (Darmstadt, Germany), GANIL/SPIRAL2 (Caen, France), JINR/SHE factory (Dubna, Russia), NSCL/FRIB (East Lansing, US), RIKEN/RIBF (Wako-shi, Japan), etc.

Certain very long-lived and naturally abundant isotopes (e.g. ^{48}Ca, ^{96}Zr, ^{116}Cd, ^{124}Sn, ^{150}Nd, etc.) are of high interest to study neutrino-less double beta decay (a promising way to advance our knowledge on the mass hierarchy of neutrinos). While first-generation demo experiments started with naturally abundant materials or with gram amounts of enriched isotopes, the upcoming next-generation experiments are planning to increase their sensitivity by amassing large quantities of enriched material, i.e. kilograms to hundreds of kilograms.

It is important to realize that all these applications are strongly interdependent because the enrichment of all elements that are not amenable to other enrichment technologies is performed with the very same EM separators, operated in Russia or the US. When the demand for one enriched product, e.g. ^{176}Yb, grows strongly, then it could exhaust the entire available EM separation capacity. Thus, all other applications of enriched isotopes could be jeopardized, namely enriched targets for the production of other medical radionuclides as well as essential enriched isotopes in completely different disciplines such as nuclear and particle physics, tracers for environmental research, etc. Such a shortage could hit countries in the EU even harder than others because today no high-throughput EM separators exist in the EU.

[111] If the SHINE accelerators are imported from the US, they would be of less benefit to the EU.
[112] Towards Optimized Use of Research Reactors in Europe

Education

Public acceptance and necessary skills remain a key question in Europe when it comes to nuclear matters. Whereas public acceptance for small accelerators should not raise particular problems (Scenario A), it may be a larger problem for large irradiation installations (scenarios B.1 & B.2).

Concerning professional skills, Scenario A encompasses decentralized cyclotrons, which multiplies the need for experienced operators and radioprotection officers, whose shortage could impair cyclotron development. In this perspective, centralized installations (scenarios B.1 and B.2) allow limitation of the needs of skilled personnel to the installation itself. On the other hand, large nuclear projects may be hindered, due to attrition of project and construction competences[113] in Europe.

Nuclear Medicine is affected by the global lack of medical physicists.[114] IRE notes as well[115] the difficulty of finding nuclear engineers. After nuclear phase-out, radioprotection competences are lacking in Germany, according to companies operating in the dismantling sector.[116] The disaffection of European students for nuclear careers appears as the most daunting threat in the long term for concretizing the benefits of nuclear applications at a time when nuclear is regaining favour in many major countries (China, India, USA, Japan, etc.), as well as in certain Central and Eastern European MS.[117]

Nuclear skills attrition in Europe is thus a real problem, and not only for nuclear medicine development. Whether expanding communication about the health benefits of nuclear applications is sufficient, and which other means should be envisaged for coping with this situation is a political subject beyond the scope of this study.

In this perspective, large installations can be focal points for attracting high-level students, as shown by Marie Sklodovska Curie Actions or the example of SCK-CEN,[118] as well as close ties between the large installations and university medical hospitals.

[113] "Rapport au Président Directeur Général d'EDF La construction de l'EPR de Flamanville." Jean-Martin Folz Octobre 2019
[114] https://www.iaea.org/newscenter/pressreleases/iaea-launches-guide-to-promote-recognition-of-medical-physicists-as-health-professionals
[115] https://www.lalibre.be/economie/entreprises-startup/erich-kollegger-patron-de-l-institut-national-des-radioelements-cela-risque-de-devenir-complique-de-recruter-des-ingenieurs-nucleaires-605c9a027b50a605171fb7fa
[116] Nucadvisor private communications with German companies
[117] https://www.sustainability-times.com/low-carbon-energy/the-competition-is-on-for-eastern-europes-nuclear-power-market/
[118] https://indico.cern.ch/event/847532/contributions/3569919/attachments/1911004/3157661/2019-09-19_PRISMA_MAP_General_Meeting_GB.pdf

3.3.3. Multi-criteria analysis: conclusion

Comparison was according to four sets of criteria:

- dependence on foreign supply for European isotopes needs,
- investment effort necessary,
- technical and regulatory aspects,
- other benefits.

For the first two criteria:

- Scenario A is the less demanding one from an investment point of view. On the other hand, with the progressive shutdown of the ageing research reactors after their life extension, Europe is gradually losing its prominent position and gradually becoming dependent upon foreign and global market decisions and policies for the bulk of non-accelerator produced nuclides.
- As the four scenarios are cumulative, Scenario A+B.2+C is best fitted for reducing European dependence on foreign supply in a proven manner.[119]
- It must be noted that for the reasons listed in §3.3.2.3, investment levels remain largely uncertain, and that optimizations are possible, balancing production of the necessary isotopes and the best-suited production means. In this perspective, the versatility of the irradiation tools, their ability to supply a large variety and quantity of isotopes simultaneously, as well as their ability to adapt to a changing landscape is an important parameter to be taken into account.

Hence, the higher the investments made, the greater is Europe's security of supply.

Many other technical parameters need to be considered carefully in the decision-making process as well: in addition to isotope production scope, technological readiness level and time-to-market, waste production, regulatory and innovation support aspects, lifetime of the installations.

In all cases, education of skilled personnel and public acceptance appear to be long-term key factors for reducing Europe's dependence on foreign supply and allowing optimum access for EU citizens to the benefits and promises of nuclear medicine for beating cancer.

[119] Pending evidence that SHINE is able to produce neutron activation products in an efficient manner.

4. General conclusion

According to the new European SAMIRA Action Plan[120], there is a need to secure the supply of medical radioisotopes in the medium to long term in order to maintain EU patients' access to vital medical procedures.

The objective of the present study was to fill gaps in the available information on the supply chains for the main established and novel radionuclides that have, or are expected to have, significant uses in Europe. The work also had the goal of preparing the ground for long-term European co-operation in this area.

The study had to meet the following specific objectives:

a. identify the main radionuclides currently in use in the European Union, and the main radionuclides expected to be used by 2030, with a particular focus on the radionuclides used in medicine;

b. identify the existing and emerging methods and technologies for production of the radionuclides covered under (a) and fully describe the main elements of their respective supply chains;

c. identify the main suppliers of source materials and technologies for production of radionuclides covered under (a) and the facilities which are part of the above supply chains;

d. develop scenarios and concrete options for sustainable and secure supply of radionuclides covered under (a) in the EU.

Accordingly, among the large number of radionuclides with development potential, a selection of nuclides has been carried out in consensus with the Steering Group of this study, and confirmed owing to an analysis of the ongoing clinical trials at a global level. It turns out that, during the next 2 decades:

- for SPECT imaging, ^{99m}Tc should continue to be the work-horse;
- for PET imaging: despite high growth expected for ^{68}Ga, ^{18}F should keep its current leader position; ^{64}Cu, ^{89}Zr and ^{124}I are challengers;
- use of radionuclides for targeted therapy will drastically increase. For the β- emitters : sharp growth is anticipated for ^{177}Lu, particularly under its non-carrier added (NCA) form; ^{131}I, ^{90}Y, ^{223}Ra should continue to be largely used. Use of ^{166}Ho and other RN should develop. R&D progresses for α-emitters (^{225}Ac, ^{212}Pb, ^{211}At), as well as for new theranostics pairs based on Terbium and Scandium.

[120] "COMMISSION STAFF WORKING DOCUMENT on a Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) 5.2.2021 SWD(2021) 14 final"

Current and future EU needs for the most important isotopes are quantified.

The isotopes-specific supply chains are analysed in detail, from source material procurement up to processing of the radiochemical ready for radiopharmaceutical labelling, to identify the main security of supply challenges that they raise.

Six findings conditioning security of supply are substantiated in this study.

1) Accelerators/cyclotrons and fission/neutron-activation installations are complementary in the long term, as covering different isotopes-scopes:

   a) accelerators/cyclotrons are particularly necessary for accompanying the anticipated development of PET imaging isotopes and, in a more distant future, for ^{225}Ac;

   b) fission/activation installations are particularly needed for the future industrial bulk of neutron-activation-produced therapeutic isotopes, including NCA ^{177}Lu.

2) If reduction of EU reliance on foreign supply is targeted, new investments are necessary in both domains, cyclotrons/accelerators and fission/activation installations, as the capability of existing installations to fulfil EU needs will deteriorate seriously. Indeed, current cyclotrons fleet will be unable to supply emerging PET isotopes. From 2035 onward, according to the life extension possibilities of BR2, HFR, Maria and LVR15, reactor's production capacities will decline. From 2040, only RJH and FRMII will remain online if no new large installations are built. Their capacities are unable to cover fully EU needs, not only for ^{99}Mo, but overall for essential therapeutic β-emitters nuclides such as NCA ^{177}Lu, ^{131}I, etc.

3) Regarding investments in large installations, several options can be envisaged: a photonuclear-based installation like SMART or an European version of Northstar, a fission-based installation like SHINE, a research reactor or a power reactor. However, the production scopes of the different options are not equivalent.

   a) Whereas a research reactor is able to produce simultaneously, in a proven and industrial manner, all nuclides generated by fission and neutron activation, both medical and industrial, it is not the case for developing options:

      i) for SMART, Go/No Go decision is scheduled by end of 2022. SMART would be able to produce essentially ^{99}Mo and, in the future, certain accelerator-produced isotopes such as ^{225}Ac. An alternative photonuclear-based installation, on the model of the US-Northstar using IBA's Rhodotron® technology could be envisaged as well, but with the same production scope;

ii) SHINE is currently being licensed in the US only for ^{99}Mo, ^{131}I, ^{133}Xe production.

b) Using power reactors, particularly CANDU reactors, is an interesting way to produce isotopes, but not all the operators are ready to take the risk of perturbing their primary power production in case of potential malfunctions of the isotopes production. In addition, only 2 CANDU reactors exist in Europe, operated by Nuclearelectrica in Romania, which currently does not plan to produce other isotopes that ^{60}Co.

4) Other critical points from a security of supply point of view are HALEU supply and the enrichment of stable isotopes:

a) HALEU is essentially supplied by the US, which anticipate possible shortages beyond 2030. The ESA Advisory Committee's Working Group on European production of low-enriched (19.75%) uranium was re-instated in spring 2021 and mandated to continue the work based on the recommendations given in the 2019 ESA report. The group will explore the necessary conditions for establishing European production capacity for HALEU to respond to the EU needs for the research reactors fuel and medical radioisotopes production;

b) concerning stable isotopes, achieving satisfactory yields will necessitate the use of costly enriched targets, which raise a dual problem: their production and their recycling. Developing cyclotrons radionuclides production will increase the need for centrifugation-enriched materials, and European capabilities will have to be expanded (Urenco, and Orano as possible new entrant). For other source materials such as enriched ^{176}Yb for NCA ^{177}Lu production, Russian electromagnetic installations are currently the main supplier, but with limited capacities. Securing such EMS-enriched isotopes for the EU would necessitate investments (either in a EU EMS-enrichment capacity or through the development of alternative manufacturing routes).

5) Co-ordination between large European research installations is key for supplying R&D isotopes and promoting new production routes. The PRISMAS-MAP initiative federates many European research and industrial organizations for producing R&D and rarer isotopes, on the model of the US National Isotopes Development Center; such kind of initiatives are to be supported.

6) Life extension and revamping of existing installations is to be considered whenever possible, as it is currently the case for BR2, HFR, Maria and LVR-15.

Based on these findings, four typical cumulative long-term scenarios are defined. With regard to their favourable cost-benefit ratio, strong coordination between large European research installations and life extension of existing installations are

assumed in the four cases. The four scenarios are analysed against a series of criteria, starting with security of supply.

- Scenario A: EU supply is based on accelerators/cyclotrons and existing installations, appropriately life-extended whenever possible. In this scenario, the EU can envisage self-reliance for all imaging isotopes including the emerging PET isotopes like ^{68}Ga, but not for the main SPECT imaging isotope ^{99m}Tc. Self-reliance can also be envisaged for developing therapeutic nuclides, namely the α-emitters, but not for the fission/neutron-activated therapeutic isotopes (NCA ^{177}Lu, etc.), which are the most interesting in the perspective of beating certain cancers in the next two decades. Import will then be necessary, and import possibilities of these isotopes will largely depend upon the success of the North American projects (SHINE, NorthStar, CANDU, etc.).

- Scenario B.1: In addition to accelerators/cyclotrons, EU supply relies on large industrial installations based on emerging production routes like SMART or SHINE. In this case, self-reliance can be envisaged for ^{99m}Tc as well, but not for all therapeutics[121] such as NCA ^{177}Lu. Like in scenario A, EU will have to rely on imports for these isotopes.

- Scenario B.2: In addition to cyclotrons/accelerators, at least one new research reactor is built in Europe. In this case, EU self-reliance can be envisaged for all necessary isotopes, in a proven manner. Such option allows to maintain the EU export position and open new export opportunities as well.

- Scenario C: With the addition of own capabilities for HALEU and stable isotopes enrichment, the EU reduces its reliance on foreign supply to a minimum.

The second set of criteria deals with investment effort. The number of installations of each type necessary for achieving EU self-reliance is first evaluated. Using unit costs for each installation type, orders of magnitude of investments are established. Though many uncertainties remain for emerging production routes (CAPEX, production yields, etc.), it turns out that:

- For scenario A, investment could be graded and optimized according to needs, development of production routes and the opportunities to co-produce several isotopes in a single installation. However, despite unit costs being relatively low, new investments in cyclotron installations (SMC & MEC) would induce very high investments due to the number of installations needed, especially for short half-life isotope production preventing long-distance shipping. Corresponding investments could amount to hundreds

[121] Pending evidence that SHINE is able to produce them in an efficient manner.

M€ for a new MEC network (~10 MEC) to more than 1 billion € for a full new SMC network (200 SMC across the EU).

- As cyclotrons/accelerators and large installations are complementary, total investments are additive. A scenario B.1 unit like SMART could represent a 200-300M€ additional investment, whereas a scenario B.2 new research reactor could cost more than 1 billion €.
- For scenario C, securing stable isotopes enrichment in the EU, along with securing HALEU supply would necessitate an additional investment of several hundred M€.
- However, the optimisation of all these new investments remains to be done, when more information will be available concerning the market needs and the performance of the emerging production installations.

Given the complementary production scope of the installations, a large fission/neutron activation installation remains necessary if reduction of EU dependence to foreign supply is targeted. Finally, the larger the investment, the larger the reduction of EU reliance on foreign supply.

Private initiatives can generally be relied upon for graded investments in relatively low-unit-price cyclotrons. However, such private initiatives are conditional upon the existence of a market. For large installations (centralized accelerators and fission-based), fully private initiatives might not be practicable, due to the known difficulty of implementing full cost recovery, the high investment costs (several hundred M€) and the relatively long durations for design, construction and licensing (pre-production).

In all cases, due to the many players involved in the investment decisions and the influence of the global market, the risk of investments not being made in a timely manner is high. Coping with such situations may thus require a mix of public incentives and private initiatives[122].

Besides their EU security of supply merits, each scenario also presents other advantages, namely for maintaining European innovation momentum in many promising domains.

However, conditioning all four scenarios is the fact that developing nuclear medicine benefits for beating cancer requires that Europe relies on all the necessary skills, that nuclear careers become appealing again for students and that public acceptance is ensured.

[122] The US domestic ^{99}Mo production program, launched in 2009 and not yet completed, is a good example of such an approach and the amount of time that its implementation requires.

Lastly, this study opens up additional subjects of discussion and/or further investigations. Among others:

- strengthen reliability of input data (EU RN needs, performances and costs of the diverse technologies and processes, workforce needs, waste generation, etc.);
- optimize the installations-mix in Europe (cyclotrons, accelerators, large industrial installations) versus relevant criteria;
- pursue investigations downstream of the supply chain, in the radiopharmaceuticals domain.

Annexes

These annexes provide, for each radionuclide selected, a detailed assessment of its current and future achievable manufacturing routes, along with a transversal analysis of the main manufacturing routes specificities (technology readiness level [123] , radionuclide quality, economics, target material, installed base capacity…). Through this analysis, the key impediments to a future sustainable supply are highlighted.

For already established supply chains, the main EU and non-EU players are identified, allowing to conclude on current independence status of the radionuclide production and to the investment needed to ensure self-reliance in the future.

When comparing manufacturing routes, a 4-levels scale is used, allowing identification of their competitive advantages and limitations.

Major differentiating factor, offering strong advantage for a manufacturing route from industrial point of view *(e.g. no need for enrichment, when natural material is only composed of the needed isotope)*

Minor differentiating factor, improving supply capacity, or current limitation that could be easily addressed for EU sustainable supply *(e.g. LEU currently supplied outside EU, a local production would be foreseeable based on existing European enrichment capacity)*

Minor limitation, considered as an impediment for radionuclide development and production, but that do not affect its widescale production capacity *(e.g. low yield achieved)*

Strong limitation, considerably decreasing manufacturing interest through the selected manufacturing route *(e.g. need for very costly material or costly irradiation equipment not widely available)*

[123] The detailed classification used to assess the Technology Readiness Level is detailed in Appendix E, based on European Commission definitions used in the H2020 programme.

Annex 1. Technetium-99m (^{99m}Tc)

A.1.1. Properties, applications and competing radionuclides

^{99m}Tc

Properties: ^{99m}Tc decays into ^{99}Tc ($t_{1/2}$=6.01 hr) through gamma emission (140keV), allowing for SPECT imaging. ^{99m}Tc is commonly produced through the decay of ^{99}Mo ($t_{1/2}$=~66h) in generators, eluted up to a few times per day (See Appendix F for detailed explanation regarding generator concept and use).

Applications & competing RN: ^{99m}Tc is the most used radionuclide in nuclear medicine, for SPECT imaging. Numerous radiopharmaceuticals are labelled with ^{99m}Tc. It should remain within the next decade the most-used radionuclide, considering its wide range of applications, its limited cost and ease of use through ^{99}Mo/^{99m}Tc generators. No replacement trend currently foreseen for ^{99m}Tc imaging examinations by another radionuclide.

Demand: as there is no direct market for ^{99m}Tc, overall demand shall be assessed based on its parent radionuclide: ^{99}Mo. Latest estimates from OECD-NEA [124] evaluate to 9500 6d Ci EOP the weekly demand of ^{99}Mo. This corresponds to roughly 40 million ^{99m}Tc procedures per year. Europe represents ~25% of world's market[125], about ~2000-2500 6d-Ci EOP of ^{99}Mo per week. Corresponding demand in terms of ^{99m}Tc is equivalent to 10 million doses per year in Europe, with an average activity injected of 650-700 MBq (17-19 mCi). In case of direct production, the production routines, density and size of ^{99m}Tc cyclotron network will size the end-of-irradiation demand.

The market is stable in EU and North America (0.5% CAGR), with main growth expected from Asia and Rest of the World (5% CAGR), resulting in a few percent total growth per year.

^{99m}Tc use in Europe is thus expected to remain steady, or with limited increase due to catching up demand in countries with currently lower use per habitant. A growth of 0,5% per year leads to a ~2200-2800 6d-Ci EOP of ^{99}Mo, equivalent to 11 million procedures per year in 2040.

A.1.2. Supply chain characterization

^{99m}Tc is commonly supplied as a decay product of ^{99}Mo, eluted from ^{99}Mo/^{99m}Tc generators, but might also be produced directly in accelerators, with "just in time" delivery. Over the last decade, many projects have been under development to provide alternatives to research reactors to produce ^{99}Mo. Under this chapter, both the reactor-based and cyclotron-based manufacturing routes are discussed.

[124] "The Supply of Medical Radioisotopes - 2019 Medical Isotope Demand and Capacity Projection for the 2019-2024 Period" - NEA/SEN/HLGMR(2019) November 2019
[125] NucAdvisor estimate, based on interviews with market players

^{99}Mo can be produced with the following reactions:

- fission of uranium-235, through the reaction ^{235}U(n,f)^{99}Mo in research reactors or alternatives (e.g. SHINE);
- activation of ^{98}Mo, through the reaction ^{98}Mo(n,γ)^{99}Mo in reactors (research reactors or power reactors);
- photonuclear reaction in ^{100}Mo target, through reaction ^{100}Mo(γ,n)^{99}Mo in accelerators (e.g. Rhodotron for NorthStar, Linear Accelerators for CII…);
- ^{99m}Tc can also directly be produced through proton irradiation in accelerators, through the ^{100}Mo(p,2n)^{99m}Tc reaction. This manufacturing route is discussed separately.

The different ^{99}Mo production routes are compared in the following table, and later developed on a case by case basis:

	Fission of uranium-235 in research reactors	**Fission of uranium-235** in SHINE (USA)	**Activation of ^{98}Mo** in power reactors[126] (CANDU in Canada)	**Photonuclear reaction in ^{100}Mo target** with Rhodotrons
Technology readiness level	**TRL 9:** Fully mature, the latest technological challenge was the transition to LEU which is almost complete.	**TRL 6:** Individual technology elements have been demonstrated at laboratory scale. Operating license submitted in July 2019, with start of production tests in 2021. Challenges could be expected during the testing phase, NRC and FDA review.	**TRL 3:** Irradiation process and processing rise limited challenges (CANDU reactors are already producing industrial RN), but innovative generator technology (due to low specific activity) remains unproven.	**TRL 7:** High power Rhodotron (40MeV – 120 kW electrons) are now off the shelf products. 10 MeV Rhodotrons (for sterilization & irradiation) are widely used in the industry. (Lighthouse project progress is less advanced and not developed here)
Production capacity	Depends on core power & number of irradiation positions (between 3000 to 7000 6d Ci per week per installation), 3-4 Tier 1 installations needed to cope with world demand	Large production capacity through multiple independent production lines (8 expected for 1st US plant) for a total prod of 4000 6d Ci per week	Large production capacity expected (Darlington site – 4 CANDU to be equipped for target irradiation), total capacity of 2500 6d Ci expected	Each pair of Rhodotron is connected to a set of targets enable to produce ~2500 Ci of ^{99}Mo. Additional production lines allow scaling (NorthStar: 4 production lines expected)
Time to market	Various new reactors projects are facing delays (RJH, PALLAS, FRMII, RA-10…), but some players are already fully operational for long-term production (OPAL)	FOAK technology, delays could reasonably be expected, with remaining key milestones, a commercial operation in 2021 can be considered optimistic. No generator licensing (raw ^{99}Mo produced)	Short term deployment expected (development in parallel of proprietary generator and CANDU modifications to allow irradiation) production by 2023 in case of no delays due to generator licensing.	Short term deployment (commissioning in end 2020 expected for NorthStar pilot plant). No new generator licensing (RadioGenix® generator to be used)

[126] Activation of ^{98}Mo in research reactors is already under commercial use by NorthStar (irradiation in MURR reactor) but should be fully replaced by future NorthStar photonuclear reaction project.

	Fission of uranium-235 in research reactors	**Fission of uranium-235** in SHINE (USA)	**Activation of ^{98}Mo** in power reactors[126] (CANDU in Canada)	**Photonuclear reaction in ^{100}Mo target** with Rhodotrons
Product quality	GMP quality	GMP to be developed and demonstrated. Laboratory first production batches showed comparable product quality to research reactors.	Low specific activity product with need for specific generators. Need for GMP development for production in CANDU	GMP to be developed and demonstrated
Target & material	Enriched ^{235}U targets, sourced from US/Russia. Possible shift to EU enrichment productors.	Enriched ^{235}U solution, used continuously (to be demonstated in industrial operation conditions)	^{98}Mo enriched target material (obtained by centrifugation), current limited supply	^{100}Mo enriched target material (obtained by centrifugation), current limited supply
Cost	Current research reactor route remains directly or indirectly subsidized by states. Full cost recovery has to be demonstrated (in case of FCR no major impact on dose price, +5% increase expected). Very affordable dose of ^{99m}Tc (~20-30€/dose).	No public information regarding future production costs. Regarding project financing, SHINE already secured more than 300M$ (as of end 2019).	No public information regarding future production costs. Marginal investment costs expected for establishing production capacity in CANDU reactors (limited to targetry system development and licensing costs).	8 Rhodotrons foreseen (listed price 6M€ each) for a total of 48 M€, without buildings, target station & plant auxiliaries. An order of magnitude of up to 150 M$ can be considered, US Federal support to be added.
Radioactive wastes	Radioactive wastes generated by research reactor operations (fuel, target, LLW)	Limited radioactive wastes expected volumes due to re-use of ^{235}U targets (to be demonstrated) and production of neutrons through accelerator/fusion chamber.	Radioactive wastes coming from power applications, limited wastes from ^{99}Mo process, limited to target processing, without Uranium & Plutonium isotopes. Target recycling expected.	Limited radioactive wastes, for both Rhodotron operation and target processing (no ^{235}U management). Target recycling expected
Irradiation tool versatility	Extremely versatile production for high-power research reactors	Production process is expected to be modified later on to allow ^{177}Lu production. Simultaneous production of various radionuclides uncertain	Limited versatility in power reactors (constraints of "irradiation positions"), drop-in/drop-out target system to be designed and validated	Production process through electron beam could be used for ^{225}Ac, ^{64}Cu, ^{67}Cu production

Table 28: Summary table for ^{99}Mo/^{99m}Tc manufacturing routes

Fission of uranium-235 in research reactors or alternatives

The current $^{99}Mo/^{99m}Tc$ supply chain through ^{235}U fission has been extensively described in the literature (OECD[127], AIPES, European Commission[128]…). The different production routes described hereafter follow similar steps (irradiation, processing, generator manufacturing…), with slight variations described.

The main steps and specificities of this manufacturing route are summarized hereafter:

- ^{99}Mo is obtained by irradiation of an enriched ^{235}U target (LEU, 19.75% enrichment) in a reactor during one week in average;
- irradiated targets are then transported (by land) in a processing facility (ideally onsite) for dissolution, purification and extraction of raw ^{99}Mo;
- raw ^{99}Mo is a worldwide market, the ^{99}Mo bulk liquid is shipped to generators manufacturing facilities all over the world (Europe, USA…) where raw ^{99}Mo is "loaded" into $^{99}Mo/^{99m}Tc$ generators;
- the generator is eluted (« milked ») by the radiopharmacist to prepare the Tc-99m doses to be injected. Generator is typically used in the radiopharmacy during 1 week before being returned to the manufacturer and replaced.

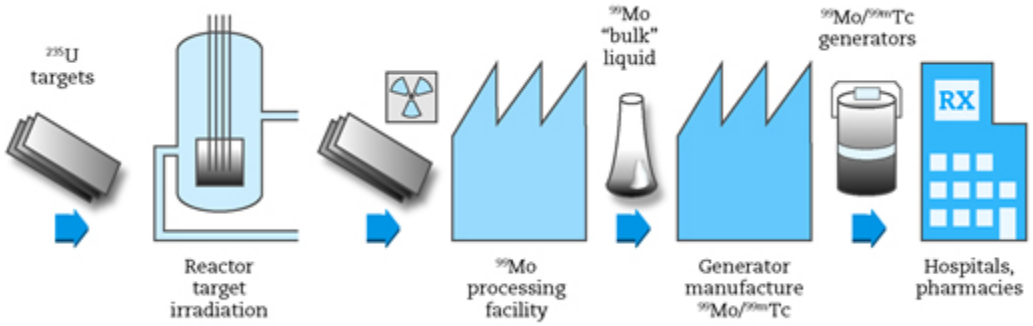


Figure 43: $^{99}Mo/^{99m}Tc$ supply chain - Source: Ponsard 2010

Fission of uranium-235 with alternative technology (SHINE)

See section 2.2.4.5

Activation of ^{98}Mo in reactors (research reactors or power reactors)

The production of ^{99}Mo in neutron sources (research reactors or power reactors) is also achievable through the reaction $^{98}Mo(n,\gamma)^{99}Mo$. The process is used in MURR Reactor for NorthStar ^{99}Mo production, BWXT (Canada) is currently working on adapting this process for production in CANDU reactors (Darlington). Orano is also involved.

See section 2.2.4.5

[127] The supply of medical radioisotopes, the path to reliability, OECD NEA 2011
[128] ENER/17/NUCL/SI2.755660 European Study on Medical, Industrial and Research Applications of Nuclear and Radiation Technology – Appendix A12

Photonuclear reaction in ^{100}Mo target in accelerators: NorthStar and SMART projects

The claimed interests of producing ^{99}Mo through photonuclear reaction, in comparison of the reactors production, are:

- the absence of proliferation risks,
- the use of an innovative accelerator system or Rhodotron,
- the negligible waste generated by the target processing. However, Supply of target material (^{100}Mo) could become an issue in the case of large production through this manufacturing route (need for ^{100}Mo enrichment).

See section 2.2.4.5

The main challenges faced by ^{99}Mo supply chain are at different stages of the supply chains, from target material to irradiation:

- the need for a European network of large irradiation facilities, to replace facilities expected to reach end of life within next decade and allowing EU to continue being the worldwide leader in radionuclide production;
- the need for sustainable supply of low enriched uranium (LEU), or molybdenum isotopes (^{100}Mo and ^{98}Mo) for targets manufacturing.

Direct production of ^{99m}Tc in accelerators

A beam of energetic protons from an accelerator (about 20 MeV) can be used to produce ^{99m}Tc via the bombardment of a ^{100}Mo target (> 99% enrichment) through the reaction ^{100}Mo(p,2n)^{99m}Tc. Direct production of ^{99m}Tc is highly dependent on the characteristics of the cyclotron used for the irradiation (energy, irradiation duration, particle flux intensity…), the optimal energy range being 16-19 MeV.

Several experiments and theoretical researches were performed in the last few years and demonstrated the technical feasibility of this manufacturing route. ^{99m}Tc produced is carrier added, impurities issues are still present, that could lead to additional dose to the patient (recent clinical tests showed up to 10% dose increase due to ^{99m}Tc impurities), or lower imaging quality (with higher $^{94\text{-}97}$Mo contents, image quality is degraded). Cost-competitiveness of direct production as compared to generator use appears as a major impediment for this route development.

	Direct production in accelerators ^{100}Mo(p,2n)^{99m}Tc
Technology readiness level	**TRL 7:** solid target technology and ^{99m}Tc associated production process should enter licensing process in 2020 in Canada (ARTMS)[129]
Supply chain	Non centralized "just in time" supply chain, with more complex production and delivery schemes. All production steps (irradiation to radiochemical preparation performed on a single site).
Availability	Back-up solution needed, as production is performed on daily basis, without security margin for user (currently provided by generator use)
Economics	High production costs, competitiveness could be improved through direct dose delivery to tens of imaging centres but transportation organization becomes a challenge in this case and offer less margin than generator delivery. Dose cost shall remain higher than for the generator route.
Radioactive wastes	Limited radioactive wastes, for both accelerator operation and target processing

Table 29: Summary table for direct ^{99m}Tc production

[129] Competition heats up to produce medical radioisotope – PHYSICS TODAY - 15 Nov 2019 https://physicstoday.scitation.org/do/10.1063/PT.6.2.20191115b/full/

Summary of current ^{99}Mo supply chain

As for most radionuclides produced at industrial scale, the ^{99}Mo market is demand driven and not a supply driven market. The current worldwide supply chain is summarized on the next page figure. It must be noted that at the exception of NorthStar production in MURR (activation of ^{98}Mo in reactors), the current supply is exclusively based on uranium-235 fission in research reactors. Due to radioactive decay, about 1% of remaining content disappears every hour.

The market players' landscape is:

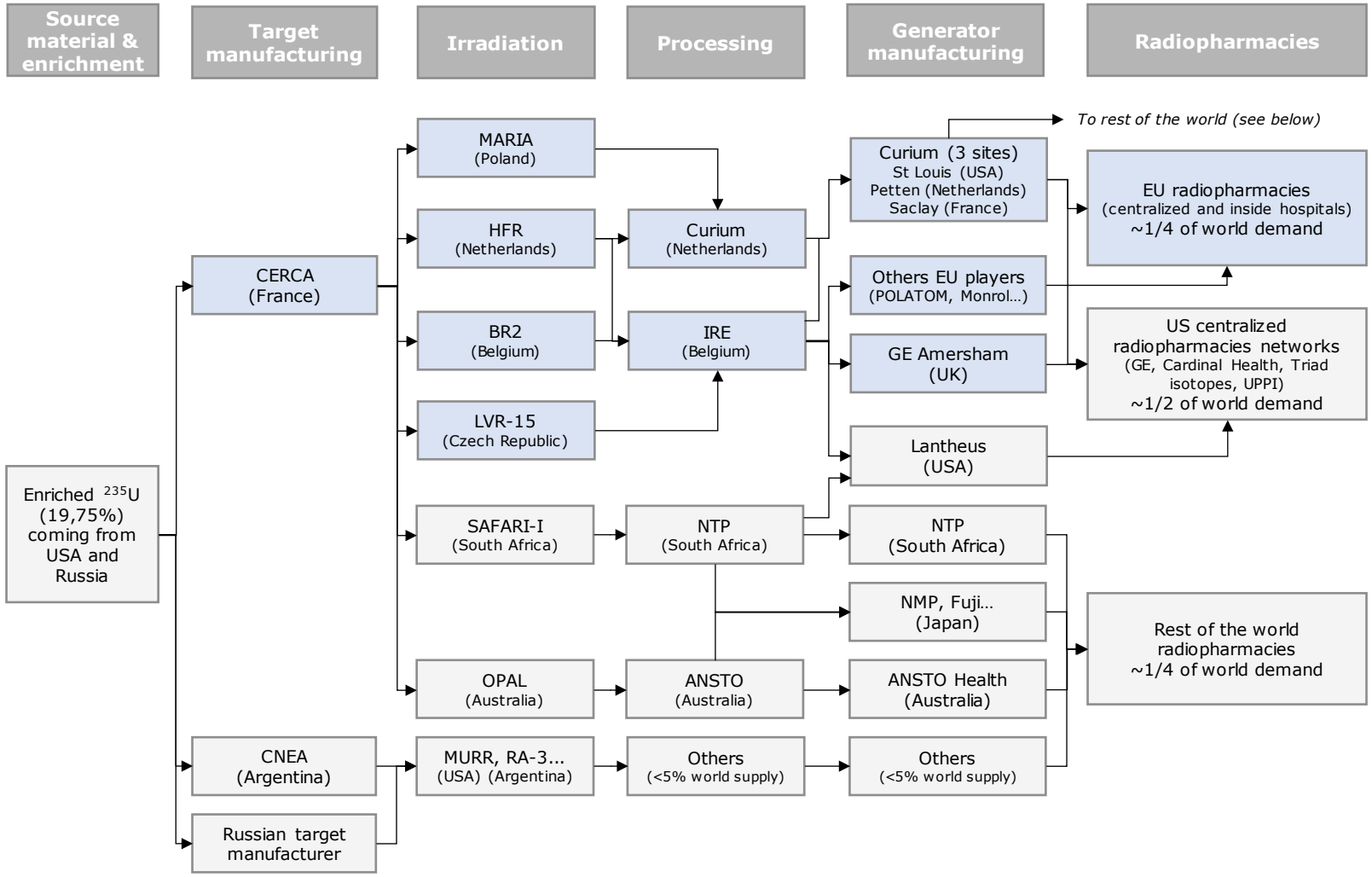
- ^{235}U targets are irradiated in 6 main reactors, 4 in Europe, 1 in South Africa and 1 in Australia. Other reactors exist, but with limited production or local needs. Targets are shipped to processing facilities, for ^{99}Mo dissolution. There are only 4 industrial processors of which 2 in Europe (Curium/Petten and IRE/Fleurus-Belgium). Curium, NTP and ANSTO facilities are close to an irradiation reactor.

  The main market players generally integrate vertically irradiation and processing capabilities. It is the case for NTP and ANSTO. It is also the case for Curium (see HFR/Curium strategic relation below) and it will be the case for future competitors like Pallas or SHINE.

- Extracted (raw) ^{99}Mo is shipped to GMP-generator manufacturers. Curium, NTP (S. Africa) and ANSTO (Australia) have their own generator manufacturing capabilities. Curium supplies raw ^{99}Mo to Curium/Saclay (France) and Curium/St Louis (USA). ANSTO, NTP, IRE supply Lantheus in the US. European generator manufacturers are supplied by European processors (Curium and IRE), and SAFARI/NTP or ANSTO in case of shortages.

- Generators are sold to about 350 customers (radiopharmacies) in the US and more than 1500 in Europe. In the US, radiopharmacies are centralized ones, supplying daily the hospitals with doses ready to be injected. In Europe, hospitals have generally their own radiopharmacy, supplied typically once a week, which prepare the doses according to their examinations schedule.

- Hence, market is local for irradiators (targets cannot be shipped by air), global for processed molybdenum, rather continental for generators, and local for ^{99}Mo doses.



Only the main fluxes have been included in the figure (e.g. NTP and ANSTO also supply ^{99}Mo to Curium)

Figure 44: ^{99}Mo/^{99m}Tc supply chain (EU players in blue)

** Amersham (GE) site now under Curium control*

Annex 2. Fluorine-18 (^{18}F)

A.2.1. Properties, applications and competing radionuclides

^{18}F

Properties: ^{18}F is almost a pure positron emitter for PET imaging with a 109,8 min half-life (β+ particle is produced in 96,9% of decay events, with a maximum energy of 0,64 MeV. The average energy of the emitted positron is quite low (249 keV) and therefore does not travel far before it annihilates leading to very good resolution in the scan images). ^{18}F decays into stable ^{18}O, without toxicity issues.

Competing radionuclides: ^{18}F should remain the most-used radionuclide for PET imaging, at least during the next decade. Some alternatives could reach the market in a few years (e.g. ^{68}Ga) and moderately impact ^{18}F use. Various RP based on ^{18}F are under development stage and could induce a second wave of growth for ^{18}F supply.

Demand: ^{18}F is currently the 2nd most-used RN after ^{99m}Tc (~10% of worldwide NM procedures). A substantial number of ^{18}F radiopharmaceuticals have proven their clinical value, with ^{18}F-FDG being the main tracer for PET. There is no market for ^{18}F alone. The current market for ^{18}F labelled RP (produced by cyclotron centre) can be estimated to roughly 1B$ (5 million procedures per year, with an average cost for ^{18}F-FDG dose around 200€), with important growth expected (from 1 to 6% CAGR depending on world region[130]).

Roughly 1 million of ^{18}F procedures are performed each year in Europe, with an average dose injected of 300-350 MBq (~10mCi). Demand at end of irradiation is strongly dependent on the users' proximity and number of daily production batches.

An increase of ^{18}F demand is expected on the period 2020-2040, driven by MS filling gaps, with overall increase of 1-2% per year lower than the one seen during the last decade of ^{18}F technology deployment (tens of % increase). This would represent a demand of 1,2-1,5 million procedures per year in 2040 in Europe.

A.2.2. Supply chain characterization

^{18}F can be produced in two different chemical forms: electrophilic fluorine (F_2) or nucleophilic fluoride (F^-) depending on the type of reusable target used (marketed by cyclotron manufacturers) with impact on the labelling approach used for radiopharmaceutical preparation[131].

[130] NucAdvisor estimate based on interviews with market players
[131] Jacobson O, Kiesewetter DO, Chen X. Fluorine-18 radiochemistry, labeling strategies and synthetic routes. Bioconjug Chem. 2015

The two most-used production reactions are:

- $^{18}O(p,n)^{18}F$, using highly enriched ^{18}O water ($[^{18}O]H_2O$) as target material, bombarded with protons (8-18MeV) and produces (nucleophilic) fluoride-18 ([18F]F-);
- $^{20}Ne(d,\alpha)^{18}F$, using ^{20}Ne gas target bombarded with deuterons (5-10MeV) and produces (electrophilic) fluorine-18 ($[^{18}F]F_2$) gas.

	Cyclotron production $^{18}O(p,n)^{18}F$	**Cyclotron production** $^{20}Ne(d,\alpha)^{18}F$
Technology readiness level	**TRL 9:** Fully mature technology, widely available through cyclotron network	**TRL 9:** Fully mature technology, but now replaced by ^{18}O route
Supply chain type	Local production, "just in time" supply by cyclotron centres established near users	
Yield	High yields obtained, improvements expected using high-power cyclotron with high current *(production of larger quantities of ^{18}F in a single batch, avoiding multiple irradiation per day and farther delivery)*	Low yields *(100 times lower than Oxygen production route)*
Purity	No contamination issue with manufacturing route	
Target material	Enriched ^{18}O water supply chain capacity higher than demand, with supply growth possible in case of demand growth.	More complex to handle and manufacture
Economics	One of the most expensive RN (and RP)	Non profitable for industrial production due to lower yields

Table 30: Summary table for ^{18}F manufacturing route

Historically, ^{18}F was produced through 2nd reaction ($^{20}Ne(d,\alpha)^{18}F$), which offers high reactive material (F_2) but with low specific activity and complex target extraction[132]. The first reaction is currently almost exclusively used, mainly for specific activity considerations[133] (~20-100 more specific activity).

Practically, both reactions require limited particle energies (10-20MeV) and can be implemented in standard PET manufacturing centres. There is no market for raw ^{18}F, as it is immediately labelled into a corresponding radiopharmaceutical. In addition to ^{18}F-Fludeoxyglucose (FDG), a few other radiopharmaceuticals based on ^{18}F (and others RN: ^{11}C, ^{15}O…) are routinely produced in these PET centres (one RP per batch).

The number of batches possible per day (or RP marketed per production centre) is the limiting factor for ^{18}F production. In case of new ^{18}F-radiopharmaceuticals

[132] Isotopes in nanoparticles – fundamentals and applications - 2016
[133] Radiopharmaceutical Production - FDG Synthesis Chemistry - IAEA

reaching the market within next decade, the current cyclotron network may not be sufficient.

The main challenges faced by ^{18}F supply chain are mainly linked to the target material (^{18}O) EU-dependency on importations and the need for irradiation installations over all EU:

- the need for a sufficiently dense cyclotron network over EU allowing local production of ^{18}F. Such cyclotron network has been under development for the past 20 years;
- the current dependency of non-EU players for ^{18}O supply and enrichment raises the question of investing in EU ^{18}O enrichment capacity.

Summary of ^{18}F supply chains

At the exception of ^{18}O enrichment, the ^{18}F supply chain is almost fully European, with cyclotrons network operated by global players (Curium, AAA/Novartis), using low-energy cyclotrons manufactured for most of them by two companies (IBA and GE Healthcare). Concerning ^{18}O supply: Japan, USA and Israel are the three main supply sources. A summary of current ^{18}F supply chain is given hereafter:

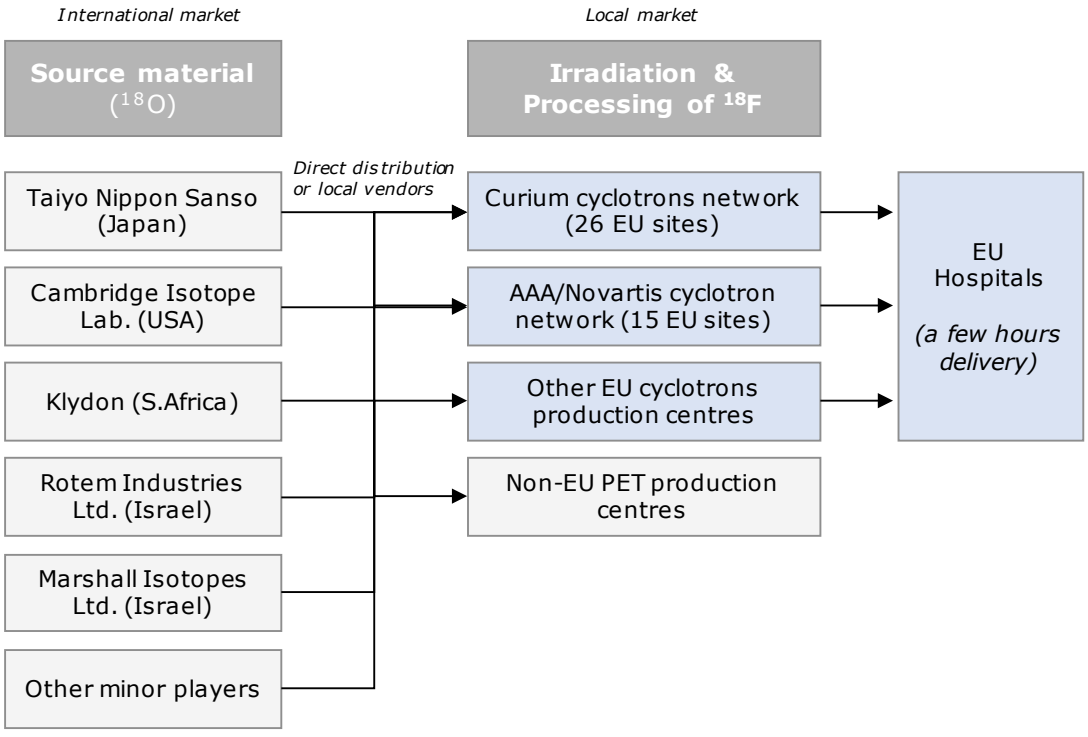


Figure 45: ^{18}F supply chain (EU players in blue)

Annex 3. Gallium-68 (^{68}Ga)

A.3.1. Properties, applications and competing radionuclides

Properties: ^{68}Ga is a positron emitter for PET imaging with a half-life of 67,7 min (β+ particle is produced in 89% of decay events, with a maximum energy of 1899 keV, three times higher than ^{18}F), decaying into stable ^{68}Zn. Like other metallic radionuclide gallium cannot be incorporated into radiopharmaceuticals vectors by covalent bonding (as opposed to ^{18}F) and must be complexed with a chelate[134].

Applications: Currently, ^{68}Ga is used for prostate cancer and neuroendocrine tumours (NET) diagnosis, and in theranostic pair with ^{177}Lu for treatment. Besides these two applications, various RP based on ^{68}Ga are under development, for breast, colorectal, renal, ovarian, gastrointestinal cancers that could largely extend ^{68}Ga use in the future[135].

Competing radionuclides: through its increasing use over the last years, ^{68}Ga can be considered as a "PET challenger". The current ^{18}F market will be partially impacted by ^{68}Ga development. Some ^{68}Ga-labeled molecules are expected to directly compete with their ^{18}F equivalents. However, a full takeover scenario of ^{18}F by ^{68}Ga is not foreseen.

Demand: ^{68}Ga experienced an important growth in the last years, with the approval in 2014 of pharmaceutical grade ^{68}Ga generator, followed by the market approval for NET tracers ([^{68}Ga]Ga-DOTA-TATE and [^{68}Ga]Ga-DOTA-TOC). Manufacturing capacities were improved in the recent years by the generator manufacturers, an order of magnitude of 1000 sites equipped with generators[136] ^{68}Ge/^{68}Ga can be considered, which corresponds to a maximum supply capacity of 1,5 million dose per year (~3 patient doses per elution, 2 elutions per day – 10 elutions per week). Actually, generator use is not optimized, and only a few hundred thousand procedures per year are performed with ^{68}Ga. If considering the pairing needs with therapeutic treatments (e.g. ^{177}Lu in the near future), a few thousand hundred patients treated with radiotherapeutics could shortly lead to more than 1 million doses administered.

^{68}Ga demand is limited in Europe: a few thousand procedures per year for largest users (in 2018: ~4000 in France, ~2000 in Sweden…). It should be in the range of 20-30k procedures per year in 2020.

[134] Morgat, Clément & Hindié, Elif & Mishra, Anil & Allard, Michèle & Fernandez, Philippe. (2013). Gallium-68: Chemistry and Radiolabeled Peptides Exploring Different Oncogenic Pathways. Cancer biotherapy & radiopharmaceuticals. 28. 85-97. 10.1089/cbr.2012.1244.
[135] Gallium-68: Radiolabeling of Radiopharmaceuticals for PET Imaging - A Lot to Consider- By Michael Meisenheimer, Yury Saenko and Elisabeth Eppard - December 23rd, 2019
[136] NucAdvisor estimate based on interviews with market players

Different parameters could drive ^{68}Ga evolution: theranostics development (pairing ^{68}Ga/^{177}Lu) and new molecules ability to jeopardize ^{18}F and ^{99m}Tc market shares. The sole use of ^{68}Ga as an imaging pair for a single ^{177}Lu treatment could lead to more than 100k procedures per year to treat 25 000 patients. Another way to assess future demand would be to consider that ^{68}Ga procedures become standardized in Europe and performed in almost all PET centres. Then considering the EU installed base of PET camera (~1200 units) (Source COCIR), with 1-2 units per site, ~900 sites will need to secure ^{68}Ga supply. With 900 generators and an average use of 2-4 procedures per day, demand could reach 0,5-1 million procedures per year by 2040 (with a 150MBq average dose injected to patient this would represent 4000-8000 Ci per year at elution or end of irradiation, considering a 50% decay loss).

A.3.2. Supply chain characterization

^{68}Ga can be produced through two different manufacturing routes, either through direct production in cyclotrons, or through the current industrial route, in long-life generators of ^{68}Ge/^{68}Ga. The two manufacturing reactions are:

- ^{68}Ge/^{68}Ga-generator, with germanium being produced in accelerators through different manufacturing routes;
- ^{68}Zn(p,n)^{68}Ga, in low-energy cyclotrons at 12MeV.

The generator-produced ^{68}Ga shall remain in the short term the main production source for regular ^{68}Ga users, especially when considering the recent investments done by the industry to cope with the demand and avoid future shortages[137]. Cyclotron production appears as a promising alternative for medical centres equipped with appropriate cyclotrons and radiopharmacy labelling capacity. Due to its short half-life, direct ^{68}Ga production should remain limited to areas with important local needs (large cities with multiple PET imaging sites).

	^{68}Ge/^{68}Ga-generator ^{68}Ge -> ^{68}Ga	**Cyclotron production** ^{68}Zn(p,n)^{68}Ga
Technology readiness level	**TRL 9:** Generators available worldwide with Market authorization or GMP grade	**TRL 8:** Liquid target systems already sold by cyclotron manufacturers, solid ones under R&D.
Supply chain type	Centralized supply chain with very limited logistics issues	Onsite production or offsite centralized supply chain with strong time constraints
Yield	Limited daily elution capacity *(from 15-30mCi of ^{68}Ga eluted per day (single*	Large daily production capacity for cyclotron production *(at least 10 times*

[137] SNMMI letter: August 6, 2018 to US FDA « Shortage of Germanium-68/Gallium-68 Generators for the Production of Gallium-68 »

	elution) during shelf-life – 60-70% yield)	*more, and up to 10Ci for potential future solid targets)*
Purity	Registered generators provide eluates meeting the specifications of the Pharm. Eur. Monograph 2464.	Impurities with other Ga isotopes (^{66}Ga and ^{67}Ga)
Target material	Limited ^{68}Ge target material supply capacity, could become bottleneck	^{68}Zn produced through ^{nat}Zn enrichment *(19% abundance)*
Economics	High generator cost, adapted for long/regular use, no investment need for radiopharmacy. Low cost per dose	Investment needed for solid target production, profitable route only in case of large number of doses sold per batch

Table 31: Summary table for ^{68}Ga production routes

^{68}Ge/^{68}Ga-generator (current manufacturing route)

For a few years, ^{68}Ga has been available through ^{68}Ge/^{68}Ga generators in Europe (e.g. Eckert & Ziegler with market authorization, ITM/ITG at GMP grade). ^{68}Ga availability through generators accelerated the dynamics of ^{68}Ga clinical developments. ^{68}Ge decays (with $T_{1/2}$ = 270,95 days) via electron capture to ^{68}Ga, making it ideal for a long-use generator. Such generators can theoretically be eluted up to 2 times a day, over long period of use (up to one year). Activity eluted remain limited (~30-35 mCi per elution) and limits the number of PET procedures for a single generator.

Although generators bring convenient use for radiopharmacies, some inherent limitations of these generators have to be mentioned: ^{68}Ge contamination can limit ^{68}Ga radiolabelling due to impurities and the difficulty of ensuring generator sterility over long period of use limits shelf-life based on a maximum number of elutions (250 – 400 depending on manufacturers).

Figure 46: Examples of commercially available generators. From left to right: Eckert & Ziegler – GalliaPharm®; Obninsk Cyclotron Ltd; IRE Elit – Galli Eo®; ITG;

^{68}Ge can be produced via a number of nuclear reaction pathways, all using charged particle induced reactions in particle accelerators (main ones being: ^{nat}Ga(p,xn)^{68}Ge at 15-20MeV; ^{69}Ga(p,2n)^{68}Ge at 15-25MeV; ^{66}Zn(α,2n)^{68}Ge at 30-40MeV[138]) with long irradiation duration (up to a few weeks). ^{68}Ge is currently

[138] Production of long-lived parent radionuclides for generators: ^{68}Ge, ^{82}Sr, ^{90}Sr and ^{188}W – IAEA 2010

produced in a few high-energy accelerators outside EU with ^{nat}Ga with limited supply capacity.
In the absence of EU supply of ^{68}Ge, the generator production in Europe is depending on importations from US players. The supply is currently limited to 5 sites producing ^{68}Ge on a regular basis[139] (iThemba laboratories - South Africa, Cyclotron Co. Ltd - Russia, Brookhaven National Laboratory - USA, Los Alamos National Laboratory - USA and Curium Saint Louis – USA). Yields depend of accelerator characteristics and irradiation duration, production capacities of about 18,5–74 GBq (0.5–2 Ci) of ^{68}Ge per batch are reported.

BNL and LANL already announced their intention to exit the market. The US production coming from public installations (Brookhaven and Los Alamos) shall thus be stopped as soon as private industrial companies will be able to cover world needs for ^{68}Ge/^{68}Ga generators[140]. As of mid-2019, DOE was still producing ^{68}Ge in its high-energy accelerators[141].

Regarding new production capacity, a few installations are considering the production of ^{68}Ge: Institute for nuclear research of Russian academy of sciences (INR RAS) that already performed sample production[142], and ARRONAX (France) that included ^{68}Ge as part of its radionuclide priority list[143]. Cyclotrons with 30MeV proton energy can produce ^{68}Ge, private production centres could initiate production in the future in case of profitable business and limited production coming from current players.

Direct production through cyclotrons (alternative manufacturing route)
The restrictions of ^{68}Ga produced through generators (high-cost, regular use needed to justify generator investment) and the limiting supply capacity fostered the development of alternative production routes, through existing medical cyclotrons (at 12MeV). Several approaches are under development for the production of ^{68}Ga with the reaction ^{68}Zn(p,n)^{68}Ga either with solid or liquid targets.

Liquid targets systems are the easiest way to produce ^{68}Ga in cyclotrons with production process close to ^{18}F one and could be implemented in most PET production centres (see nevertheless chapter 3 of this report). The use of solid target systems necessitates specific investments (target holder, cooling capacity, automated target transfer and processing systems) but leads to better yields per target (3 times more for same quantity of ^{68}Zn, with possibility to use more Zn in

[139] Production of long-lived parent radionuclides for generators ^{68}Ge, ^{89}Sr, ^{90}Sr and ^{188}W – IAEA 2010 / Addressing societal challenges through advancing the medical, industrial and research applications of nuclear and radiation technology – Curium – Roy W. Brown – March 20, 2018
[140] Record of Decision to Withdraw from Production and Distribution of the Radioisotope Germanium-68 Used for Calibration Sources - A Notice by the Energy Department on 09/02/2014
[141] DOE Isotope Program Overview 2019 – June 2019 – Dr Jehanne Gillo
[142] Production of medical radionuclides in Russia: Status and future - a review, B.L. Zhuikov, 2013
[143] Arronax website – https://www.arronax-nantes.fr/production-des-radionucleides/ - 06/04/2020

solid targets[144], up to 10Ci per batch could be obtained with improved solid targets[145]).

Liquid target systems are already marketed by cyclotrons manufacturers (IBA, GE…) while standardized solid targets systems are still under development for widescale use and would need full integrated solutions to be marketed (target holder, automated transfer and processing systems). The preference towards liquid or solid targets will be driven by local needs and investment capacity.

While already available with liquid targets of ^{68}Zn, industrial production will need solid targets for achieving appropriate yields. Cyclotrons players and laboratory equipment manufacturers are working on solid target solutions, that should be made available within the next decade.

This manufacturing route also leads to side-products contaminations issues (^{66}Ga and ^{67}Ga), that are mitigated through ^{68}Zn high target purity and optimized proton energy.

The main challenges faced by ^{68}Ga supply chain are mainly linked to the limited ^{68}Ge supply for the generator route, and the availability of solid targets systems allowing better yields to compete with the generator approach:

- the need for sustainable ^{68}Ge, for generator manufacturing, currently still largely coming from large public institutes;
- the need for solid targetry systems for cyclotron production of ^{68}Ga, to allow for large centralized production.

Summary of ^{68}Ga supply chains

Regarding supply chain players:

- The target material (^{nat}Ga, ^{69}Ga or ^{68}Zn) can be sourced from most of stable isotopes sellers and does not appear as a bottleneck. Different ^{nat}Ga targets types are being used (^{nat}Ga metal eNCApsulated in a Nb container, Ga/Ga_2O_3, Ga_4Ni…) and are directly manufactured onsite. Primary high-purity refined gallium production in 2019 was estimated to be about 205 tons. China, Japan, Slovakia, and the United States were the known

[144] Taking cyclotron 68Ga production to the next level: Expeditious solid target production of 68Ga for preparation of radiotracers - January 2020 / Cyclotron production of Ga-68 for human use from liquid targets: From theory to practice - 2017

[145] https://physicsworld.com/a/cyclotron-based-gallium-68-generator-breaks-production-records/

principal producers of high-purity refined gallium[146]. Zinc isotopes are obtained with high purity levels through gas centrifugation.

- Curium is the world's largest producer of 68Ge. Ga-Ni alloy targets are used and bombarded with protons from a 30 MeV cyclotron (MEC), with beam current up to 1,000 μA, the ^{68}Ge is then purified and sold to ^{68}Ga generator manufacturers. ^{68}Ge is also used for PET source calibration.

- The ^{68}Ge/^{68}Ga generators manufacturers supplying registered generators (for nuclear medicine use) are mainly EU-players: Eckert and Ziegler (Germany) and IRE Elit (Belgium). Others as ITG (Germany) and iThemba Labs (South Africa) supplying chemical grade generators. Eckert & Ziegler is currently the main market player. Generators shortages could be observed in the US in the last years and were mainly caused by Eckert & Ziegler limited production capacity. E&Z expanded their manufacturing facility[147] with manufacturing license issued in mid-2019.

A summary of the current ^{68}Ga supply chain through generator is given in the following figure:

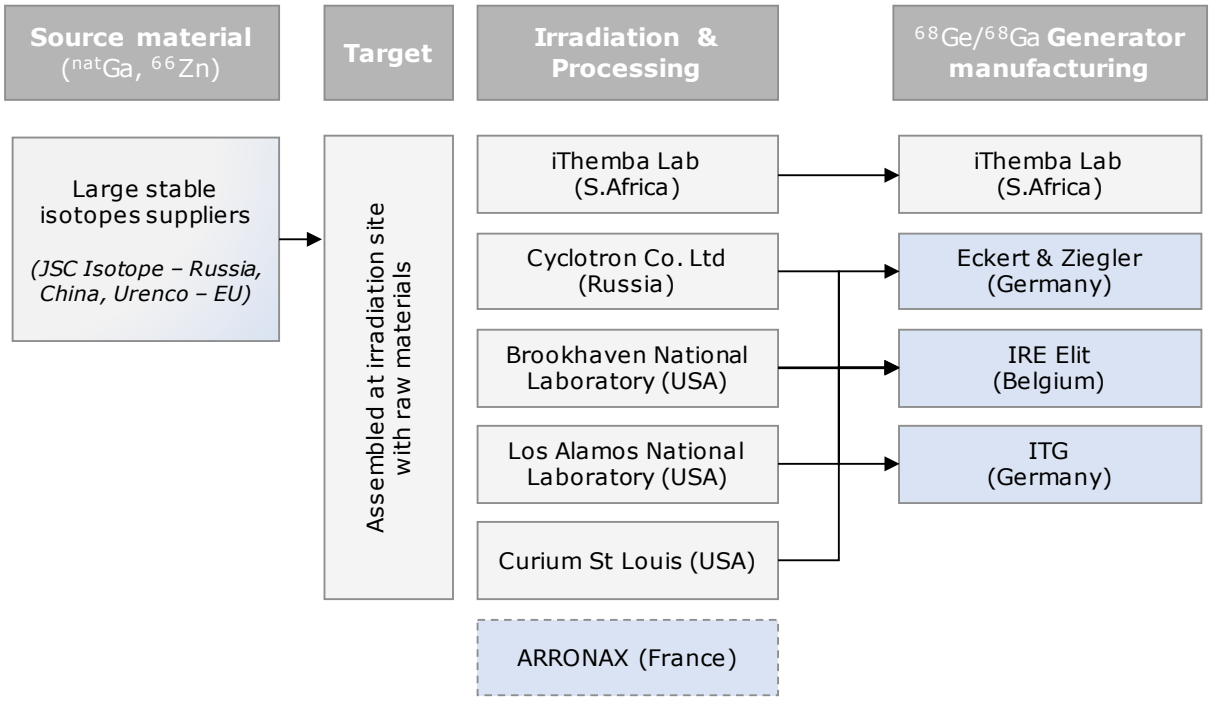


Figure 47: ^{68}Ga supply chain through generators (EU players in blue, dotted line for potential future player)

[146] https://pubs.usgs.gov/periodicals/mcs2020/mcs2020-gallium.pdf
[147] Eckert & Ziegler: additional production capacities for Gallium-68-Generators released by supervisory authorities, Berlin, 27 August 2019

Annex 4. Lutetium-177 (^{177}Lu)

A.4.1. Properties, applications and competing radionuclides

^{177}Lu

Properties: Lutetium-177 (^{177}Lu) has physical properties that make it among the most-promising radionuclide candidates for targeted beta therapy. A 6,65 days half-life minimizes decay losses during processing, transportation, distribution, labelling and allows for regional centralized production. ^{177}Lu decays in stable ^{177}Hf in 76% with emission of β^- particles which have limited soft tissue penetration, making it ideal for delivering cytotoxic radiation to small volumes and metastatic cancer sites (see figure below). The decay into excited states (~23% occurrence) of ^{177}Hf ultimately generates photons that can be used for imaging. ^{177}Lu has a favourable chemistry, with a large variety of potential molecular carriers (small molecules, peptides, proteins and antibodies).

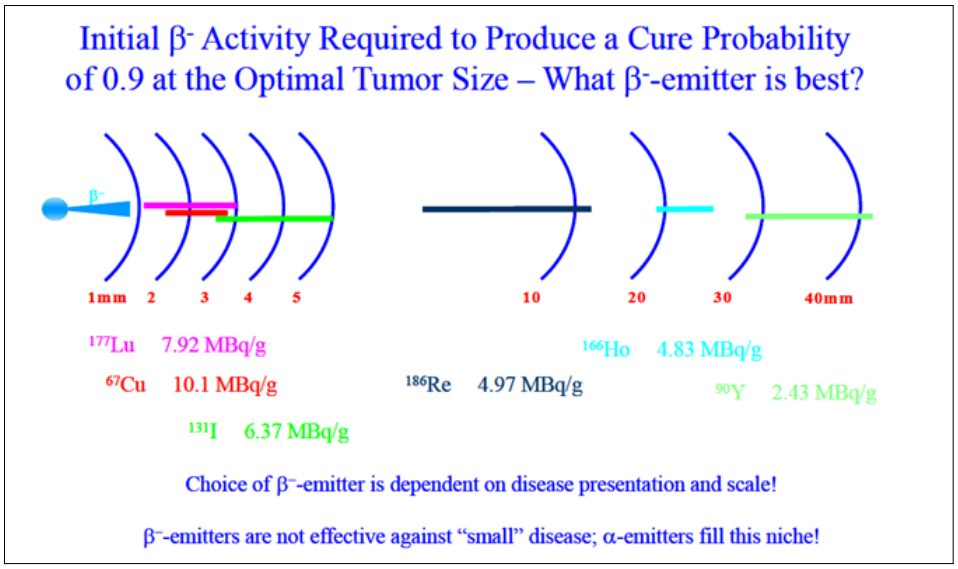


Figure 48: Complementarity of β^- emitters according to the tumour size – Source Journal of Nuclear Medicine 1995,36

Applications: Among the radionuclides suggested for targeted therapy, research with ^{177}Lu-based radiopharmaceuticals has demonstrated spectacular growth in recent years. Less than 10 papers were published about lutetium-177 (^{177}Lu)-labelled radiopharmaceuticals in the last century, whereas far more than 500 publications (as of 2014[148]) demonstrate the increasing interest in the use of ^{177}Lu. Monoclonal antibodies, peptides, phosphonate ligands, particulates, steroids, and other small molecules have been radiolabelled with ^{177}Lu for the development of a wide variety of therapeutic radiopharmaceuticals.

[148] Lutetium-177 Therapeutic Radiopharmaceuticals: Linking Chemistry, Radiochemistry, and Practical Applications. Sharmila Banerjee, M.R.A. Pillai, F.F.(Russ) Knapp, Chem. Rev. 2015, 115, 2934−2974. *Also used in other parts of this chapter.*

The success of treating patients suffering from neuroendocrine tumours with ^{177}Lu-labeled (DOTA-TATE) Lutathera®, a somatostatin analogue peptide, is the single most important example that has contributed to the worldwide interest and growth of ^{177}Lu as a therapeutic radionuclide. Several other ^{177}Lu based compounds are very promising for other cancer indications (prostate, kidneys, GEP-NET…) and are close to market approval.

Competing radionuclides: In terms of energy and radiation profile, ^{177}Lu is close to ^{67}Cu (currently on early development stage).

Although decay and chemical properties are an important consideration for selection of a therapeutic radionuclide, the success of using any radionuclide as an integral part of a radiopharmaceutical depends also on the feasibility of its production in high specific activity levels with acceptable quality and the ease of its transportation to nuclear medicine facilities, which is the case for ^{177}Lu.

Demand: ^{177}Lu demand is limited but currently increasing (Lutathera®: 1st RP with MA had a turnover of 400M$ in 2019).

Radiopharmaceutical EU demand for ^{177}Lu is almost exclusively on Lutathera® (AAA/Novartis), which represented in 2019 over 1000 patients in Western Europe (UK, DE, ES, IT, FR), with a standard treatment composed of 4 injections. Considering also clinical trials and compassionate use needs, ~10 000 doses per year are currently needed. An average injected dose of 200 mCi can be considered, representing a total demand per year of 2000 Ci (equivalent to 40 Ci per week), while irradiation demand could be up to two times more (decay losses and unused activity...).

^{177}Lu use in Europe is expected to face high growth, in line with theranostics development. By 2040, if a ^{177}Lu RP is used to treat 20-30k patients per year, this corresponds to a demand of 100k doses per year per RP (400 Ci per week per RP). With 5 to 10 ^{177}Lu-based RP, demand could exceed 100 000 Ci or 0,5 million procedures.

A.4.2. Supply chain characterization

In a nuclear reactor, ^{177}Lu can be prepared by neutron activation using direct activation of enriched ^{176}Lu ("direct route") or through the indirect route by activation of ^{176}Yb followed by β^- decay to ^{177}Lu. The indirect route (non-carrier added) is currently preferred over direct route (carrier added) due to ^{177m}Lu by-product issue and should continue to be favoured if this issue remains unresolved.

Although ^{177}Lu can be produced by charged particle acceleration (through the ^{176}Yb(d,p)^{177}Yb$\rightarrow^{177}$Lu reaction and decay) using a cyclotron, neutron irradiation in a nuclear reactor is the most practical and cost-effective route. Radioactivity yields and specific activity by charged particle acceleration route are much lower, and

the process is more expensive, thus making this method an impractical one for industrial production and has been discarded.

The table below summarizes the characteristics of reactor production routes:

	Direct reactor production route $^{176}Lu(n,\gamma)^{177}Lu$	**Indirect reactor production route** ^{177}Yb -> ^{177}Lu
Technology Readiness Level	**TRL9:** both routes are currently already used by European radionuclide industry for ^{177}Lu production	
Installed capacity	High number of RR can cost-efficiently produce ca ^{177}Lu	A higher neutron flux is needed, limiting production to a more limited number of reactors
Yield	High yields *(1000 times more than through indirect route, per mg of pure target)*	Low yields, partially compensated by high fluxes and enriched targets
Specific activity	Low to medium, thus limiting clinical applications with high activity needed	High activity, suitable for all clinical applications (3-4 times more than carrier-added route)
Purity	Presence of ^{177m}Lu, leading to higher dose for patient, waste disposal of ^{177m}Lu	No presence of long-lived radioactive impurities (^{177m}Lu), thus limiting radiation protection and waste issues
Target	^{176}Lu targets, good behaviour under irradiation, easy procurement	Enriched ^{176}Yb target needed, costlier
Processing	Simple & fast irradiated target processing. The facility required for target processing is straightforward to install and maintain.	The effective separation of $^{177}Lu/^{176}Yb$ requires an elaborate radiochemical separation and purification procedure
Cost	Based on all previous parameters, very affordable production cost, (cheaper than Mo-99 per Ci)	High production cost

Table 32: Summary table for ^{177}Lu manufacturing routes

Indirect reactor production route

The reaction implemented in this route is $^{176}Yb(n,\gamma)^{177}Yb$, which is followed by the decay (T½ 1,9 h) of ^{177}Yb into ^{177}Lu, implemented by neutron bombardment of Yb_2O_3 targets enriched in ^{176}Yb. ^{177}Lu is then separated from the Yb_2O_3 target by delicate radiochemical processes. The major advantages of this route are that it provides NCA (non carrier-added) ^{177}Lu of high specific activity[149] and the product formed is free from ^{177m}Lu, the long-lived (T½ = 160.5 days) radionuclidic

[149] High specific activity of the radio-labelled agent is of prime importance for the design of therapeutic radiopharmaceuticals since the target sites and density for attachment of the radiopharmaceuticals are usually limited, especially for those therapeutic agents which bind to specific receptors. This is not the case for agents such as 177Lu-based phosphonates where the targeting mechanism does not involve binding with limited expression of receptors on tumour tissue (like for bone pain palliation for instance)

impurity. The disadvantages are that it necessitates ^{176}Yb enriched targets and relatively high thermal neutron flux reactor (typically >1 × 10^{14} n/cm^2/s).

The target material for NCA ^{177}Lu is ytterbium, which pertains to the rare earth elements. This mineral is found with other rare earth elements in several rare minerals. It is most often recovered commercially from monazite sand (0,03% ytterbium). The element is also found in euxenite and xenotime. The main mining areas are China, the United States, Brazil, India, Sri Lanka, and Australia. The world production of ytterbium is only about 50 tonnes per year, reflecting that it has few commercial applications. Reserves of ytterbium are estimated as one million tonnes. For this target material, shortage risks are thus limited.

Direct reactor production route

On the contrary, the direct production route can be implemented even in medium flux reactors. Indeed, for the reaction implemented (^{176}Lu(n,γ)^{177}Lu) the neutronic absorption of ^{176}Lu is hundreds of time higher than the one of ^{176}Yb, allowing for more easily for important Lu yields. Extraction of Lu from the targets is basically a simple dissolution with acid. However, ^{176}Lu remaining, which can hardly be separated from ^{177}Lu, limits to 10-30% of the maximum specific activity (SA) the ^{177}Lu SA produced in a medium flux reactor, whereas ^{177}Lu SA produced by the indirect production route may be close to 100% of max SA. In addition, undesirable ^{177m}Lu[150] is also produced in the reaction, which cannot either be easily separated from ^{177}Lu.

Alternatives to reactors

Aside from research reactors, and based on the same direct or indirect routes, irradiation could also be performed in power reactors (CANDU)[151]. Such approach is currently under early development.

Direct production through cyclotrons

None of the cyclotron production routes can economically produce large ^{177}Lu quantities and are not presently considered as potential supply alternatives.

The main challenges faced by ^{177}Lu supply chain are mainly linked to the target material (^{176}Yb) for the non-carried added route, that is currently only sourced from Russian manufacturer. The need for an electromagnetic enrichment capacity in EU (calutron) might be a major challenge.

Summary of ^{177}Lu supply chains

^{177}Lu is currently produced through two main manufacturing routes, that currently coexist providing either CA or NCA grade ^{177}Lu. EU is a large contributor of ^{177}Lu

[150] ^{177m}Lu may raise waste management problems in the hospitals
[151] Companies work on securing medical isotope supplies – WNN - February 2020

manufacturing, either through irradiation (HFR, MARIA for CA or BR-2 for NCA), while different players are supplying ^{177}Lu radiochemical (Polatom, ITM) or GMP produced with marketing authorization (IDB/AAA – LuMark®). Conversely, EU is fully depending on Russian supply for target material.

A summary of the ^{177}Lu supply chains (direct and indirect routes) is given in the following figure:

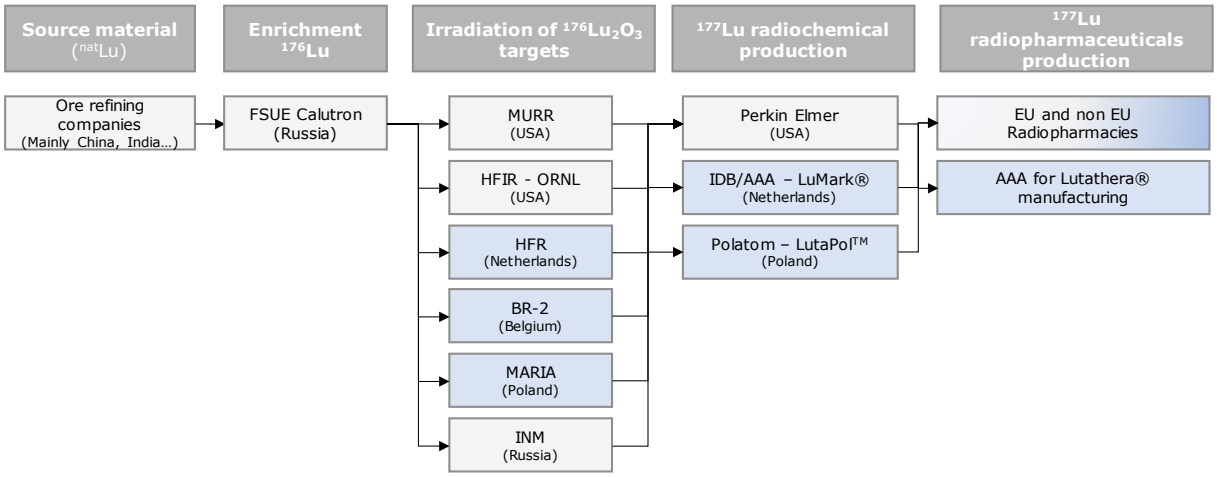


Figure 49: Summary of current carrier-added ^{177}Lu supply chain

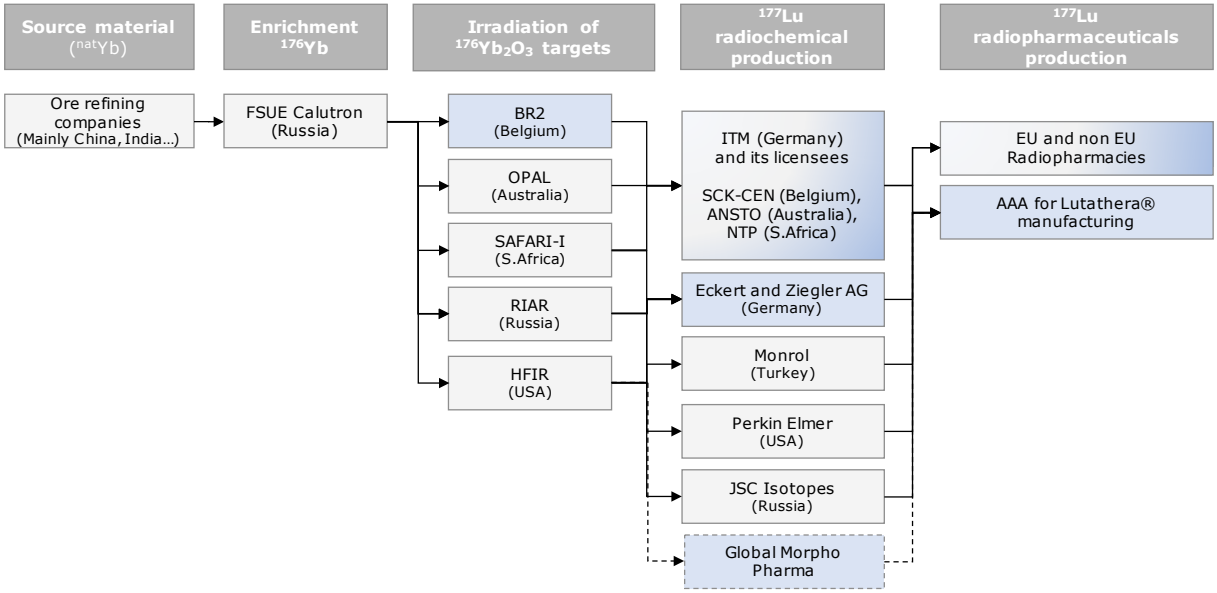


Figure 50: Summary of current non-carrier-added ^{177}Lu supply chain *(India and China non-considered as they are essentially centred on their domestic market)*

Annex 5. Yttrium-90 (^{90}Y)

A.5.1. Properties, applications and competing radionuclides

^{90}Y

Properties: ^{90}Y is a pure β-emitter with one of the highest β-energy that decays ($t_{1/2}$=64hours) into ^{90}Zr.

Applications: ^{90}Y use depends of the product quality, carrier-added can be used for brachytherapy (labelled microspheres) and radiosynoviorthesis applications. The non-carrier added ^{90}Y is used for TRNT tumours treatments.

Competing radionuclides: With its high β-energy, ^{90}Y is competing with ^{166}Ho and is more adapted to large tumours treatment.

Demand: Before the recent development of Lutathera® and Xofigo®, ^{90}Y Zevalin® was one of the most used therapeutic agents on the market. ^{90}Y demand remains important, the CA ^{90}Y is largely used for radiosynoviorthesis applications (tens of thousands of procedures in EU per year, without growth perspectives), while NCA use is currently more limited (less than 10 thousand procedures in EU per year) but could increase in the future in case of success of new TRNT products under development.

A.5.2. Supply chain characterization

^{90}Y can be produced through two manufacturing routes, either directly, leading to carrier-added ^{90}Y or indirectly through ^{90}Sr decay, leading to NCA ^{90}Y:

- direct route, through neutron irradiation in research reactors of enriched ^{89}Y targets, ^{89}Y(n,γ)^{90}Y;
- indirect route through production of ^{90}Sr (fission product of ^{235}U), then decay in ^{90}Y ($t_{1/2}$=28.8 years), harvested in industrial generators.

Both direct and indirect routes are discussed in the following table:

	Direct route ^{89}Y(n,γ)^{90}Y	**Indirect route** Industrial generator ^{90}Sr/^{90}Y
Technology Readiness Level	**TRL9:** both routes are currently already used by European radionuclide industry for ^{90}Y production, no direct "competition" is existing between the two, the different product grade being used for different applications.	
Applications	Used for radiosynoviorthesis and as microspheres for brachytherapy applications	Used for TRNT
Installed capacity	Neutron irradiation of ^{89}Y targets (Y_2O_3) or ^{89}Y microspheres can be performed in low neutron flux	Installed capacity is directly proportional to existing stockpiles of ^{90}Sr, issued from ^{235}U fission (5,77% yield).

Supply chain type	Due to its important half-life, production can be done on a centralized basis with European/International distribution.	Industrial generators cannot be operated by small or onsite radiopharmacies (^{90}Sr is highly radiotoxic), they are located at radiochemical producers' plants and doses are directly distributed. ^{90}Y half-life allows centralized distribution.
RN quality	Low specific activity, with presence of impurities (^{89}Sr)	High specific activity and no impurities. Need for efficient separation process to avoid ^{90}Sr impurities
Cost	Cheapest form of ^{90}Y available on the market	More costly to produce than CA ^{90}Y

Table 33: Summary table of ^{90}Y manufacturing routes

Summary of ^{90}Y supply chain

The two manufacturing routes of ^{90}Y are not in competition, providing two different products qualities, used for distinct applications. Instead of using existing ^{90}Sr stockpile, issued from power plants reprocessing, another route would deserve to be studied: in parallel of ^{99}Mo, research reactor targets also contains ^{90}Sr, which could be isolated owing to an adaptation of the ^{99}Mo extraction process.

The current EU supply chains for NCA ^{90}Y route is summarized below:

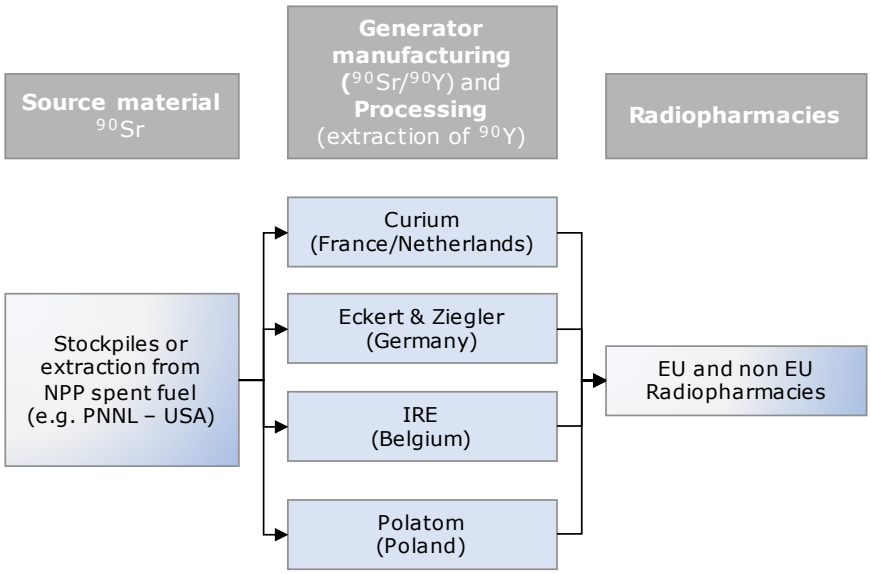


Figure 51: Summary of current EU NCA supply chain

Regarding carrier-added ^{90}Y, its radiosynoviorthesis use is limited, while microspheres supply is not an "open" market, with BTG and SIRTEX controlling internally all supply chain.

Annex 6. Iodine-131 (^{131}I)

A.6.1. Properties, applications and competing radionuclides

^{131}I

Properties: Iodine-131 decays with both photon (gamma) and beta particle emission with a half-life of 8 days. The different radioactive isotopes of Iodine (^{131}I, ^{123}I…) have been extensively used in nuclear medicine due to the thyroid gland's natural affinity for Iodine.

Applications: ^{131}I is used for both thyroid imaging and therapy of different types of thyroid cancers.

Competing radionuclides: ^{131}I use is standardized and should remain limited to thyroid treatment applications. As compared to promising radionuclides for therapy (^{177}Lu, ^{225}Ac…) there is currently no strong interest to develop new ^{131}I labelled radiopharmaceuticals.

Demand: Based on EU statistics of use, an order of magnitude of a few tens of thousands ^{131}I procedures per year are performed in EU. A limited growth has been reported from market players. Injected doses vary from imaging (a few mCi) to treatment (50-200mCi).

A.6.2. Supply chain characterization

^{131}I is indirectly produced through two different manufacturing routes in research reactors:

- through the neutron irradiation of tellurium-130 targets, (^{130}Te(n,γ)^{131}Te) followed by decay into ^{131}I
- or as a side product of ^{99}Mo manufacturing, ^{131}I being one fission product of ^{235}U (~2.9% yield).

The two manufacturing routes are described in the following table:

	Tellurium-130 targets ^{130}Te(n,γ)^{131}Te -> ^{131}I	**Side product of ^{99}Mo manufacturing** ^{235}U(n,f)^{131}I
Technology readiness level	**TRL 9:** Manufacturing route in use in research reactors for decades *(e.g. ^{131}I NRU production based on this route)*	**TRL 9:** Main ^{99}Mo processing facilities are used to extract ^{131}I from ^{235}U targets used for ^{99}Mo production (NTP, IRE…)
Radiation protection	For both manufacturing routes the management of ^{131}I represents a challenge for radiation protection and radionuclide monitoring, leading to additional constraints for handling and radiopharmaceuticals production.	

	Tellurium-130 targets $^{130}Te(n,\gamma)^{131}Te$ -> ^{131}I	**Side product of ^{99}Mo manufacturing** $^{235}U(n,f)^{131}I$
Supply chain type	Centralized production	Centralized production, process fully dependent of ^{99}Mo supply. Past incidents in ^{99}Mo production lines impacted ^{131}I supply *(e.g. NTP facilities shutdown in 2018/2019)*
Yield & purity	High yield, with high specific activity and no impurities (NCA product), growing interest for NCA.	Limited yield but balanced by large production volumes of ^{99}Mo. Lower specific activity but enough for imaging & therapy.
Target material	^{nat}Te contains 33,8% of ^{130}Te, limiting the use of enrichment only for high specific activity ^{131}I *(or for local production in low neutron flux reactors)*	Standards LEU ^{235}U targets used for ^{99}Mo production *Cf. §2.1 for ^{99}Mo production*
Economics and market trends	More expensive, but higher specific activity. Growing interest for ^{131}I produced through this manufacturing route.	Production at marginal costs, ^{131}I obtained at ^{99}Mo purification process step, with mutualization of infrastructure costs (reactor, processing facility…).

Table 34: Summary table for ^{131}I manufacturing routes

Tellurium-130 targets

The irradiation is performed with TeO_2 targets (^{nat}Te) irradiated in research reactors during a few days. The ^{131}Te produced decays ($t_{1/2}$=25min) into ^{131}I which is then separated from target with dry distillation technique.

Side product of ^{99}Mo manufacturing

Production of ^{131}I from ^{99}Mo manufacturing only differs at the processing stage. After dissolution of ^{235}U irradiated targets, ^{131}I is separated from ^{99}Mo through ion-exchange chromatography combined with a distillation step. The first batches of LEU-targets-based ^{131}I by IRE[152] has been produced in early May 2020 with a full transition by 2022. SIRE supply will be limited during this period.

Production in cyclotron (deuterium flux)

Despite ^{131}I production in cyclotrons is achievable (in deuterium beams), this manufacturing route is not foreseen to compete with reactor production (less cost-efficient).

The ^{131}I supply chains do not have specific challenges that need to be addressed to ensure sustainable supply for next decades, except the more generic challenge of the research reactors (see chapter 2).

[152] Belgium starts producing Mo-99 using LEU - 04 May 2020
https://world-nuclear-news.org/Articles/Belgium-starts-producing-Mo-99-using-LEU

Summary of 131I supply chains

^{131}I has been produced through these two manufacturing routes during the last 20 years. At the time where NRU was the main ^{99}Mo and ^{131}I producer, ^{130}Te targets was the main source of ^{131}I. With NRU end-of-life joint production with ^{99}Mo became the new standard (IRE, NTP). A growing trend for NCA ^{131}I can be observed, pushing for increased production with ^{130}Te.

A summary of ^{131}I current supply chain is given in the following figure:

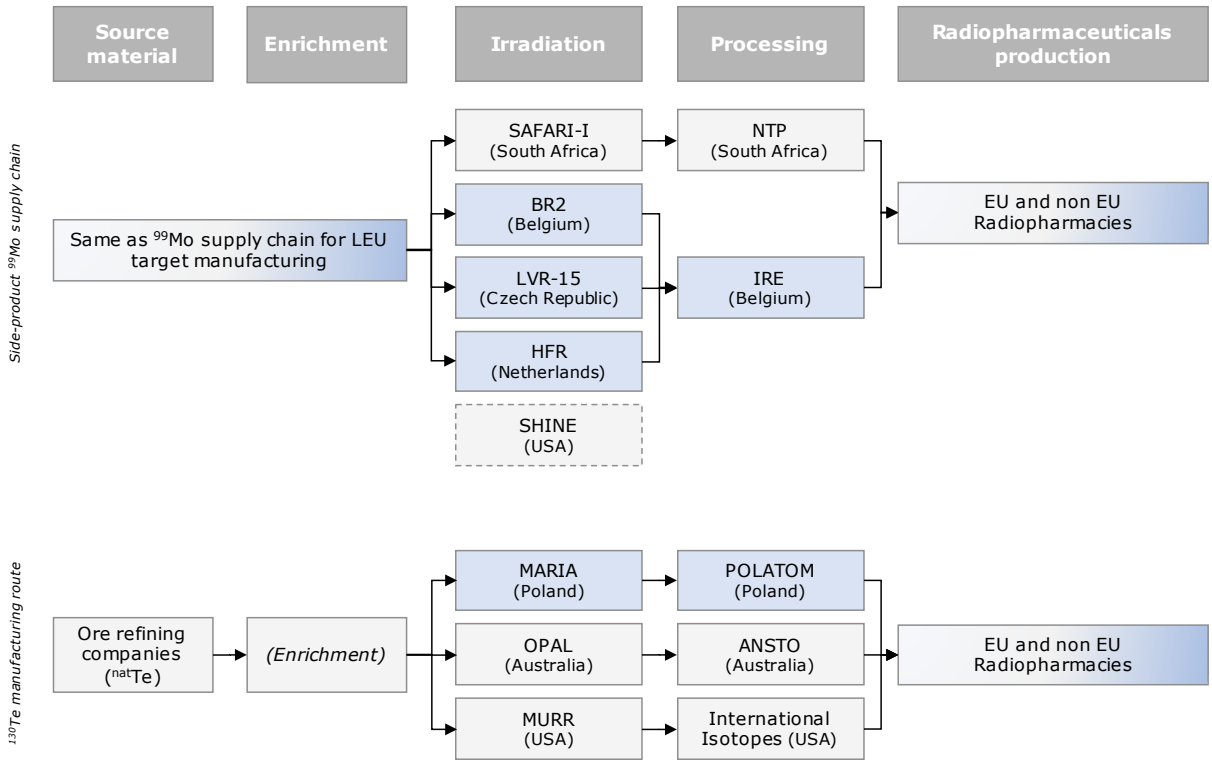


Figure 52: Summary of current ^{131}I supply chains through ^{99}Mo supply chain (upper part) and direct production (lower part) – EU players in blue

Annex 7. Iodine-123 (^{123}I)

A.7.1. Properties, applications and competing radionuclides

^{123}I

Properties: ^{123}I is a γ-emitter compatible with SPECT imaging, with a relatively long half-life for an imaging radionuclide ($t_{1/2}$=13,3hours).

Applications: ^{123}I progressively replaced ^{131}I for thyroid imaging (lower absorbed doses to patient) and become essential for some applications without alternatives, such as [^{123}I]-I-MIBG (Metaiodobenzylguanidine) for endocrine tumour imaging.

Competing radionuclides: ^{123}I is the second most-used SPECT radionuclide, without alternative RP for some applications.

Demand: ^{123}I demand is in the range of tens of thousands of procedures in the EU, far less than ^{99m}Tc imaging. Its use should at least remain stable for the next decade, considering the lack of alternatives and its superiority for thyroid imaging. Current and future demand for ^{123}I will be intrinsically linked to ^{131}I, as it is mainly used for thyroid imaging.

A.7.2. Supply chain characterization

^{123}I can be produced through various manufacturing routes, either directly or through ^{123}Xe decay. Two of these routes can be considered as the two major ones, largely used:

- direct route, through proton irradiation of tellurium-124 targets in accelerators through reaction ^{123}Te(p,n)^{123}I;
- indirect route, through decay of ^{123}Xe, also produced in cyclotrons through reactions ^{124}Xe(p,2n)^{123}Cs that successively decays into ^{123}Xe then ^{123}I or ^{124}Xe(p,n)^{123}Xe followed by decay into ^{123}I.

	Direct route	Indirect route through ^{123}Xe decay
Technology readiness level	**TRL9:** both routes have been industrialized and used in the past, targets and targetry systems are widely available	
Target material	Need for enriched ^{123}Te to decrease by-products. Enrichment by gas centrifugation possible (natural abundance of 0.9%).	^{nat}Xe is a by-product of air distillation plants, as many other rare gas. Need for enriched Xe, through gas centrifugation, ^{124}Xe has a low natural abundance of 0.09%
Target	Solid targets of Te, often mixed with aluminium to increase heat transfer. No particular issue	As ^{124}Xe and ^{123}Xe are under gas form, additional constraints are taken to avoid any gas leak. Gas targets are standardized and extensively used.

	Direct route	Indirect route through ^{123}Xe decay
Irradiation means	Low energy cyclotron 10-20MeV, more widely available	Medium-energy cyclotrons 20-30MeV
Yield and purity	Co-production of ^{124}I, limiting shelf-life of ^{123}I produced.	High purity ^{123}I and easy separation with target material (^{124}Xe). High yields as compared to direct route.
Supply chain type	For both routes, supply chain is semi-centralized. ^{123}I half-life allows longer transportation time than standard PET radionuclides produced in cyclotrons. However, a few production centres in EU are needed to cover needs. Multiple sites in EU are equipped with cyclotrons having enough energy to produce ^{123}I, but almost all of them do not have GMP production centre attached.	

Table 35: Summary table for ^{123}I manufacturing routes

Summary of ^{123}I supply chain

Among these two manufacturing routes, the indirect one is largely preferred for industrial production, as it leads to better yields, easier separation/processing. However, the limited availability of medium-energy cyclotrons (20-30MeV) dedicated to RN production is an important limitation for the use and development of some radionuclides (^{123}I or ^{111}In).

Current industrial EU supply chain of ^{123}I (indirect route) is summarized in the following figure:

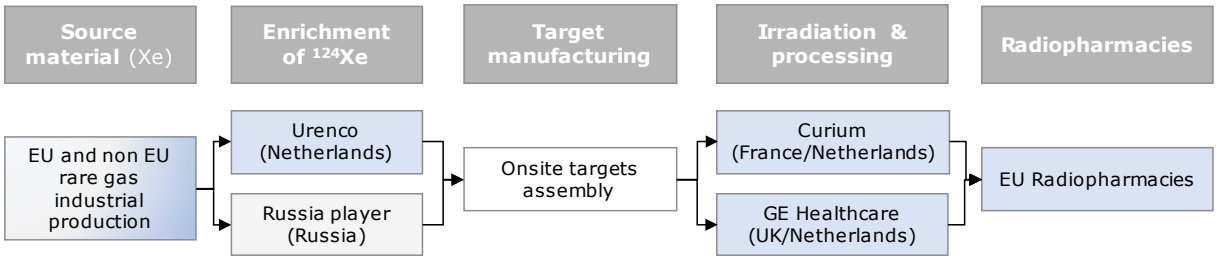


Figure 53: Summary of current ^{123}I supply chain (EU players in blue)

Annex 8. Iodine-124 (^{124}I)

A.8.1. Properties, applications and competing radionuclides

^{124}I

Properties: ^{124}I is a long-life ($t_{1/2}$=4.2d) positron emitter for PET imaging. It has a complex decay scheme before reaching stable ^{124}Te, with multiple gamma and beta emission of high-energy, of which 23% of its disintegrations result in positron emission.

Applications: the development of imaging applications based on ^{124}I have been limited in the past due to the high-energy of the γ emissions[153]. The patient dosimetry remains an open issue for health authorities. Different RP are under development for ^{124}I PET imaging, with a focus on long biological processes due to ^{124}I long half-life.

Competing radionuclides: Among the different candidates for slow biological process imaging, ^{124}I and ^{89}Zr are both currently under development and should impact each other future. ^{89}Zr displays a better dosimetry[154] to the patient than ^{124}I, despite being high as compared to short half-life radionuclides.

Demand: The development of ^{124}I-labelled RP should remain focused on some slow biological process imaging, limiting ^{124}I use as compared to others short half-life imaging PET radionuclides (^{18}F, ^{68}Ga).

A.8.2. Supply chain characterization

^{124}I can be directly produced in medium-energy accelerators through multiple manufacturing routes: $^{123\text{-}126}$Te(p,xn)^{124}I, ^{123,124}Te(d,xn)^{124}I, ^{121,123}Sb(α,xn)^{124}I and ^{123}Sb(^{3}He,2n)^{124}I nuclear reactions[155]. Among these different reactions, the ones relying on proton beams (or deuterium beams to a lesser extent) present more interest from an industrial standpoint, considering their wider availability. Antimony reactions are not developed hereafter.

The proton irradiation route using ^{124}Te targets (^{124}Te(p,n)^{124}I) is currently foreseen as the future standard production route, due to low target material cost and lowest impurities. This centralized manufacturing route and its main variants are discussed in detail in the following table:

[153] ^{124}Iodine: A Longer-Life Positron Emitter Isotope—New Opportunities in Molecular Imaging – Hindawi Publishing Corporation - BioMed Research International - Volume 2014
[154] ^{89}Zr-Labeled Versus ^{124}I-Labeled αHER2 Fab with Optimized Plasma Half-Life for High-Contrast Tumor Imaging In Vivo - J Nucl Med July 1, 2015 vol. 56 no. 7 1112-1118
[155] Production of novel diagnostic radionuclides in small medical cyclotrons - EJNMMI Radiopharmacy and Chemistry volume 3, (2018)

	$^{124}Te(p,n)^{124}I$	$^{124}Te(d,2n)^{124}I$ $^{125}Te(p,2n)^{124}I$
Technology readiness level	**TRL9:** production route under use, targetry systems and processing available for industrial production	**TRL 6:** technology developed at laboratory scale, not pushed anymore by research and industry.
Target material	Enriched ^{124}Te (>99%) in the form of tellurium oxide (TeO_2), must be recycled to improve economics yield	^{125}Te is also expensive and need recycling, more expensive than ^{124}Te
Irradiation means	Standard medical cyclotrons with optimal range 8-12 MeV	High energy proton flux (15-21MeV) or deuterium flux (10-14MeV) needed, more costly and less widely available
Purity	Impurities: 1% of ^{123}I and less than 0.1% of ^{125}I, manufacturing route with lower impurities levels	For $^{124}Te(d,2n)^{124}I$, 1.7% of ^{125}I impurity, while $^{125}Te(p,2n)^{124}I$ leads to 7.4% of ^{123}I and 0.9% of ^{125}I impurities, as compared to ^{124}I

Table 36: Summary table for ^{124}I manufacturing routes

Summary of ^{124}I supply chain

The potential future development of ^{124}I manufacturing, to cover demand for a ^{124}I labelled RP, will not face any major challenge. The long half-life of ^{124}I allows for a centralized production in a more limited number of installations. A few hundred doses could be prepared by a single site each day, enough for covering European needs with only a few production sites.

Industrial supply of ^{124}I is currently limited in EU, BV Cyclotron VU stopped production[156] in 2020, and ^{124}I is not part of Curium products (despite having been previously part of IBA Molecular one's).

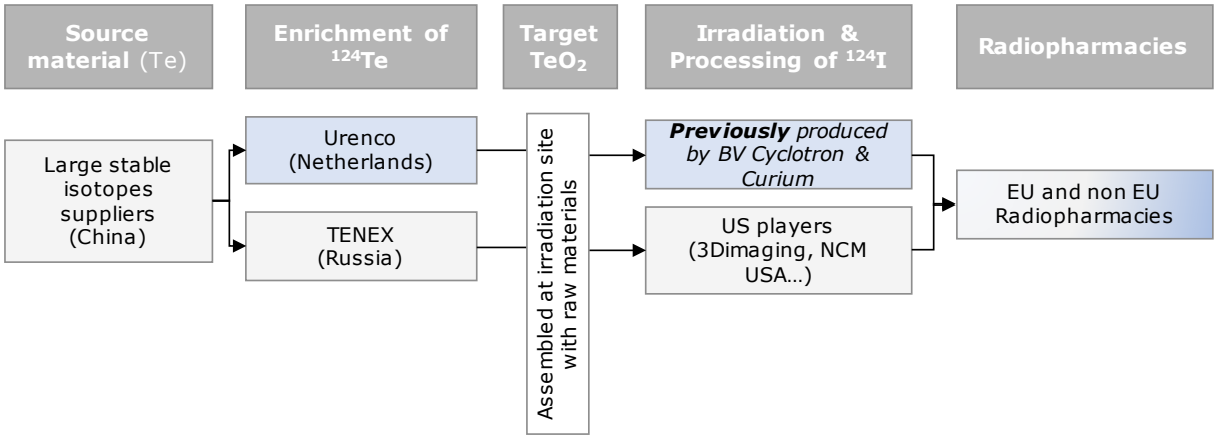


Figure 54: Summary of current ^{124}I supply chain (EU players in Blue)

[156] https://www.cyclotron.nl/iodine-124__2_3_2

Annex 9. Zirconium-89 (^{89}Zr)

A.9.1. Properties, applications and competing radionuclides

^{89}Zr

Properties: ^{89}Zr is a pure positron emitter for PET imaging with a long half-life ($t_{1/2}$=78,4hours) as compared to others PET radionuclides. It fully decays into stable ^{89}Y.

Applications: ^{89}Zr long half-life is particularly suited to imaging of slow biological processes. Despite different types of applications are under development (large long circulating protein labelling, inflammation studies…), the labelling of antibodies for PET imaging is currently the main application under development for ^{89}Zr (immuno-positron emission tomography).

Competing radionuclides: Among the different candidates for slow biological process imaging, ^{124}I and ^{89}Zr are both currently under development and should impact each other future. ^{89}Zr displays a better dosimetry[157] to the patient than ^{124}I, despite being high as compared to short half-life radionuclides.

Demand: the development of ^{89}Zr-labelled RP shall remain limited to immuno-PET, limiting ^{89}Zr use as compared to other, short half-life, imaging PET radionuclides (^{18}F, ^{68}Ga).

A.9.2. Supply chain characterization

^{89}Zr can be directly produced in medium-energy accelerators through different manufacturing routes:

- proton irradiation or deuterium irradiation of ^{89}Y in medium energy cyclotrons (protons 14MeV or deuterium up to 20MeV) through the reactions ^{89}Y(p,n)^{89}Zr or ^{89}Y(d,2n)^{89}Zr. Natural yttrium is only composed of ^{89}Y isotope. Hence, no need for enriched targets;
- ^{nat}Sr(α,xn)^{89}Zr, which requires the use of less widely available α-beams and produces impurities due to different strontium isotopes (^{86}Sr 9.9%; ^{88}Sr 82.6%; ^{87}Sr 7%; ^{84}Sr 0.6%), thus necessitating an additional enrichment step. For these reasons, the industry is not developing this manufacturing route.

The proton irradiation route (^{89}Y(p,n)^{89}Zr) is expected to become the standard production route in the near future, without any major production limitation. This manufacturing route and its deuterium irradiation variant are discussed in detail in the following table:

[157] ^{89}Zr-Labeled Versus ^{124}I-Labeled αHER2 Fab with Optimized Plasma Half-Life for High-Contrast Tumor Imaging In Vivo - J Nucl Med July 1, 2015 vol. 56 no. 7 1112-1118

	^{89}Y(p,n)^{89}Zr	^{89}Y(d,2n)^{89}Zr
Technology readiness level	**TRL9:** mature route *(cyclotron, target, processing)* with manufacturing sites already operational (USA, EU, Japan…)	**TRL 6:** technology developed at laboratory scale, not pushed anymore by research and industry. Recent IAEA coordinated research project[158] excludes this route.
Supply chain type	Centralized supply chain. ^{89}Zr long half-life enables to only have a very limited number of production installation per world region with long range delivery. A single production centre in EU could cover needs for a single ^{89}Zr labelled RP.	
Irradiation means	Standard medical cyclotron technology, already widely available and mastered for ^{18}F prod.	Less available equipment. High-energy deuterium beam needed to achieve reasonable yields (20MeV), standard medical cyclotrons have (when available) lower deuterium fluxes (<10MeV)[159]
Yield & purity	The biggest challenge for ^{89}Zr was the need for efficient purification process for impurities (^{88}Zr inseparable and its daughter ^{88}Y). Automated processing equipment are now available[160]. Good yields achieved with commercially available solid targets (1-2 GBq of ^{89}Zr in 1-2 irradiation time). Lower yields observed with liquid targets.	
Target material	No availability issue with ^{nat}Y supply, absence of enrichment due to the presence of the single isotope ^{89}Y also making target recycling useless. Due to small quantities needed by RN production, supply of yttrium is not an issue (world supply is dominated by China[161], Estonia is 2nd largest producer ~5%).	
Economics and market trends	Production of ^{89}Zr should be cost effective through this route (dose expected to be cheaper than ^{18}F), allowing commercial production.	Limited information available, but higher production costs due to lower yields, and higher investment costs (to ensure 20MeV deuterium fluxes)

Table 37: Summary table for ^{89}Zr manufacturing routes

[158] IAEA CRP: Zr-89 Production and Zr-89 Radiopharmaceuticals (F22071) – Approved in Dec 2018
[159] Production of novel diagnostic radionuclides in small medical cyclotrons - EJNMMI Radiopharmacy and Chemistry volume 3, (2018)
[160] A new Zr-89 solution installed at Yokohama – IBA – April 2018
Supplying High-Quality Cancer-Imaging Isotopes – Feb 2019 – US DOE
[161] https://pubs.usgs.gov/periodicals/mcs2020/mcs2020-yttrium.pdf

Summary of ^{89}Zr supply chain

Production of ^{89}Zr is not expected to face important challenges to reach industrial worldwide large-scale production. The medical cyclotron, proton irradiation route shall become the reference route in the future. ^{89}Zr is already commercially available from different suppliers.

Aside from BV Cyclotron VU (Netherlands), there are no European players producing ^{89}Zr on a regular basis for commercial use[162], despite a large part of European PET cyclotron network could produce this radionuclide. Upon arrival on market of ^{89}Zr labelled RP, it is expected that dedicated production sites (one per RP in EU) could be established, allowing radiopharmaceuticals companies to control the full manufacturing and delivery of their RP[163].

The current ^{89}Zr supply chain is summarized in the following figure:

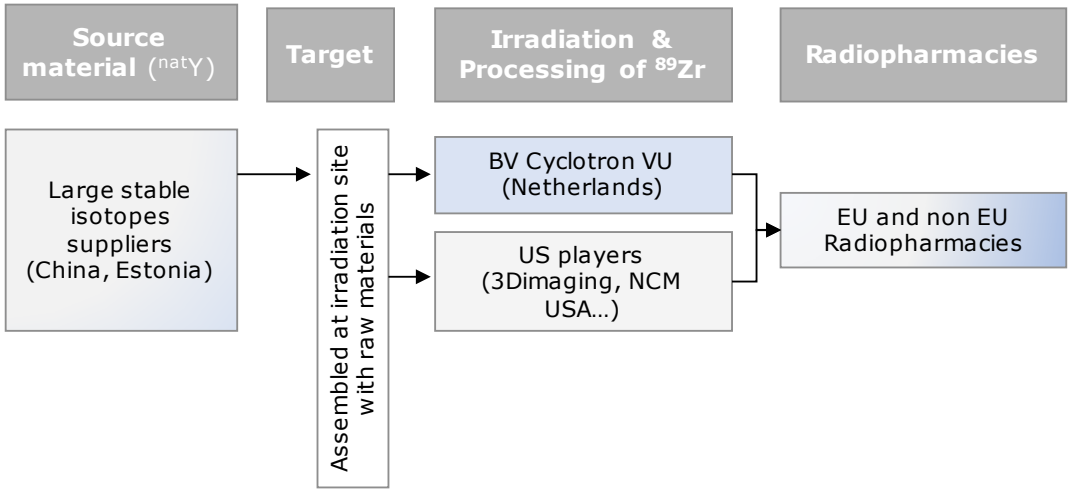


Figure 55: Summary of current ^{89}Zr supply chain (EU players in Blue)

[162] BV Cyclotron VU – ^{89}Zr webpage https://www.cyclotron.nl/2_3_1
[163] Medraysintell - Paul-Emmanuel Goethals & Richard Zimmermann

Annex 10. Radium-223 (^{223}Ra)

A.10.1. Properties, applications and competing radionuclides

^{223}Ra

Properties/applications: ^{223}Ra is an alpha emitter ($t_{1/2}$ = 11,4 days) with 4 α-emissions in the decay chain. $RaCl_2$ is currently used as a palliative treatment for prostate cancer. ^{223}Ra is the first alpha-emitting isotope that obtained its market authorization for the treatment of cancer.

Competing radionuclides: ^{223}Ra is expected to compete in the near future with first TRNT applications based on ^{177}Lu or ^{225}Ac that could bring wider benefit to patients currently treated with ^{223}Ra for metastatic castration resistant prostate cancer.

Demand: Aside from research applications, the current ^{223}Ra demand is essentially limited to ^{223}Ra-radium dichloride (Xofigo®). Demand is expected to remain stable over the next decade, considering that Bayer's Xofigo® turnover[164] reached its peak in 2018 (415 M$), and no new RP is under advanced development stage. Current supply capacity shall then remain sufficient to cover demand. It is estimated that EU demand shall remain in the range of 20-40 thousand doses per year.

A.10.2. Supply chain characterization

^{223}Ra is indirectly produced through ^{227}Ac decay ($t_{1/2}$ = 21,8 years, first decaying into ^{227}Th, ^{223}Fr). ^{227}Ac is produced in reactors through neutron irradiation of ^{226}Ra targets. Due to its long half-life, ^{223}Ra can be regularly extracted from ^{227}Ac stockpile, in a similar way ^{225}Ac is harvested from ^{229}Th.
Aside from this indirect route, production of ^{223}Ra could be performed in high energy accelerators[165,166] (from 90 and up to 800MeV), through proton irradiation of ^{nat}Th.

These two manufacturing routes are discussed hereafter:

	Indirect production from ^{227}Ac decay	**Direct production from proton irradiation**
Technology readiness level	**TRL 9**: neutron irradiation of ^{226}Ra targets for ^{227}Ac is performed in research reactors. Different players regularly extract ^{223}Ra from their ^{227}Ac stockpiles (SCK-CEN in Belgium, ORNL in US)	**TRL 3:** cross sections and yields have been measured, but no industrial development is underway to set an accelerator production route

[164] Bayer ceased to publicly communicate Xofigo turnover since 2019,
[165] ^{225}Ac and ^{223}Ra production via 800 MeV proton irradiation of natural thorium targets – LANL July 2012.
[166] Proton-induced cross sections relevant to production of 225Ac and 223Ra in natural thorium targets below 200 MeV – LANL -

	Indirect production from ^{227}Ac decay	Direct production from proton irradiation
Supply chain type	Centralized supply chain, with ^{223}Ra extracted from ^{227}Ac, directly at RP production facilities (e.g. Xofigo Bayer plants) or from production centre (SCK-CEN, ORNL).	Centralized supply chain
Yield & purity	High purity and high specific activity	Different isotopes of radium are also produced (^{225}Ra, ^{226}Ra and ^{228}Ra), further research needed to assess need for separation. Production of ^{227}Th through this route could also be used to directly produce high purity ^{223}Ra (extraction of ^{227}Th followed by extraction of ^{223}Ra)
Target material	^{226}Ra needed for neutron irradiation is recovered from legacy wastes through DOE isotope program in the US. Handling and use of ^{226}Ra targets raise several issues (RP, safety…). Otherwise ^{226}Ra is a by-product of uranium that is no more retrieved, stockpiles are currently the only source of supply	No limitations for ^{nat}Th
Economics and market trends	Production costs are not optimized due to low production volumes.	No economics projections at this stage, but the production route shall remain expensive considering the use of large accelerators and the complex purification process.

Table 38: Summary table for ^{223}Ra production routes

Aside from these two manufacturing routes, a variant of ^{226}Ra irradiation in research reactors has been investigated by University of Missouri Research Reactor Centre[167]. The indirect neutron flux generated in PET cyclotrons for ^{18}F production (^{18}O(p,n)^{18}F) could be used to irradiate ^{226}Ra targets. Such approach based on PET cyclotrons network remains more complex to implement than reactor irradiation (need to adapt standard cyclotrons) and offer limited yields.

A second production route[168] could lie in the potential future cyclotron production of ^{225}Ac, as one of the by-products is ^{227}Ac.

[167] Characterization and utilization of neutron radiation from a PETTrace cyclotron - John Brockman, Brad Jefferies, Chris Algiere, Peter Norgard, and John Gahl - University of Missouri Research Reactor Center
[168] A Radium-223 microgenerator from cyclotron-produced trace Actinium-227 - November 2016.

Summary of ^{223}Ra supply chain

Considering the steady demand for ^{223}Ra, the current supply chain should support the worldwide use of the only ^{223}Ra-labelled RP for the next decade (DOE signed a 10-year supply agreement with Bayer in 2017). Purified ^{227}Ac is either sent to RP producers (Bayer – Xofigo®), or ^{223}Ra is regularly harvested and sent to EU and non-EU radiopharmacies.

A summary of ^{223}Ra current supply chain is given in the following figure:

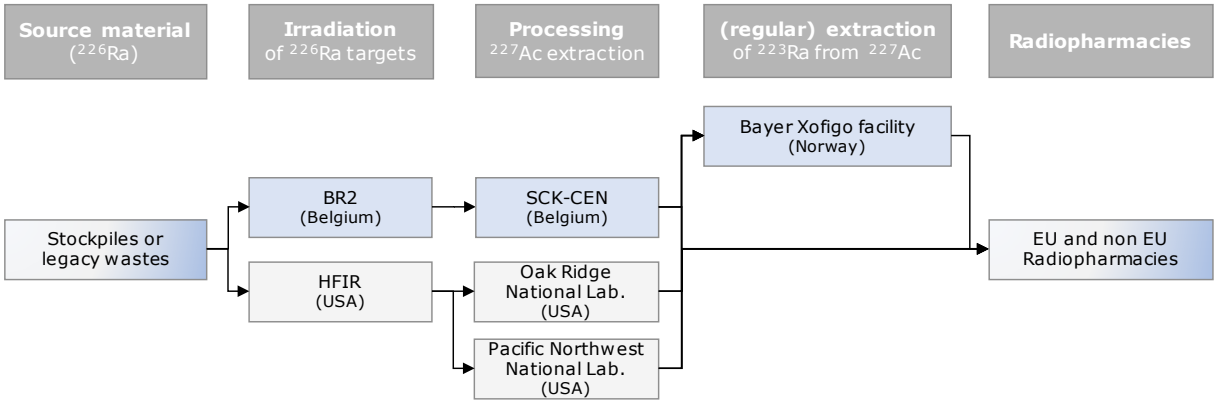


Figure 56: Summary of current ^{223}Ra supply chain (EU players in blue)

Annex 11. Actinium-225 (^{225}Ac)

A.11.1. Properties, applications and competing radionuclides

^{225}Ac

Properties: ^{225}Ac ($t_{1/2}$ = 10d) ultimately decays into ^{209}Bi after 6 different daughters. In total, a single ^{225}Ac decay yields net 4 alpha (in the range 6-8 MeV) and 3 beta disintegrations, along with 2 gamma emissions (218 & 440 keV) that can be used for imaging applications. ^{225}Ac decay profile, high particle energy produced, and long half-life make it a very promising candidate for TAT.

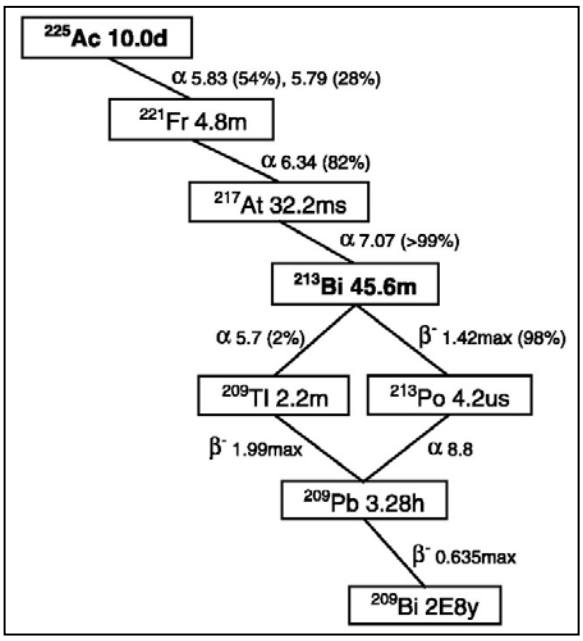


Figure 57: ^{225}Ac decay scheme (incl. half-lives, decay modes, branching fractions, and maximum energies). Source: Clinical Cancer Research - February 2006 Volume 12, Issue 3

Its complex decay scheme raises nevertheless concerns on the toxicity of the various daughters (current challenge for research is to find a way to efficiently trap francium, astatine, thallium, polonium or lead in the ^{225}Ac-labelled compound) and could generate additional constraints for clinical use.

Among its daughters, ^{213}Bi is also considered as itself as a potential candidate for TAT, as it presents a more limited (less daughters) decay profile, different supply (generator ^{225}Ac/^{213}Bi) and better product purity.

Applications: Different radiopharmaceuticals based on ^{225}Ac are currently under development, with a wide range of applications (NET, prostate cancer, leukaemia…). ^{225}Ac-PSMA617 for prostate cancer therapy is currently the most advanced one, with administration performed on hundreds of patients[169]. RP is currently at pre-clinical stage and is part of Endocyte (AAA/Novartis) pipeline[170].

Competing radionuclides: Other α-emitting radionuclides candidates for TAT exist (^{223}Ra, ^{211}At…).

Demand: With the development of new supply capacity and the recent breakthrough of ^{225}Ac-PSMA-617, it is expected that ^{225}Ac might play a significant role within the next decade. Current supply capacity is not sufficient to cover increasing needs. Current demand is limited to clinical trials, a maximum of tens

[169] Supply and Clinical Application of Actinium-225 and Bismuth-213 - Alfred Morgenstern, PhD, Christos Apostolidis, PhD, and Frank Bruchertseifer, PhD - 2020
[170] AAA website www.adacap.com on 17/04/2020

to hundreds of doses per year. Injected doses to patient range from 20 to 50 MBq (0.5 to 1.5 mCi). Overall limited EU demand is in the range of a few hundred mCi.

Future demand is uncertain at this stage, RP labelled with ^{225}Ac are only in early development phase. Based on figures from the American Cancer Society, TerraPower estimated that roughly 550 000 new patients in the US could benefit from ^{225}Ac treatment. Considering same ratio, an order of magnitude of 700 000 patients in the EU could benefit from ^{225}Ac treatments (prostate cancer, melanoma, leukaemia…). Considering competing treatments, demand would be lower than that, 10 to 100k patients/doses per year.

A.11.2. Supply chain characterization

^{225}Ac can be produced through many manufacturing routes, in addition to the historical one through natural decay of thorium-229. Different approaches are currently under development with the objective to cope with expected increasing needs of ^{225}Ac. Irradiation of radium-226 targets with proton/deuterium and spallation of thorium-232 are under evaluation.

The different manufacturing routes are the following:

- successive decays route: ^{233}U → ^{229}Th, followed by ^{229}Th → ^{225}Ac (current main source of production);
- ^{232}Th spallation through the reaction ^{232}Th(p,x)^{225}Ac with very-high energy protons (up to 480MeV protons);
- ^{226}Ra irradiation with different particles:
  - ^{226}Ra(d,3n)^{225}Ac in linear accelerators (<20MeV);
  - ^{226}Ra(p,2n)^{225}Ac in medium-sized cyclotrons (<20MeV);
  - ^{226}Ra(γ,n)^{225}Ra in high-intensity electron beams, followed by decay ^{225}Ra → ^{225}Ac;
  - ^{226}Ra(n,2n)^{225}Ra in reactor, followed by decay ^{225}Ra → ^{225}Ac.

These manufacturing routes are at different development stage: R&D, early development stage, industrial demonstration stage…

Among these different approaches, radiochemical extraction from ^{227}Th will need alternatives manufacturing routes to cope with increasing demand. ^{232}Th spallation production capacity are under development and should add large supply capacity, with currently a strong limitation due to the presence of long-life ^{227}Ac. Proton irradiation of ^{226}Ra appears as a promising alternative, with limited investment needed (15 MeV cyclotrons centre), but the use of ^{226}Ra targets makes the whole process complex.

The table on next page summarizes the characteristics of the different production routes.

	Radiochemical extraction of ^{225}Ac from ^{229}Th	**Spallation of Thorium-232**	**^{226}Ra irradiation with proton (or deuterium)**	**^{226}Ra irradiation with photons, followed by ^{225}Ra decay**
Technology maturity	**TRL9:** Main production route for decades, research oriented and generator-based	**TRL9:** Regular production available since 2018 at US DOE Tri-Lab	**TRL4:** Advanced R&D stage, with research focused on ^{226}Ra targets issues	**TRL4:** Early R&D stage
Installed capacity	Supply capacity limited to ^{229}Th reserves, future large increase (TerraPower) but not enough for ^{225}Ac RP wide use	Limited number of production sites (CERN and ARRONAX in EU), need for high energy protons (>100 MeV)	SMC/MEC cyclotrons, need for specific infrastructures and probably exclusive production of ^{225}Ac. Limited investment costs	Limited number of high-energy electron beams installations
Yield	Production limited to ~1.9Ci/yr of ^{225}Ac, production to be multiplied by up to 100 times	High yields expected, hundreds of Ci/year per installation	High yields achieved *(more than 0,1 Ci of ^{225}Ac per batch)*, higher yields with deuterium route	Theoretical yields obtained with standard LINAC limited, yields with high e- beams uncertain
Purity	No contamination by other Ac isotopes	Production of long-lived ^{227}Ac limiting RP drug use, interest for ^{225}Ac/^{213}Bi generators	Only short half-life Ac isotopes, managed through decay (^{226}Ac and ^{224}Ac)	No contamination by other Ac isotopes
Target & material	Limited reserves of ^{229}Th, aside from stockpiles, new production uncertain	^{232}Th non-expensive and widely available, no target issue	^{226}Ra targets are main limitation, with complex target management irradiation and processing (radiotoxicity, reactivity, decay into Rn), need for ^{226}Ra recycling for improved yields. ^{226}Ra could be supplied through uranium mining (currently a waste product).	
Processing	Monthly elution, no continuous production	No specific issue	Complex processing to trap radon and to manage radiotoxicity, through dedicated hot cells and automated process	
Cost	High production cost due to limited production capacity	Lower cost than thorium extraction if large production is achieved	Unknown at this stage	

Table 39: Summary table for ^{225}Ac manufacturing routes[171]

[171] *The manufacturing route based on neutron irradiation of ^{226}Ra is not included in the table, considering that no industrial development is expected due to large impediments expected*

Radiochemical extraction of ^{225}Ac from ^{229}Th (current production route)

^{229}Th ($t_{1/2}$ = 7340 years) decays into ^{225}Ra which in turn decays into ^{225}Ac. The method of production consists in an anion and cation chromatography in multiple steps (first to separate decay products from ^{229}Th then ^{225}Ac from ^{225}Ra). This process offers the advantage of pure ^{225}Ac (no others Ac isotopes).

The present worldwide supply capacity is limited by stocks of ^{229}Th in the four main sites offering medical grade ^{225}Ac: Directorate for Nuclear Safety and Security of the JRC of the European Commission in Karlsruhe (Germany), Oak Ridge National Laboratory (ORNL - USA) and at the Institute of Physics and Power Engineering (IPPE - Obninsk, Russia), and more recently, Canadian Nuclear Laboratories (CNL - Canada). In total the supply capacity of these four players is ~1.9 Ci/year[172] of ^{225}Ac (to be compared with average dose injected, less than 1 mCi), with ORNL responsible for more than 50% of world supply.

In order to increase the supply capacity through the extraction route, it is necessary to increase existing thorium stockpile, either by securing unused military materials or directly through the production of new ^{229}Th.

TerraPower planned to use former US DOE stocks of ^{233}U, to access to ~45g of ^{229}Th, after separation by ion exchange. Thus, it is expected that they will be able to drastically increase the supply of ^{225}Ac through this route (up to 100 times[173] more than current supply capacity). Project is progressing with recent signing of partnership between Isotek Systems (in charge of ^{233}U retrieval), TerraPower and the US Department of Energy (DOE). Production of ^{225}Ac was expected to start in 2020.

US DOE is currently assessing the production of ^{229}Th in HFIR reactor[174] (High Flux Isotope Reactor). R&D is currently underway (target designs, yields…). It is expected that hundreds of mCi of ^{229}Th could be produced on a yearly basis (equivalent to a few tenths of mCi of ^{225}Ac). Uncertainties remain for such manufacturing route, with limited yields, high production costs and difficulties linked with ^{226}Ra targets.

The increase of ^{229}Th stocks in the USA will not solve the ^{225}Ac supply issue and launching a new production supply chain does not appear a sustainable route. Thus, EU shall focus on alternative technologies while continuing production at JRC Karlsruhe Centre to cope with part of research needs in the next years.

[172] Report on joint IAEA-JRC workshop "supply of Actinium-225" IAEA, Vienna, October 2018 (Supply capacity: ORNL ~1Ci/year, EC JRC ~0,35Ci/year, IPPE ~0.42Ci/year, ORNL ~0,1Ci/year)
[173] Partnership to produce medical isotope from legacy waste - 25 November 2019 – WNN
[174] United States Department of Energy Production of Actinium-225 from Thorium-229 - M. Garland - DOE Isotope Program - IAEA-JRC workshop "Supply of Actinium-225" - 2018

Spallation of thorium-232

^{225}Ac can be produced through spallation of ^{232}Th with the reaction ^{232}Th(p,x)^{225}Ac. A few accelerators in the world can deal with high energy protons (>100 MeV) and could be used in the future for production of ^{225}Ac. Supply material is not an issue, ^{232}Th being inexpensive and available in large quantities and does not raise specific irradiation issues. The spallation approach also generates multiple other products, including ^{227}Ac that cannot be easily separated from ^{225}Ac. This might represent a limitation for future ^{225}Ac based radiopharmaceuticals (licensing, waste management…).

In the US the routine production through spallation is now available through the joint initiative of US DOE Tri-Lab (BNL, ORNL, LANL) and could be replicated in Europe through a European network of accelerators (CERN/Arronax…) in the frame of the PRISMAP initiative.

^{226}Ra irradiation with protons

Production of ^{225}Ac can be performed in medium-energy cyclotrons at 15 MeV through reaction ^{226}Ra(p,2n)^{225}Ac. This approach would allow daily production of ^{225}Ac with large yields allowing centralized production (hundreds of doses for a single cyclotron)[175]. As opposed to spallation route, the impurities are mainly short half-life ones (^{226}Ac with $t_{1/2}$=29h and ^{224}Ac with $t_{1/2}$=2,9h) that can be managed through sufficient cooling and optimized proton energy. Yet, the main challenge is the use of ^{226}Ra targets.

^{226}Ra high radiotoxicity, reactivity (with air and water) and decay profile (^{226}Ra decay into ^{222}Rn) complexifies the manufacturing, irradiation and processing of targets. Necessary additional equipment, infrastructures (dedicated hot cells, radon gas monitoring, dedicated storage rooms…) and production specificities will offset the better production yields, increase production costs and limit supply capacity to a limited number of sites able to make the corresponding investments for adapting to these constraining manufacturing standards. The development of ^{225}Ac cyclotrons-based production route will depend of the feasibility of ^{226}Ra target use. This currently raises a series of safety, handling and waste challenges that could be considered for the time being as a major impediment for the industrial development of this production route.

^{226}Ra irradiation with deuterium

This manufacturing route can be considered as an improvement to the proton one, that could ultimately lead to better yields, with deuteron beams energy of 18,5 MeV.

This improved yield is balanced by two additional limitations:

[175] Supply and Clinical Application of Actinium-225 and Bismuth-213 - Alfred Morgenstern

- the limited installed base of cyclotron able to perform deuteron irradiation at such energy
- and the higher co-production of ^{226}Ac that will lead to longer cooling time.

^{226}Ra irradiation with photons

^{225}Ra could be produced through photonuclear reaction ^{226}Ra(γ,n)^{225}Ra, with high-energy electron beams. This route is currently in early stage (laboratory scale demonstration) and economic efficiency of industrial scale production would need to be demonstrated.

^{226}Ra irradiation with neutrons

^{225}Ra could also be produced in reactors through the reaction ^{226}Ra(n,2n)^{225}Ra but presents some major limitations. Neutrons of more than 6.4 MeV are needed for the reaction, drastically limiting the number of reactors eligible, while lower energy neutrons produce ^{227}Ac in large quantities that cannot be separated from ^{225}Ac and may prevent clinical use.

The challenges faced by ^{225}Ac supply chains are multiple, at different supply chain levels (from target material to irradiation capacity):

- the need for higher ^{229}Th supply capacity to increase the production of current main production route;
- the challenges linked to the use of ^{226}Ra target for cyclotron production of ^{225}Ac;
- the need for a joint initiative of high-energy protons installations for the supply through spallation of ^{232}Th.

A summary of the current ^{225}Ac supply chain is given in the following figure:

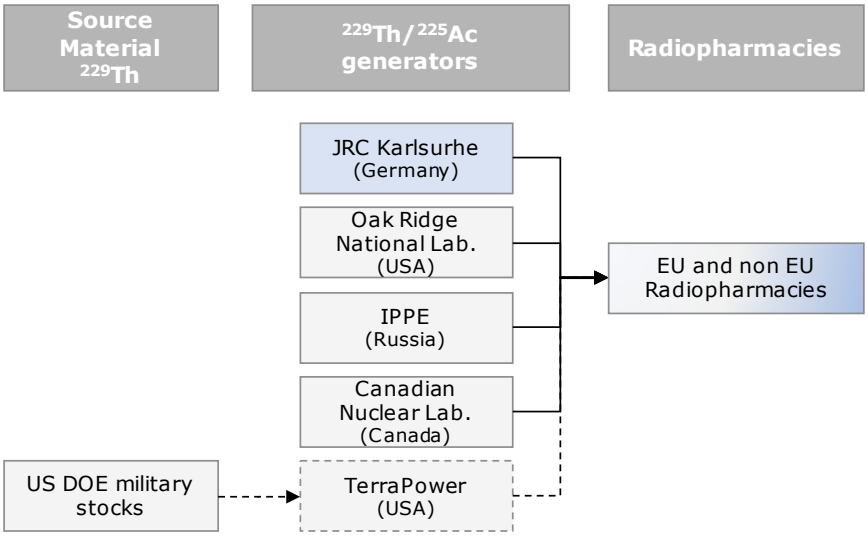


Figure 58: Current supply chain for radiochemical extraction of ^{225}Ac from ^{229}Th

Production through spallation route is currently only performed through the Tri-lab Actinium-225 Research Collaboration (LANL, Brookhaven BNL, and ORNL).

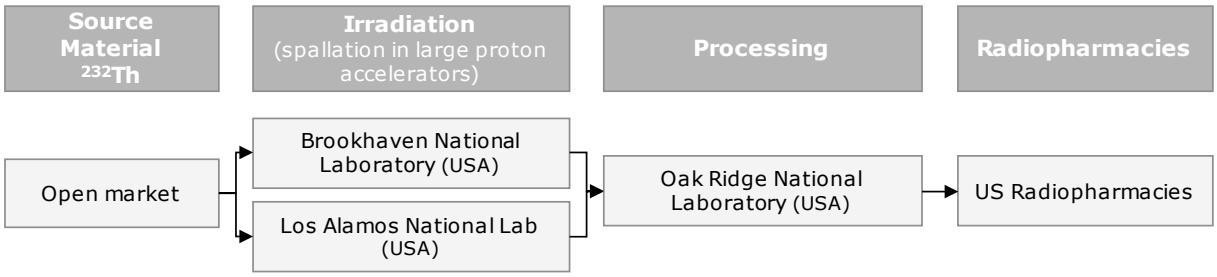


Figure 59: Current ^{225}Ac spallation supply chain

Annex 12. Lead-212 (^{212}Pb)

A.12.1. Properties, applications and competing radionuclides

^{212}Pb

Properties: ^{212}Pb is a β-emitter ($t_{1/2}$=10,6 hours) and has a single alpha emission in its decay chain, limiting unwanted radiation emitted by daughter product. Its daughter radionuclides ^{212}Bi and ^{212}Po undergo α-decay. ^{212}Pb is thus considered as an in vivo α-particle generator.

Applications: Different ^{212}Pb labelled RP are under development: for NET (Radiomedix – Clinical trial phase I), Leukaemia (Nordic Nanovector), and different solid tumours (Roche, Orano Med, Cellectar Bioscience…). ^{203}Pb is foreseen as a potential SPECT imaging agent ($t_{1/2}$=51.9h) to be used in pair.

Competing radionuclides: ^{212}Pb is one of the many Targeted Alpha Therapy radionuclides under study.

Demand: Demand is currently limited to research and early clinical studies, and should remain limited during the next years, as the different RP labelled with ^{212}Pb are still in early development phase.

A.12.2. Supply chain characterization

There is only a single manufacturing route under development for ^{212}Pb production, using a ^{224}Ra/^{212}Pb generator [176]. ^{228}Th ($t_{1/2}$=1.9yr) is retrieved from ^{232}U (stockpiles) or natural thorium salts (Orano Med) and is used as a "cow" to produce ^{224}Ra ($t_{1/2}$=3.7days), which is loaded on a generator from which ^{212}Pb can be ultimately eluted.

This manufacturing route is discussed in the following table:

	Indirect production in generators Decay of ^{224}Ra in ^{212}Pb
Technology readiness level	**TRL9:** since 2015, generators for research purpose are available[177] through US National Isotope Development Center (NIDC). Process is limited to a purification step (extraction of ^{228}Th from ^{232}U).
Supply chain type	Fully centralized supply chains, with continuous production of ^{224}Ra/^{212}Pb generators coming from ^{228}Th stockpile. Generators can be used during a few days. For research purpose only, OranoMed also directly distributes ^{212}Pb.

[176] These generators also allow the direct elution of ^{212}Bi, a ^{212}Pb daughter product
[177] http://viewpointmt.com/doe-announces-availability-of-lead-212-generators/

	Indirect production in generators Decay of ^{224}Ra in ^{212}Pb
Yield & purity	Currently, the main differentiating factor among players is the quality (purity, yields) of the ^{228}Th extraction process. If ^{212}Pb reach industrial scale production, then the quality of the ^{228}Th extracted can provide a large advantage to one of the few players.
Target material	Generators target material (^{224}Ra) is either retrieved from DOE stockpiles of ^{228}Th (ORNL) or from natural thorium ^{232}Th salts (Orano Med or RadTran). Supply is then "limited" to a purification step, no irradiation needed.
Economics and market trends	Current supply chain is in line with research needs.

Table 40: Summary table for ^{212}Pb manufacturing route

Summary of ^{212}Pb supply chain

Different players are currently mobilized to supply ^{224}Ra/^{212}Pb generator for research purpose.

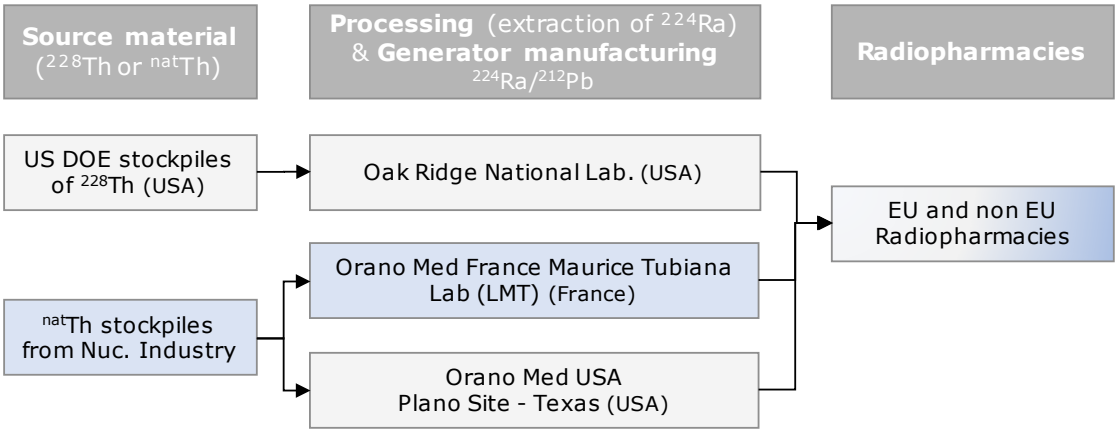


Figure 60: Current ^{212}Pb supply chain (EU players in Blue)

RadTran appears as a potential third player [178] in the ^{212}Pb production, a proprietary-based ^{224}Ra extraction process and purification being under development.

[178] https://radtran.com/

Annex 13. Holmium-166 (^{166}Ho)

A.13.1. Properties, applications and competing radionuclides

^{166}Ho

Properties: ^{166}Ho is both a, β and γ emitter that directly decays into stable ^{166}Er, with a half-life ($t_{1/2}$=26,6hrs) making it suitable for targeted therapy modalities with SPECT imaging in parallel. Holmium is paramagnetic and therefore also visible by MRI.

Applications: Over the years, multiple applications based on ^{166}Ho properties have been developed: targeted therapies, radiosynoviorthesis, brachytherapy (intra-tumoral cancer treatment). Selective internal radiation therapy (SIRT, also called radioembolization) for cancer liver, showed increasing interest in the last years, with growing use in Europe since its market approval in 2015.

Competing radionuclides: Among β-emitters, ^{166}Ho is in competition with ^{90}Y, having similar range of half-life and β energy. Aside from specific applications such as SIRT, ^{166}Ho will compete with ^{177}Lu for TRNT use, with a currently net advantage in favour of ^{177}Lu.

Demand: Considering the increasing interest for ^{166}Ho in the last decade[179], and the different applications already in use (microspheres for liver treatment, TRNT for bone metastases and hepatocellular carcinoma), ^{166}Ho use should continue to grow in the future.

A.13.2. Supply chain characterization

^{166}Ho can be produced through two manufacturing routes in reactors:

- the direct route, through neutron irradiation of ^{165}Ho (equivalent to ^{nat}Ho) in a reactor with the reaction ^{165}Ho(n,γ)^{166}Ho;
- the indirect route, through neutron activations of ^{164}Dy then ^{165}Dy, followed by decay into ^{166}Ho, through reactions ^{164}Dy(n,γ)^{165}Dy(n,γ)^{166}Dy ^{166}Dy(β decay)^{166}Ho.

	Direct route ^{165}Ho(n,γ)^{166}Ho	**Indirect route** ^{164}Dy(n,γ)^{165}Dy(n,γ)^{166}Dy->^{166}Ho
Technology readiness level	**TRL9:** manufacturing route currently used at GMP scale	**TRL6:** laboratory scale manufacturing demonstrated, applications needing no-carrier-added and high specific activity could foster the commercial development of this route

[179] The various therapeutic applications of the medical isotope holmium-166: a narrative review - EJNMMI Radiopharmacy and Chemistry volume 4 (2019)

	Direct route $^{165}Ho(n,\gamma)^{166}Ho$	**Indirect route** $^{164}Dy(n,\gamma)^{165}Dy(n,\gamma)^{166}Dy->^{166}Ho$
Target material	^{165}Ho has an isotopic abundance of 100%, natural holmium can be directly used without enrichment. No supply issue.	^{nat}Dy is composed of 7 isotopes, with ^{164}Dy isotope accounting for 28.2%. Irradiation of ^{nat}Dy produces various Dy and Ho isotopes, but extraction chromatography allows to fully isolate the ^{166}Dy. Dy supply faces tensions and China is the sole supplier
Yield and purity	Carrier-added product (presence of ^{166m}Ho), with low specific activity.	Non carrier-added ^{166}Ho (RN purity over 99.9%), after ^{166}Dy extraction and elution[180] of ^{166}Ho. High specific activity ^{166}Ho
Supply chain type	Both manufacturing routes are centralized and necessitate limited neutron flux (10^{12}-$10^{13}ncm^{-2}s^{-1}$), allowing to produce it in various reactors in the world (Reactor Institute Delft, HFR, BR-2, McMaster Nuclear Reactor…).	

Table 41: Summary table for ^{166}Ho manufacturing routes

Summary of ^{166}Ho supply chain

^{166}Ho current supply chain is based on the direct route, through the irradiation of non-radioactive ^{165}Ho microspheres or standard ^{165}Ho targets. ^{166}Ho microspheres' use is now well established in Europe, production in the US is secured and will support future clinical trials[181].

The indirect route could be preferred for applications that would necessitate high specific activity and NCA ^{166}Ho. The development of both routes will be closely linked to the development of ^{166}Ho labelled RP for TRNT, and the competition with others therapeutic radionuclides.

Currently a single RP based on ^{166}Ho is available, but only for the South Korean market. Its supply chain is thus not included hereafter.

No major challenges are associated to production of ^{166}Ho (both routes), aside from securing a GMP grade supply in Europe, and potentially implementing an industrial supply through indirect route (development of industrial process).

[180] Production of no-carrier-added Ho-166 for targeted therapy purposes – NSTRI/IAEA 2016
[181] Development of a North American supply of holmium-166 microspheres for Selective Internal Radiation Therapy (SIRT) of liver malignancies - Nucl Med May 1, 2019

The current supply chain structure is summarized in the following figure.

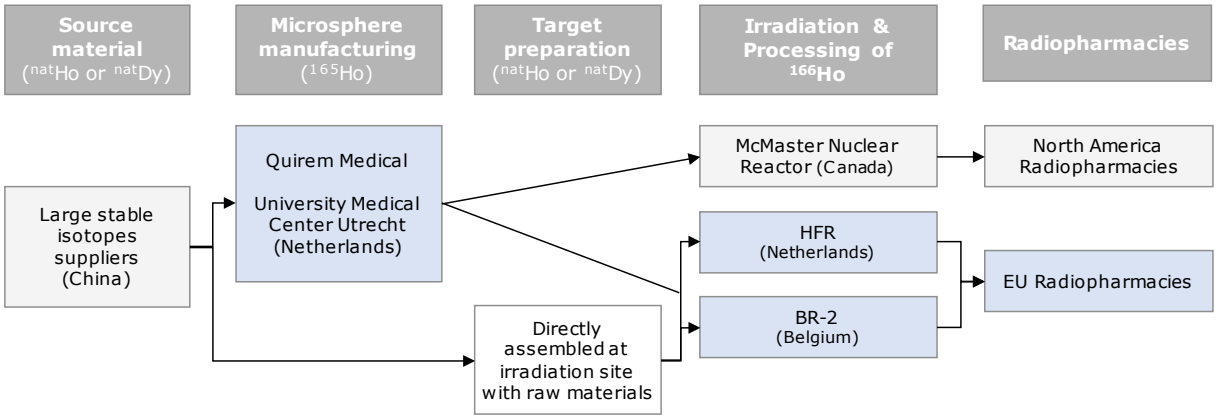


Figure 61: Current ^{166}Ho supply chain (EU players in Blue)

Annex 14. Rhenium-188 (^{188}Re)

A.14.1. Properties, applications and competing radionuclides

^{188}Re

Properties: ^{188}Re is both a high energy β emitter ($E_β$ =2,1MeV) and γ emitter, decaying into stable ^{188}Os with a short half-life ($t_{1/2}$=17 hrs). Rhenium has chemical similarities with technetium, paving the way for theranostic pairing. Adaptation of ^{99m}Tc-labelled RP to ^{188}Re [182] could be foreseen, despite complex chemistry.

Applications: ^{188}Re is already used for bone pain palliation, along with liver therapy[183]. Future uses could include bone or brain cancer therapy.

Competing radionuclides: ^{188}Re has been extensively studied over the last decades, yet with lower interest (in terms of volume of publications) than ^{177}Lu or ^{90}Y. The limited availability of pharmaceutical grade ^{188}Re and its complex chemistry could explain such difference. However, the future pharmaceutical availability of ^{188}W/^{188}Re generators could accelerate ^{188}Re development.

Demand: ^{188}Re demand is currently limited for NM applications, only used for bone pain palliation in EU. Its future demand will be linked to market approval of new RP labelled with ^{188}Re. In the meantime, the availability of a generator will increase demand, fostering clinical developments.

A.14.2. Supply chain characterization

^{188}Re can be produced through two manufacturing routes in reactors:

- the direct route, through neutron irradiation of enriched targets of ^{187}Re in a reactor through the reaction ^{187}Re(n,γ)^{188}Re;
- the indirect route, through ^{188}W/^{188}Re generators, through neutron activations of ^{186}W then ^{187}W, followed by decay into ^{188}Re, through reactions ^{186}W(n,γ)^{187}W(n,γ)^{188}W followed by ^{188}W(β decay) ^{188}Re.

Both direct and indirect routes are discussed in the table below:

	Direct route ^{187}Re(n,γ)^{188}Re	**Indirect route through generators** ^{188}W/^{188}Re
Technology readiness level	**TRL7**: manufacturing route not operational on a commercial basis	**TRL9:** GMP grade generators are already on the market, but not for pharmaceutical use.

[182] Rhenium-188 labelled Radiopharmaceuticals: Current Clinical Applications in Oncology and Promising Perspectives - Front. Med., 14 June 2019 | https://doi.org/10.3389/fmed.2019.00132
[183] HCC – hepatocellular carcinoma

	Direct route $^{187}Re(n,\gamma)^{188}Re$	**Indirect route through generators** $^{188}W/^{188}Re$
Target material	Only two natural isotopes of rhenium (^{187}Re 62,6% and ^{185}Re 37,4%), enrichment needed.	Enriched ^{186}W (calutron or gas centrifugation) needed for targets (natural of abundance 28%). Significant stocks available in US side (ORNL) or in Russia.
Targets	No specificities for ^{187}Re targets	Need for high density pressed targets and target recycling instead of standard low density eNCApsulated ^{186}W targets
Irradiation means	Production achievable with low flux reactors.	Long (few weeks) double neutron activation in high thermal neutron flux needed for effective production (10^{14} flux), making production limited to relatively high-power reactors.
Yield and purity	Low specific activity and ca ^{188}Re	High specific activity and NCA ^{188}Re
Supply chain type	Centralized supply chain, not compatible with onsite labelling. Need for centralized production and labelling site.	Centralized production, long generator lifetime (a few months). Rapid ^{188}Re daughter generator growth (~60% in 24h), allowing daily use of generator.
Economics	Less costly to produce, but need to deliver large amounts of doses to be competitive	Costly generator, without lack of optimization use if ^{188}Re is not widely needed. Possibility to have centralized radiopharmacies to reduce dose cost.

Table 42: Summary table for ^{188}Re manufacturing routes

Summary of ^{188}Re supply chain

$^{188}W/^{188}Re$ generators appears as the most convenient and cost-effective route[184], allowing to daily supply NCA ^{188}Re. The reactor direct route should remain limited to ^{188}Re supply for non-high specific activity applications, and where generator use, or supply is not possible. In EU, generator-based ^{188}Re should remain the preferred manufacturing route.

The main challenges linked with ^{188}Re are the need for a pharmaceutical grade generator, securing enriched ^{186}W supply that is partly produced in non-EU calutrons. A high flux reactor will also be needed, close to a generator production installation (such as IRE-Elit one, already producing GMP grade $^{188}W/^{188}Re$ generators).

[184] Production of Long-Lived Parent Radionuclides for Generators: 68Ge, 82Sr, 90Sr and 188W – IAEA Vienna 2010

The current supply chain structure of ^{188}Re through generators is summarized in the following figure. Since ORNL ceased production, IRE Elit "Rheni Eo" and ITG generators are the only GMP grade generators available.

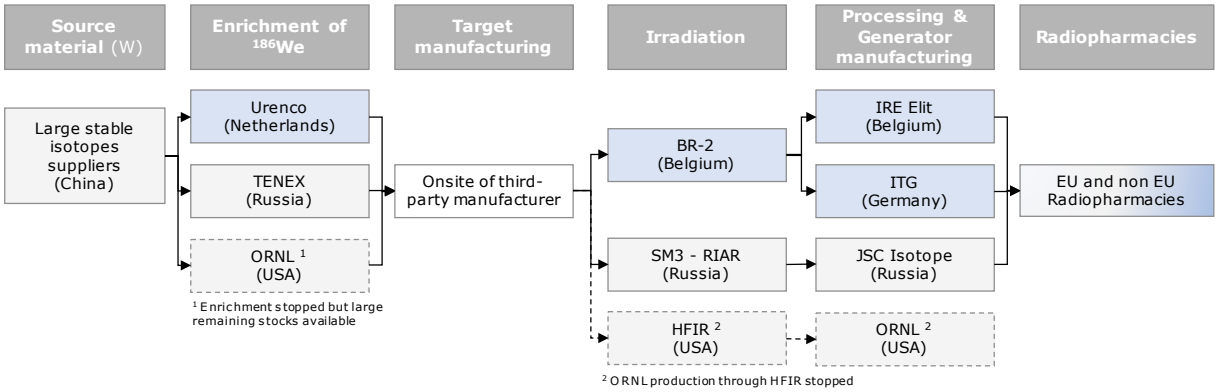


Figure 62: Current ^{188}Re supply chain through non-GMP generators (EU players in Blue)

Annex 15. Astatine-211 (^{211}At)

A.15.1. Properties, applications and competing radionuclides

^{211}At

Properties: Astatine-211 (^{211}At) has properties that make it among the most-promising radionuclide candidates for targeted alpha therapy (TAT)[185]. It has an excellent decay profile, with one alpha particle generated per decay (through two branches) along with daughter product generating x-rays (70-90keV) allowing for imaging and simple detection. ^{211}At has a 7,2 hours half-life, suitable for various treatment options and for centralized production and shipping to hospitals. No toxic decay products (^{207}Bi & stable ^{207}Pb) are produced and, as a halogen, it has chemical characteristics close to iodine.
Despite that, important grey areas still exist on ^{211}At chemical behaviour, that will necessitate additional developments in the future.

Applications: a few phase I/II clinical trials have been/are performed with ^{211}At for various conditions: leukaemia, post-surgery boost treatment for brain or ovarian cancers…

Competing radionuclides: Other α-emitting radionuclides candidates for TAT exist (^{225}Ac, ^{223}Ra, ^{213}Bi…).

Demand: Chances for ^{211}At-labelled RPs to reach the market in the next decade seem limited. Its radiochemical properties would nevertheless necessitate a "limited" supply chain in EU, in order to satisfy ^{211}At demand for clinical research needs. Currently, the scarce availability of ^{211}At is a strong factor limiting the research on this radionuclide.

A.15.2. Supply chain characterization

^{211}At can be manufactured through two main routes:

- directly with medium energy cyclotrons (at 28 MeV) through the reaction ^{209}Bi(α,2n)^{211}At;
- indirectly with a generator ^{211}Rn/^{211}At, with ^{211}Rn being potentially manufactured through reaction ^{209}Bi(^{7}Li,5n)^{211}Rn or ^{227}Th(p,2α)^{211}Rn.

Among the two manufacturing routes, the direct production (^{209}Bi(α,2n)^{211}At) should remain the main production route in the near future, considering its relative simplicity and more widely available production means. However, in case of rapid growth, these production means may appear insufficient.

[185] Yana Dekempeneer, Marleen Keyaerts, Ahmet Krasniqi, Janik Puttemans,Serge Muyldermans, Tony Lahoutte, Matthias D'huyvetter & Nick Devoogdt (2016) Targeted alpha therapy using short-lived alpha-particles and the promise of nanobodies as targeting vehicle, Expert Opinion on Biological Therapy

	Cyclotron production $^{209}Bi(\alpha,2n)^{211}At$	**Generator production** ^{211}Rn -> ^{211}At
Technology readiness level	**TRL6:** Limited number of medium-energy cyclotrons in the world, and only a few currently available for ^{211}At production. No commercial system available for target processing, need for automated systems.	**TRL 3:** Very limited number of high-energy accelerators able to perform these irradiation types
Irradiation means	Limited installed base for cyclotrons with high energy α-beams	^{211}Rn production through ^{209}Bi necessitates very specific particle beam (^{7}Li) scarcely available
Supply chain type	Local (few hours of transportation) production	(Limited) centralized production ($t_{1/2}$ of 14,6 hours)
Purity	No contamination by ^{210}At for beam energy lower than 29.5 MeV.	*Unknown at this stage*
Target	Non-expensive and cost-effective targets (natural bismuth), with simple manufacturing process.	*Unknown at this stage*
Target material	Abundant, allowing sustainable supply *(other TAT RN relying generally on stockpile materials)*	No issue for ^{209}Bi, but ^{227}Th supply is more complex (α-emitter with 19 days half-life)
Economics	Affordable production route, production cost price of ~30$$_{2012}$/mCi	*Unknown at this stage*

Table 43: Summary table for ^{211}At manufacturing routes

Direct production through cyclotrons

Currently, the standard method used to produce ^{211}At is through irradiation of natural bismuth targets in cyclotrons by α-particles at 28-29,5 MeV (peak being at 31MeV, but such energy results in the production of ^{210}At, that decay at 99% into ^{210}Po with high toxicity to bone marrow). Cooling target is another issue, as bismuth has a low melting point (272°c). Yields of 16,3 to 41 mCi/µA.h have been observed[186] (150-175 mCi for 4 hours irradiation).

Regarding target material supply, natural bismuth is only constituted of ^{209}Bi, and no enrichment is needed for target material. Bismuth is a by-product of other metals processing (lead in particular). Roughly 60% of the production is coming from China. There is no major issue for ^{nat}Bi supply, due to limited quantities needed for therapeutic use, as compared to large needs for other industries.

Indirect production through $^{211}Rn/^{211}At$ generator

^{211}Rn having a 14,6 hours half-life, it allows more flexibility for manufacturing and distribution than direct production of ^{211}At. However, this route requires heavy ion irradiation capacity (through ^{209}Bi route) or high-energy protons for spallation

[186] Astatine-211: Production and Availability - Michael R. Zalutsky and Marek Pruszynski – Nov. 2012

(through ^{227}Th route). Currently only a few installations worldwide are able to provide such irradiation capacity. Moreover, the produced Rn requires specific management to ensure containment of Rn gas produced. The research on generator route is currently focused on the irradiation stage, by large research institutes with public funds (Argonne National Laboratory[187] – USA or Triumf[188] – Canada).

The main challenge faced by ^{211}At supply chain is concerning the irradiation step: the need for a dedicated α 30MeV cyclotron network allowing for an equal access to ^{211}At.

Summary of ^{211}At supply chains

A summary of the ^{211}At current supply chain is given in the following figure:

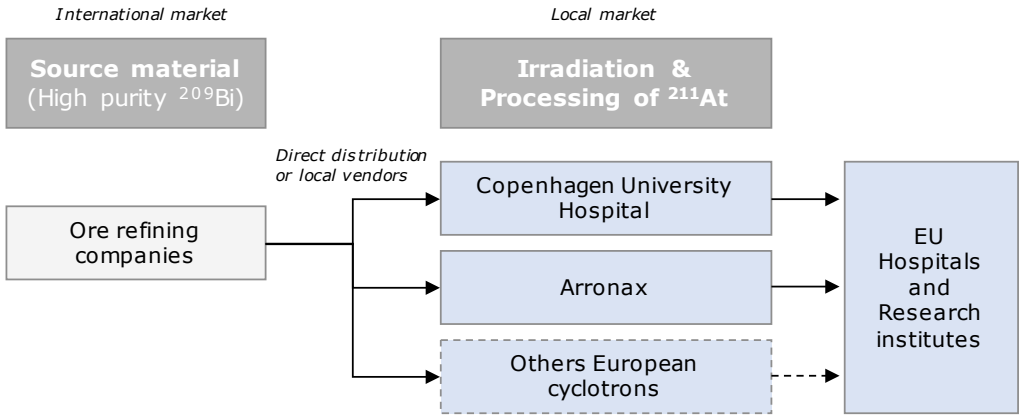


Figure 63: ^{211}At supply chain through direct production in cyclotrons (EU players in blue, dotted line for potential future player)

[187] Development of 211At Production via Continuous Extraction of 211Rn - Nolen, Jerry et al. Journal of Medical Imaging and Radiation Sciences, Volume 50 – March 2019
[188] Conference on the Application of Accelerators in Research and Industry, CAARI 2016, Medical isotope production at TRIUMF – from imaging to treatment

Annex 16. Copper-64 (^{64}Cu)

A.16.1. Properties, applications and competing radionuclides

^{64}Cu

Properties: ^{64}Cu ($t_{1/2}$=12,7h) has a quite unique profile, as it decays through three different processes: positron emission, beta decays and electron capture, making ^{64}Cu appropriate for both PET imaging and targeted-therapy applications.

Applications: there is currently no clinical RP based on ^{64}Cu, research is investigating potential applications for targeting neuroendocrine, prostate and hypoxic tumours. Developments are still in early clinical trials stage, at the exception of ^{64}Cu-Dotatate for PET imaging, with first drug application filed to US FDA for NET imaging[189].

Competing radionuclides: ^{64}Cu currently foreseen applications are directly competing with imaging/therapeutic RP in development or already available, decreasing chances to raise high interest for ^{64}Cu development. A breakthrough treatment for other pathologies could nevertheless boost ^{64}Cu development.

Demand: ^{64}Cu demand is currently limited to R&D needs, this is expected to change with market approval in the USA of first RP based on ^{64}Cu (September 2020). There is currently no industrial demand in EU for ^{64}Cu, in the absence of EU market approval of ^{64}Cu-labelled RP. As an imaging agent, an order of magnitude of 50-100 000 doses per year can be considered as a standard demand in case of commercial success of first RP.

A.16.2. Supply chain characterization

Given the interest of ^{64}Cu, the potential production routes have been widely studied and experimented over the past decades. ^{64}Cu can be produced through different routes:

- the accelerator route which asserted itself as the easiest route to implement and is currently the most widely used for R&D needs, with proton beam (deuterium beam alternative under R&D):
  - (^{64}Ni(p,n)^{64}Cu) from 12-16 MeV in cyclotrons, with commercial production being achieved in medium-energy cyclotrons with their higher beam current (1000µA);
  - (^{64}Zn(d,2p)^{64}Cu) with variable energy deuteron (10 to 40 MeV), currently at early R&D stage;
- the reactor route with fast neutrons through the reaction ^{64}Zn(n,p)^{64}Cu that do not present anymore interest, considering its low yields (due to

[189] RadioMedix and Curium Announce FDA Filing of copper Cu-64 dotatate injection New Drug Application - January 07, 2020 Source: Curium

significant production of ^{65}Zn impurity) and centralized production not compatible with ^{64}Cu short half-life.

The table below summarizes the characteristics of both accelerators production routes; reactor route is not developed in this table considering its lack of interest for future production.

	Accelerator (protons) ^{64}Ni(p,n)^{64}Cu	**Accelerator (deuterium)** ^{64}Zn(d,2p)^{64}Cu ^{nat}Zn(d, x) ^{64}Cu
Technology maturity	Widely available technology, with already standardized targets systems for typical ^{18}F cyclotrons for small quantity production, while commercial production is performed in MEC with higher current (1000µA) to produce Ci quantities of ^{64}Cu	Limited installed capacity of large high-energy deuterium fluxes, less industrialized than with protons.
Yield	Production of Ci amounts of high specific activity material in MEC	Similar yields to be achieved
Purity	No carrier added product, after purification of ^{67}Ga ($t_{1/2}$=72 h)	Production of ^{65}Ni ($t_{1/2}$=2.5 h) and stable ^{65}Cu
Target material	Enriched ^{64}Ni (>99%) to limit side products impurities. Need for recycling target material, due to high price of ^{64}Ni (around 30 k€ per gram).	Low cost for ^{nat}Zn and ^{64}Zn enriched targets, without supply limitations
Economics	Expensive production cost (2 to 4.5k$ for a 200mCi dose[190]) that should be reduced in case of large production scale.	Improved economics expected due to less expensive target material

Table 44: Summary table for ^{64}Cu manufacturing routes

Accelerator production route

Production of ^{64}Cu with proton or deuterium particles can be performed through various nuclear reaction using ^{nat}Zn, ^{64}Zn, ^{66}Zn, ^{68}Zn or ^{64}Ni.

- The ^{64}Ni(p,n)^{64}Cu is the most-used route, resulting in commercial high production yields with medium-energy cyclotrons (16 MeV proton beam from MEC 30MeV/1000µA), despite the high-cost of ^{64}Ni enriched targets (due to very low abundance of ^{64}Ni, only 0,926%). The use of liquid target systems instead of historical solid ones would enable more efficient production process (possibility to precisely control ^{64}Ni quantity and scale production, simplified processing…).

- The reactions based on deuterium irradiation are scarcely used, due to the global lack of installations being able to produce high energy deuterium

[190] The Center for Molecular and Genomic Imaging – USA California
https://cmgi.ucdavis.edu/facility-use/using-the-facility-overview/recharge-rates/

beam (>20 MeV). Limited gain is expected on yield, but production costs could be largely reduced due to low target material cost.

Regarding target processing, the production process of ^{64}Cu in cyclotrons is now mature[191] with standardized equipment and processes allowing automatized target treatments, like for widely used radionuclides (e.g. ^{18}F), with satisfying recovery process (>90%).

Reactor production route

In order to produce high-specific activity ^{64}Cu in reactor, fast neutrons are used through the reaction ^{64}Zn(n,p)^{64}Cu. However, ^{65}Zn is produced as a long life ($t_{1/2}$=245 days) by-product due to parasite reaction with thermal neutrons. Low yields could be observed (5-10 times lower than for the accelerator route) along with low-specific activity.

The main challenge faced by ^{64}Cu supply chain is linked to the availability of a large EU cyclotron network.

Summary of ^{64}Cu supply chains

In the absence of large demand, there is currently no EU industrial supply of ^{64}Cu. In the US, Curium is already producing Ci quantities per batch in a 30 MeV cyclotron (extracting a beam at 16MeV with a 1000µA current).

A cyclotron network similar to ^{18}F one would be needed (~50 production sites) to cover EU needs. Aside from limited supply for research, no GMP industrial production site is established in EU.

[191] Production of copper-64 and gallium-68 with a medical cyclotron using liquid targets - Modern Physics Letters A - Vol. 32, No. 17 (2017)

Annex 17. Copper-67 (^{67}Cu)

A.17.1. Properties, applications and competing radionuclides

^{67}Cu

Properties: ^{67}Cu is a short-range β-emitter for therapeutic use ($t_{1/2}$=62 hours), with low energy offering treatment possibilities for small tumours. Its β decay is followed by a γ-emission, allowing direct SPECT imaging (or as a theranostic pair with ^{64}Cu).

Applications: ^{67}Cu is foreseen as a targeted therapeutic RN for various types of cancer: blood, colon, breast, prostate, bladder and brain, with several clinical trials underway in phase I/II.

Competing radionuclides: ^{67}Cu will mainly compete with others low energy β-emitters such as ^{177}Lu or ^{131}I. ^{67}Cu has a β-energy close to ^{177}Lu (~0,6 mm tissue penetration for both RN), while potentially offering more flexible production through LINAC, with comparable production costs[192].

Demand: ^{67}Cu demand has been limited in the past due to scarce supply sources and high production costs. The recent availability of US DoE routine production should foster clinical research and increase demand[193]. Demand should remain limited to clinical trials prior to the market authorization of a first ^{67}Cu labelled RP.

A.17.2. Supply chain characterization

^{67}Cu is a complex radionuclide to manufacture for NM applications. Over the last decades, small quantities with different product quality of ^{67}Cu have been produced through different manufacturing routes (reactors, proton accelerators), active developments are underway for alternative routes (deuterium and photon irradiation).

The different routes are described hereafter:

- neutron irradiation in high fast neutrons flux reactors through reaction ^{67}Zn(n,p)^{67}Cu;
- proton irradiation in medium energy accelerators (16 MeV) with the reaction ^{70}Zn(p,α)^{67}Cu, or in high-energy accelerators (from 50 MeV and up to 425 MeV) through reaction ^{68}Zn(p,2p)^{67}Cu;
- photonuclear reaction in high energy eLINACs (30-60 MeV) or Rhodotrons through ^{68}Zn(γ,p)^{67}Cu;
- deuterium irradiation through reaction ^{64}Ni(α,p)^{67}Cu in a linear accelerator (in early development stage, with TRL2).

[192] Clarity Pharmaceuticals - https://www.claritypharmaceuticals.com/technology/copper-isotopes/
[193] National Isotope Development Center – Newsletter Spring 2020

	Neutron irradiation $^{67}Zn(n,p)^{67}Cu$	**Proton irradiation** $^{70}Zn(p,\alpha)^{67}Cu$ $^{68}Zn(p,2p)^{67}Cu$	**Photonuclear reaction** $^{68}Zn(\gamma,p)^{67}Cu$
Technology readiness level	**TRL9:** production in reactors performed in the past, but with low quality and yields (a few mCi/g)[194]. Manufacturing route currently no more considered as as Tier 1 option for industrial development	**TRL9:** small non-regular production, non-industrialized (at Paul Scherer Institute), ARRONAX currently involved in research programme for this route.	**TRL9**: small routine production at laboratory scale (Argonne), need to industrialize production for standardized use. NorthStar[195] working on such development.
Target material & targets		Use of enriched targets, ^{68}Zn preferred. ^{70}Zn requires more complex enrichment (natural abundance of 0,6%).	Enriched targets of ^{68}Zn (natural abundance of 19%) through gas centrifugation, no supply issue for target material.
Irradiation means		Require high or very high proton energy, limited installed capacity and costly installations.	Require a medium to high energy LINAC (threshold at 15MeV and peak at 26MeV). One or two installation(s) would be needed in EU to satisfy a RP product.
Yield and purity		Better yields achieved in large accelerators but remain low and necessitates long irradiation time. Co-production of ^{64}Cu, no separation process available.	High specific activity (100mCi/mg). 1Ci per batch, possibility to increase prod. up to hundreds of Ci in dedicated irradiation tool.

Table 45: Summary table for ^{67}Cu manufacturing routes

[194] Research Reactor Production and Purification of 64Cu and 67Cu Using Enriched Zinc Target Materials
[195] NorthStar Medical Technologies Signs Letter of Intent with Clarity Pharmaceuticals to Supply Therapeutic Radioisotope Copper-67 (Cu-67) (2020)

Summary of ^{67}Cu supply chain

Among these different routes, the photonuclear reaction is currently becoming the more advanced route towards an industrial production.

The single routine production of ^{67}Cu is performed through the DoE at Argonne Laboratory (eLINAC), and NorthStar (USA) recently announced the development of industrial production capacity of ^{67}Cu for Clarity Pharmaceuticals, in their recently acquired Rhodotron (see §2.1 for ^{99}Mo production). In Europe, ^{67}Cu can also be sourced from PSI, but in limited quantities.

The slow development of ^{67}Cu-labelled RP can be explained by the limited and non-commercially viable sources of supply. The main challenges to be faced by European RN industry to set up clinical trials then industrial scale supply chains for ^{67}Cu are diverse:

- securing a high-energy proton network for semi-centralized production of ^{67}Cu in EU, or the development of electron accelerator network of medium energy (30 MeV) for ^{67}Cu production;
- securing enriched Zn isotopes supply for ^{64}Cu and ^{67}Cu production.

Annex 18. Scandium-44 (^{44}Sc)

A.18.1. Properties, applications and competing radionuclides

^{44}Sc

Properties: ^{44}Sc is a positron, β and γ emitter with a long half-life as compared to standard imaging radionuclides ($t_{1/2}$=4hours), that decays into stable ^{44}Ca. Its high γ-energy could however become a limiting factor for its development.

Applications: ^{44}Sc is expected to be used as a PET imaging radionuclide in pair with ^{47}Sc therapeutic applications.

Competing radionuclides: As compared to standard PET imaging radionuclides (^{18}F, ^{68}Ga), ^{44}Sc offers a longer half-life allowing for more centralized production, and/or longer biological imaging processes. Its low positron energy offers better spatial resolution than ^{68}Ga. It also has a chemistry similar to those of the lanthanide family, making pairing use with ^{177}Lu possible in theory.

Demand: ^{44}Sc demand is currently limited to R&D. When considering that ^{44}Sc-labelled RP are only in early development stage, demand should remain low within the next decade.

A.18.2. Supply chain characterization

^{44}Sc can be produced through two different routes:

- the direct route, through proton irradiation in a cyclotron of ^{44}Ca targets through the reaction ^{44}Ca(p,n)^{44}Sc;
- the indirect route, through ^{44}Ti/^{44}Sc generators, where ^{44}Ti is produced in high energy proton accelerators (40-50 MeV) or through spallation.

Both direct and indirect routes are discussed in the table below[196],[197]:

	Direct route ^{44}Ca(p,n)^{44}Sc	**Indirect route through generators** ^{44}Ti/^{44}Sc
Technology readiness level	**TRL3**: for both routes, it can be considered that developments are only at laboratory scale. Proof of concept have been demonstrated for both direct and indirect routes, raising a certain number of limitations and issues to be solved in the future to allow development of these routes.	

[196] A Step-by-Step Guide for the Novel Radiometal Production for Medical Applications: Case Studies with 68Ga, 44Sc, 177Lu and 161Tb – 2020
[197] Pre-Therapeutic Dosimetry Employing Scandium-44 for radiolabelling PSMA-617 (2018)

	Direct route $^{44}Ca(p,n)^{44}Sc$	**Indirect route through generators** $^{44}Ti/^{44}Sc$
Target material & targets	Recycling or enriched ^{44}Ca through electromagnetic process (2% natural abundance) will be needed to avoid undesired products such as ^{44m}Sc, ^{47}Sc & ^{48}Sc. Different types of targets are under investigation (solid & liquid). Solid targets offer higher yields, ^{44}CaO targets would avoid CO_2 emissions during irradiation as compared to $CaCO_3$ targets.	^{44}Ti is produced through proton irradiation of ^{45}Sc (only natural isotope of scandium), without needs for enrichment.
Irradiation means	Different irradiation fluxes are considered (proton, deuterium, α), with best RN purity achieved by α, followed by deuterium.	^{44}Ti production necessitates high proton flux and long irradiation time. Spallation could also be considered but leads to complex radiochemistry for product purification.
Yield and purity	Low yield and NCA ^{44}Sc obtained through direct route.	High purity achieved; first clinical studies performed with generator produced ^{44}Sc.
Supply chain type	Non centralized supply chain, with production centre delivering doses to multiples radiopharmacies.	Centralized production, with generators used during long duration in large radiopharmacies, able to manage long-lived RN
Waste management	/	^{44}Ti has a 60 years half-life, complexifying waste management

Table 46: Summary table for ^{44}Sc manufacturing routes

Summary of ^{44}Sc supply chain

There is currently no established supply chain for ^{44}Sc, its use being limited to preclinical R&D.

The main challenges to be faced by European RN industry to set up industrial scale supply chain for ^{44}Sc are diverse, either for direct or indirect routes:

- the sustainable supply of enriched ^{44}Ca,
- the availability of a EU-wide cyclotron network for target irradiation, (by decreasing product purity order: α, deuterium or proton),
- the availability of large proton irradiation facility for ^{44}Ti production or spallation sources,
- and more widely, the development of GMP practices for ^{44}Sc production, along with specific equipment and production processes.

The development of a ^{44}Sc supply chain is challenging and costly, investments would be consented only after sustainability of ^{44}Sc use is demonstrated. In the meantime, securing a supply for R&D purposes in EU is recommended.

Annex 19. Scandium-47 (^{47}Sc)

A.19.1. Properties, applications and competing radionuclides

^{47}Sc

Properties: ^{47}Sc is a low-energy β-emitter with a long half-life ($t_{1/2}$=3,35days). ^{47}Sc is also a γ-emitter, allowing SPECT imaging during treatment delivery.

Applications: ^{47}Sc is foreseen as a future therapeutic RN, used in pair with ^{44}Sc or ^{43}Sc. Its low energy β emission would be particularly appropriate for small tumours.

Competing radionuclides: Scandium imaging pairs could represent an interesting alternative to currently growing ^{68}Ga/^{177}Lu pair, or any other diagnostic/therapeutic pair currently under development (^{64}Cu/^{67}Cu, Terbium isotopes).

Demand: ^{47}Sc demand is currently limited to preliminary R&D. When considering that ^{47}Sc-labelled RP are only in early development stage, demand should remain low within the next decade.

A.19.2. Supply chain characterization

Multiple ^{47}Sc manufacturing routes are under consideration, based on different irradiation fluxes (p, n, γ & α) and particles energy, either through direct or indirect routes:

- through proton irradiation in accelerators: ^{48}Ti(p,2p)^{47}Sc or ^{50}Ti(p,α)^{47}Sc or ^{48}Ca(p,2n)^{47}Sc,
- through photonuclear reaction in electron linear accelerator: ^{48}Ti(γ,p)^{47}Sc,
- through neutron irradiation: ^{48}Ca(n,γ)^{47}Sc or ^{47}Ti(n,p)^{47}Sc or ^{46}Ca(n,γ)^{47}Ca followed by decay into ^{47}Sc,
- or through α-beam in high-energy accelerator ^{44}Ca(α,n)^{47}Sc.

As these routes are still in early development stage for in vitro applications and all present important limitations that will have to be solved to obtain radionuclide quality for clinical use (availability of irradiation tool, impurities, separation technologies…), only the most documented and promising ones are assessed on an individual basis.

Manufacturing routes	Process, limitations and advantages
$^{46}Ca(n,\gamma)^{47}Ca$ then decay into ^{47}Sc	The $^{47}Ca/^{47}Sc$ generator approach could offer good specific activity and purity. However, the ^{46}Ca target material natural abundance is very limited (0.004%), thus needing important enrichment steps, up to a threshold of 30%. This makes target material expensive, with need for target recycling. Radionuclidic purity over 99% was achieved experimentally through this route.
$^{47}Ti(n,p)^{47}Sc$	Irradiation in fast neutron reactors (E_n > 1 MeV), leading to lower radionuclidic purity and yields than for the $^{46}Ca(n,\gamma)^{47}Ca$ route. The need for fast neutrons will limit the production to a more limited number of research reactors.
$^{48}Ti(\gamma,p)^{47}Sc$	Production through this route has been demonstrated[198] (enriched ^{48}Ti targets in high intensity eLINAC ~40 MeV), but radionuclidic purity and yield remains limited by the cross-section reaction. The use of enriched ^{48}Ti (99.6%) is needed to limit the co-production of ^{46}Sc and ^{48}Sc (high natural abundance of 73.7%).
$^{48}Ti(p,2p)^{47}Sc$ $^{50}Ti(p,\alpha)^{47}Sc$ $^{48}Ca(p,2n)^{47}Sc$	Cyclotron production through these different routes leads to the production of ^{46}Sc and ^{48}Sc. The irradiation of ^{48}Ca enriched targets to decreased impurities is limited by high enriched target material cost.
$^{44}Ca(\alpha,p)^{47}Sc$	Compared to proton irradiation in cyclotrons, this route showed lower yield and radionuclidic purity[199].

Summary of ^{47}Sc supply chain

There is currently no established supply chain for ^{47}Sc, its use being limited to scares preclinical R&D. ^{47}Sc has already been produced in EU at Institut Laue Langevin reactor (France)[200], at the spallation-induced neutron source SINQ in Paul Scherrer Institut[201] (PSI), and in BR-2 reactor (Belgium).

The main challenges to be faced by European RN industry to set up industrial scale supply chains for ^{47}Sc are diverse, either for direct or indirect routes. Currently the indirect route $^{46}Ca(n,\gamma)^{47}Ca$ followed by decay into ^{47}Sc, and the photonuclear reaction $^{48}Ti(\gamma,p)^{47}Sc$ appear as the most promising ones. They will necessitate:

- the sustainable supply of enriched ^{46}Ca and ^{48}Ti,
- the availability of fast neutron irradiation means, or a network of photon accelerators, currently not widely available at EU-scale.

[198] Photonuclear production, chemistry, and in vitro evaluation of the theranostic radionuclide 47Sc - EJNMMI Res. 2019
[199] Production of scandium-43 and Scandium-47 from a powdery calcium oxide target via the (nat/44)Ca(α,x)-channel. - Appl Radiat Isot. 2016 Oct.
[200] Promising Prospects for 44Sc-/47Sc-based Theranostics: Application of 47Sc for Radionuclide Tumour Therapy in Mice - J Nucl Med. 2014 Oct
[201] 47Sc as useful β—emitter for the radiotheragnostic paradigm: a comparative study of feasible production routes - Domnanich et al. EJNMMI Radiopharmacy and Chemistry (2017)

Annex 20. Terbium isotopes (^{149}Tb, ^{152}Tb, ^{155}Tb & ^{161}Tb)

A.20.1. Properties, applications and competing radionuclides

Tb
isotopes

Properties: terbium isotopes family is unique, covering the different disciplines of nuclear medicine (SPECT and PET imaging, TRNT with β-emission and α-therapy). The pairing possibilities (SPECT/PET with therapeutic applications) with same element is an asset in nuclear medicine.

^{155}Tb is a γ-emitter ($t_{1/2}$=5,3 days) compatible with SPECT imaging. ^{152}Tb is a positron emitter ($t_{1/2}$=17,5 hours) compatible with PET imaging. ^{161}Tb is a pure β-emitter ($t_{1/2}$=6,9 days), that also emit Auger electrons with potential use in TRNT, with similar profile to ^{177}Lu. ^{149}Tb is an α-emitter, that could present interest for TAT.

Applications: terbium isotopes use is currently limited to preclinical evaluations and proof-testing. At this stage no specific clinical applications have been identified yet but are under active development. Regarding therapeutic applications of ^{161}Tb, its chemical properties are close to ^{177}Lu (being both lanthanides), and similar applications could be foreseen.

Competing radionuclides: terbium isotopes appear as challengers to other theranostics pairs under development (Ga/Lu, Cu, Sc…).

Demand: The demand for terbium radionuclides is limited, partially due to limited supply sources. It is expected that demand will remain capped by production capacity in the next decade. Within 2030, demand should be restricted to a few preclinical and early clinical applications.

A.20.2. Supply chain characterization

Terbium radioactive isotopes production is challenging, explaining the currently low interest of the industry, along with the limited research performed on these isotopes in the past.

The supply of the different Terbium isotopes is not currently at similar levels of development, ^{161}Tb is the "easiest" one to produce, with a supply similar to ^{177}Lu NCA in research reactors. Regarding the 3 other nuclides, they can be produced in high-energy proton accelerators (70 MeV) with specifically enriched gadolinium targets or through high-energy proton irradiation of tantalum foil, followed by a mass isotope separation process (ISOLDE/CERN).

The current most promising production route for each isotope are described hereafter[202,203].

Tb isotope	Qualitative description of most promising production route
^{161}Tb	^{161}Tb production could be performed in research reactors, similar to NCA ^{177}Lu production, with good yields. An enriched target of ^{160}Gd (enrichment through electromagnetic separation) is irradiated in a thermal neutron flux in a research reactor through the reaction ^{160}Gd(n,γ)^{161}Gd. Then, ^{161}Gd decays ($t_{1/2}$=3,6 min) into ^{161}Tb and is extracted through ion exchange chromatography. Such route has been demonstrated in Europe at PSI or ILL. The main limitation for the industrial development of ^{161}Tb is the supply of enriched ^{160}Gd (21,9% isotopic abundance).
^{149}Tb ^{152}Tb ^{155}Tb	Production of other isotopes require the use of a high-energy proton flux (up to 70 MeV). The different types of targets used (^{152}Gd or ^{155}Gd) lead to the production of different terbium isotopes and impurities. A standard chemical separation process cannot be used. Thus, mass separation technology is mandatory to isolate the wanted isotopes. The availability of highly enriched ^{152}Gd and ^{155}Gd could lead to high purity ^{155}Tb and ^{152}Tb, through high-energy proton irradiation.

Summary of Terbium isotopes supply chain

There is currently no routine production of terbium. Aside from ^{161}Tb supply chain in research reactor that could be based on existing installations (with the challenge of enriched ^{160}Gd supply), the others terbium radionuclides currently rely on complex manufacturing solutions (scarcely available high-energy proton accelerators, mass separators…), limiting wide-scale deployment.

[202] Terbium Radionuclides for Theranostics Applications: A Focus On MEDICIS-PROMED - Physics Procedia 90 (2017)
[203] Scandium and terbium radionuclides for radiotheranostics: current state of development towards clinical application – Apr 2018

Annex 21. Cobalt-60 (^{60}Co)

A.21.1. Properties, applications and competing radionuclides

^{60}Co

Properties and applications: ^{60}Co decays into stable ^{60}Ni ($t_{1/2}$=5,2 years) with the emission of two gamma rays (1,17 and 1,33 MeV). Depending on the type of application, either low or high specific activity ^{60}Co is used (LSA or HSA). The gamma rays produced by ^{60}Co sealed sources are widely used in industrial and medical applications (Cancer Treatment in teletherapy and radiosurgery machines, medical devices and food irradiators, radiography…), with sterilization being by far the most used application for ^{60}Co sources.

Competing radionuclides: among the different applications introduced previously, ^{60}Co is not competing with any other radionuclides. However, for security considerations, some international initiatives are in favour of some long-life sealed sources replacement. ^{60}Co could be replaced in some cases by linear accelerators, electron and x-ray beams[204]. In the case of ^{60}Co, such replacement is very challenging for multiple reasons: technical, operational or regulatory requirements, higher costs of alternative technologies[205]…

Demand: ^{60}Co demand has been increasing through the years, the main markets players (Canada and Russia) took measures to secure and increase production for the future through additional production sites, thus confirming this growing trend[206,207].

A.21.2. Supply chain characterization

There is only a single manufacturing route for ^{60}Co, with thermal neutron irradiation of natural cobalt sources (100% of ^{59}Co isotope) in reactors, through reaction ^{59}Co(n,γ)^{60}Co. The neutron flux employed is 10^{12}–10^{15}n/cm2-sec and the conversion is close to 99%.

	Direct production - ^{59}Co(n,γ)^{60}Co
Technology readiness level	**TRL9:** ^{60}Co has been produced through this route (HSA and LSA) for decades in reactors. Whereas power reactors were focused on LSA production, Canada is now producing both grades in Bruce Power CANDU reactors[208].

[204] The 2018 radiation source protection and security task force report
[205] See IIA White Paper, "A comparison of gamma, e Beam, X-ray and Ethylene-oxide technologies for the industrial sterilization of medical devices and Healthcare products", 31/8/2017
[206] Nordion Acquires Technology to Expand Future Global Cobalt-60 Supply - Feb 2019
[207] Russia starts cobalt-60 production at Kursk plant – WNN - Nov 2018
[208] A Nuclear Power Side Venture: Medical Isotope Production – POWER – April 2020

	Direct production - $^{59}Co(n,\gamma)^{60}Co$
Target material	^{Nat}Co yearly demand for ^{60}Co production remains very limited as compared to the 120 000 tons of yearly needs for chemical applications (batteries) and metallurgical uses. However, ^{nat}Co supply chain remains problematic, with 60% of world resources coming from the Democratic Republic of the Congo (DRC), with Cobalt being a side-product of Copper and Nickel mining.
Yield & purity	Depending on the grade of ^{60}Co produced (HSA or LSA), irradiation duration and target systems are different: – High specific activity (HSA) ^{60}Co – (from tens up to hundreds of Ci/g – 50-300 Ci/g), is mainly produced in research reactors (including production in EU research reactors); – Low specific activity (LSA) ^{60}Co – (tens of Ci/g) is produced in power reactors, with Russia and Canada having the highest international market shares.
Target and processing	Different target systems are used for HSA or LSA, to cope with longer irradiation periods and neutron flux. Targetry systems are not standardized, and specific to each power or research reactor.
Supply chain type	^{60}Co manufacturing supply chain is centralized, due to irradiation means (reactors) and ^{60}Co long half-life.

Summary of ^{60}Co supply chain

The current supply of LSA ^{60}Co is essentially performed by Russia and Canada, each player controlling respectively roughly 50% of the world market:

- Russia: ^{60}Co is produced at Leningrad NPP (inside RBMK-1000) that is expected to shut down in 2024. Investments were made in Smolensk and Kursk NPP to ensure future production. Future production in Russian fast reactors (BN-600 & BN-800) is currently under investigation;

- Canada: Bruce Power reactors have been used for nearly 30 years for LSA ^{60}Co production. In addition to production in Canadian CANDU reactors, Nordion started, in the last 3 years, a worldwide development program[209] through various partnerships (India, USA, Romania) for ^{60}Co production.

The current supply of HSA ^{60}Co is less centralized, with production being performed in various research and small power reactors. Following NRU shutdown in Canada, Nordion developed a programme for HSA ^{60}Co production in power reactors, first batches from Bruce Power were harvested in 2019, after 2 years of irradiation inside Bruce Power unit 7.

[209] Collaboration agreement signed with SNN (Nationala Nuclearelectrica SA) in Romania for production at Cernavoda NPP, collaboration with Westinghouse for development of ^{60}Co production in PWR, purchase agreement with BRIT (India) for ^{60}Co export from India.

Europe is currently dependent of Canadian/Russian supply for most of its LSA ^{60}Co use, and still produces in more limited quantities HSA ^{60}Co in EU research reactors. Production of LSA was performed in EU in the past (e.g, in BR-2).

EU has a strong experience in research reactors irradiation. Recent collaboration between Nordion and Romania could add a large supply of LSA ^{60}Co on EU soil and solve the issue of import dependence.

Yet, this dependence issue does not appear critical, as supply capacity is increasing in the world (Canada, Russia) and no shortages are expected in the near future.

The current supply chain structure for HSA and LSA are summarized in the following figure:

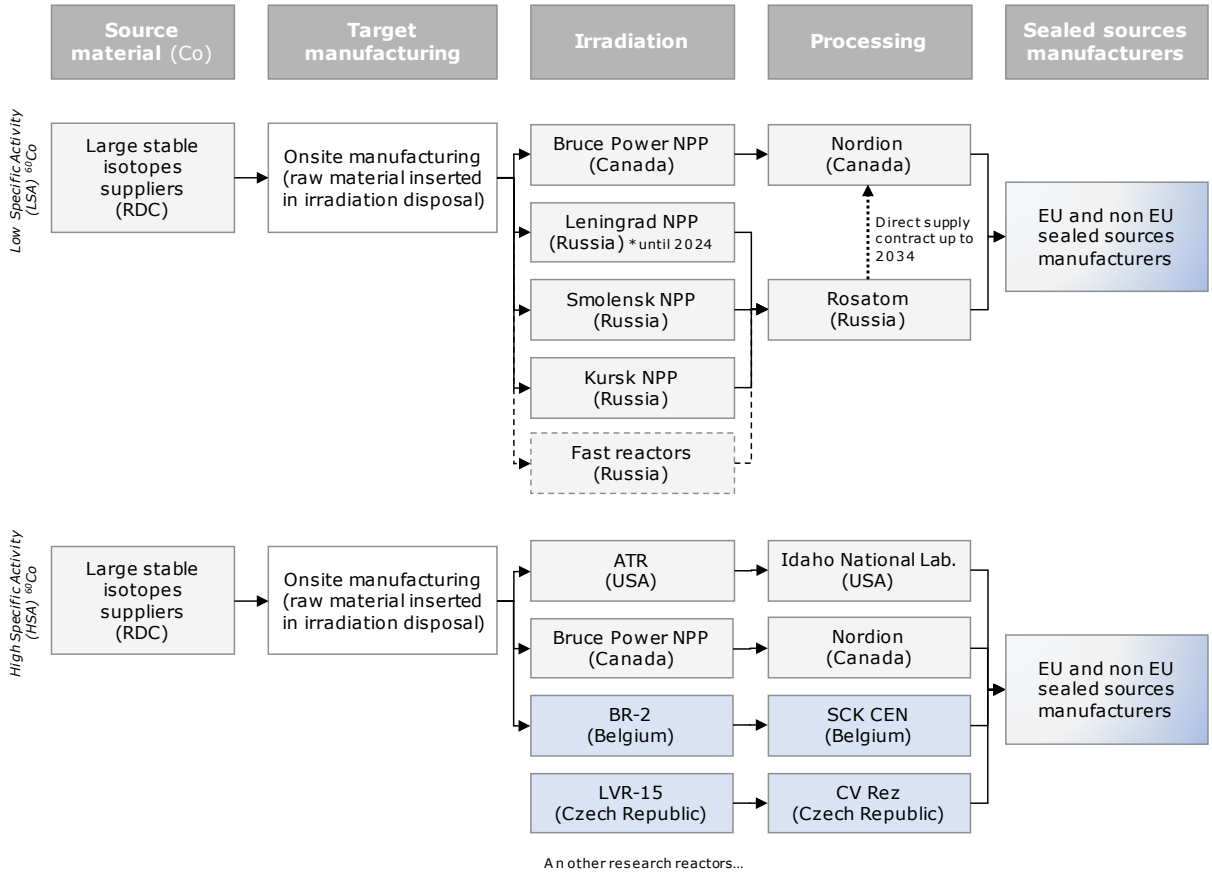


Figure 64: Current supply chains for ^{60}Co, for HSA (upper figure) and LSA (lower figure) National production for local markets (India, China) is not included

Annex 22. Industrial radionuclides

A.22.1. Industrial demand and supply of radionuclides are not following same approaches than medical ones

The development and establishment of a dedicated supply chain is usually justified by economic and technical constraints, to ensure a routine production volume with standardized parameters (activity, impurities…). Pharmaceutical demand is based on such principle, while it's less widely the case for industrial radionuclides.

At the exception of ^{60}Co, that represents a large and growing international market, allowing players to invest and collaborate to expand production (see Annex 21), most of industrial radionuclides use was developed as by-product of nuclear-related processes (nuclear fuel management, mining and enrichment activities…). The market related to industrial radionuclides is mature, with limited evolutions in terms of demand and R&D for new uses. Most of industrial applications have been routinely used for decades (welding verification, thickness and density measurement…), with radionuclide demand being fostered only by equipment replacement needs.

RN	Applications	Volume of Use	Market trend
Co-60	Industrial radiography, industrial sources for irradiators (including sterilization)	Common	Growing
Ir-192	Industrial gamma-ray sources for industrial radiography	Common	Mature
Cs-137	Industrial gauging, thickness and density measurements, medical sterilization	Common	Mature
Am-241	Industry (and smoke detectors)	Common	Mature
Kr-85	Industrial weight measurement	Limited	Mature
Sr-90	Industry	Limited	Mature
Pm-147	Used in various equipment, with very limited use	Very limited	Mature
Se-75		Very limited	Mature
Yb-169		Very limited	Mature
Cf-252		Very limited	Mature

Table 47: Radionuclides used in industrial applications

This chapter illustrates industrial radionuclides specificities, through different examples.

A.22.2. Krypton-85 (^{85}Kr), a nuclear fuel retreatment side-product

Krypton-85 is used under gas form in sealed sources for various applications (thickness gauge, gauge switch, high-density discharge lamps…), due to its physical properties ($t_{1/2}$=10 years) and emitting profile (both γ and β emitter). The main manufacturing route for this radionuclide is derived from nuclear spent fuel retreatment.

After irradiation in nuclear reactors, spent fuel contain various fission and activation products (^{241}Am, ^{137}Cs, ^{85}Kr, ^{147}Pr and ^{90}Sr). Aside from uranium and plutonium that can be retrieved for new fuel manufacturing, some radionuclides can routinely be separated during reprocessing activities. FSUE Mayak (Russia) is a main producer of ^{85}Kr, through retreatment activities[210].

Spent fuel retreatment operations are complex industrial processes, unique for each installation (Orano La Hague – France, Sellafield – UK, MAYAK – Russia), the capability of radionuclide extraction at an industrial level cannot be added afterwards to a facility, especially when it is considered as far from the main purpose of such installations.

Radionuclide production derived from nuclear fuel cycle activities must be monitored from a security of supply basis. No private/industrial investment in alternative production means could be made possible through current market conditions (limited demand and no growth expected, with societal trend for sealed sources replacement). Availability of these radionuclides (^{85}Kr, ^{241}Am…) shall be considered with an opportunistic view.

Market being mature, the existing supply chains shall be maintained as long as possible to ensure mid-long-term supply, while ensuring that alternative technologies could be made available in case of cessation of supply.

A.22.3. Californium-252 (^{252}Cf), a regular production relying on a single national subsidized research installation

Californium-252 is a strong neutron emitter (1 µg of ^{252}Cf emits 2,3 x 10^6 neutrons per second), with a 2,6 years half-life, that is used as a neutron source in various applications: nuclear power reactor start-up rods, well logging in oil industry, portable isotopic neutron spectroscopy… Like some other radionuclides with limited demand, ^{252}Cf is regularly produced in dedicated production campaigns.

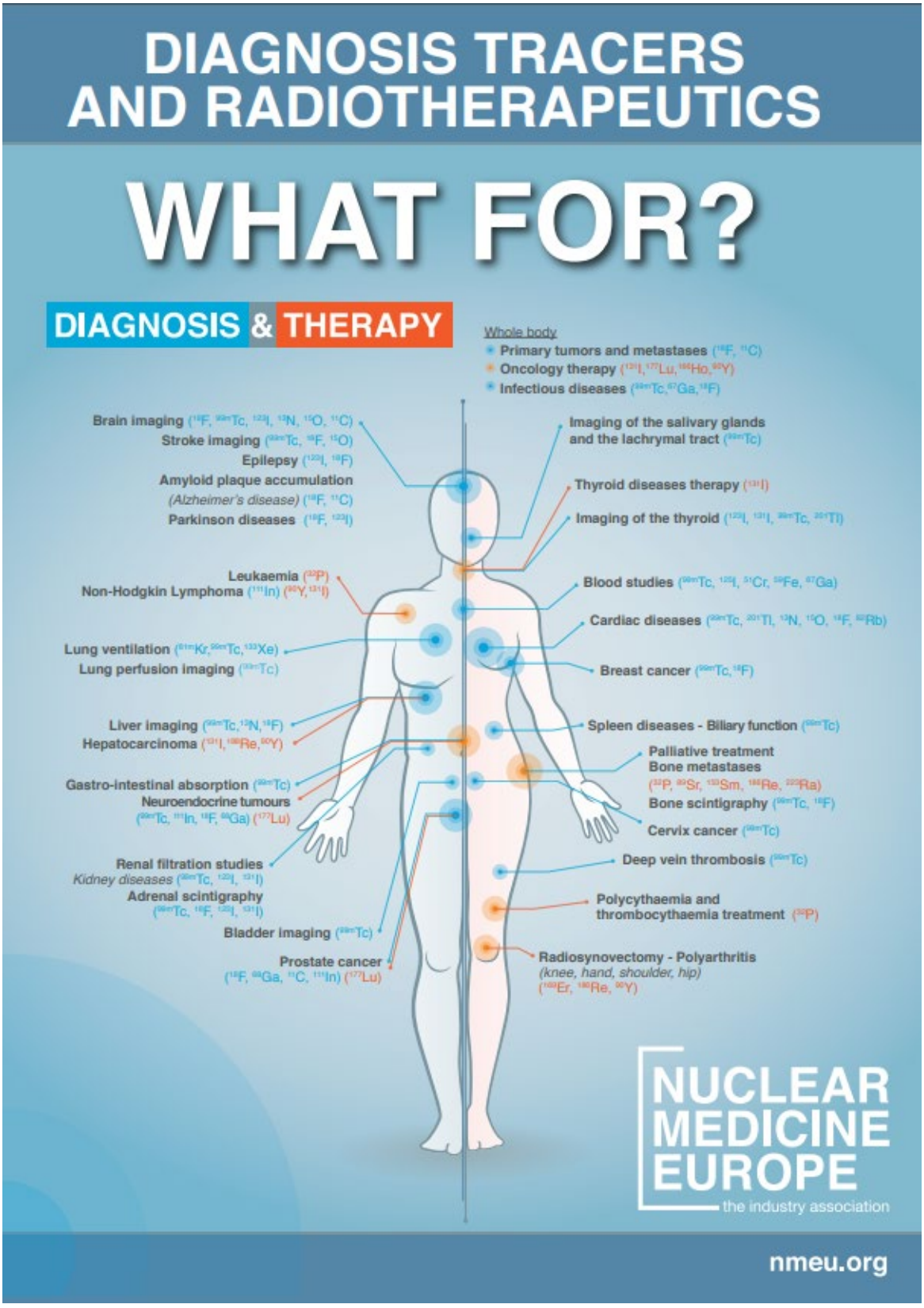
^{252}Cf production has been re-established in the US in 2009 and is now regularly produced at Oak Ridge National Laboratory - ORNL (~25 mg of ^{252}Cf per year), accounting for ~70% of world production[211]. ^{249}Bk targets are irradiated during a few months in HFIR reactor and ultimately form ^{252}Cf under high thermal neutron flux. Targets are then dissolved through a specific process at ORNL to retrieve ^{252}Cf.

[210] IAEA Nuclear Energy Series - No. NW-T-1.11 - Available Reprocessing and Recycling Services for Research Reactor Spent Nuclear Fuel
[211] Cleaning up and simplifying californium production - New ligand could eliminate acid work-up and waste involved in isolating the superheavy isotope - Sam Lemonick 2019

Like ^{252}Cf, some radionuclides have a very limited demand and long half-life allowing to regularly build up stockpiles to be depleted within years or decades. Production is generally centralized over one or two public research institutes (in the US or Russia).

Appendixes

A. "The Birth of Hygiea" from Nuclear Medicine Europe



Nuclear Medicine Europe – "The Birth of Hygiea" – Courtesy of NMEu

B. Overview of radiopharmaceuticals in use in the EU

An overview of nuclear medicine current practices in EU is presented in the following tables [212], based on "European Nuclear Medicine Guide" by EANM (European Association of Nuclear Medicine) and the "The birth of Hygiea", a publication of the Innovation Working Group of NMEu.

A special acknowledgement to European Association of Nuclear Medicine (EANM) and Nuclear Medicine Europe (NMEu) that reviewed the following tables.

Application & Imaging tool		Radionuclides and radiopharmaceuticals	
Blood studies	SPECT	^{125}I ^{51}Cr	[^{125}I]I-Human Serum Albumin (HSA) [^{51}Cr]Cr-Red Blood Cell (RBC)
Cardiac function, ERNA &/or FPRNA[213]	SPECT	^{99m}Tc	[^{99m}Tc]Tc-human albumin (HSA) [^{99m}Tc]Tc-pertechnetate [^{99m}Tc]Tc-pentetate (DTPA)
Cardiac imaging	SPECT	^{99m}Tc	[^{99m}Tc]Tc-Etidronate (DPD & PYP)
Cardiac imaging	PET	^{11}C	[^{11}C]C-mHED
Deep vein thrombosis	SPECT	^{99m}Tc	[^{99m}Tc]Tc-human albumin
Myocardial perfusion	PET	^{13}N ^{15}O ^{82}Rb	[^{13}N]NH^3 (Ammonia) H_2[^{15}O]O [^{82}Rb]Rb-Chloride
Myocardial perfusion	SPECT	^{201}Tl	[^{201}Tl]Tl-Thallous Chloride
Myocardial perfusion & Cardiac function / FPRNA	SPECT	^{99m}Tc	[^{99m}Tc]Tc-sestamibi [^{99m}Tc]Tc-tetrofosmin
Myocardial viability	PET	^{18}F	[^{18}F]FDG

Table 48: Cardiovascular imaging radiopharmaceuticals summary table

Application & Imaging tool		Radionuclides and radiopharmaceuticals	
Assessment of renal function and transit	SPECT	^{99m}Tc	[^{99m}Tc]Tc-Ethylene Dicysteine (EC) [^{99m}Tc]Tc-Mertiatide (MAG3)
Assessment of renal function and transit and clearance methods (Kidneys)	SPECT	^{123}I	[^{123}I]-Iodohippurate (OIH)
Assessment of renal function and transit (Bladder)	SPECT	^{99m}Tc	[^{99m}Tc]Tc-pentetate (DTPA)
Bile acid investigation	SPECT	^{75}Se	[^{75}Se]Se-Tauroselcholic acid (SeHCat)
Clearance methods (kidneys)	SPECT	^{99m}Tc	[^{99m}Tc]Tc-pentetate (DTPA)
Colon transit	SPECT	^{111}In ^{99m}Tc	[^{111}In]In-Chloride [^{99m}Tc]Tc-pentetate (DTPA)
Liver (hepatocytic function)	SPECT	^{99m}Tc	[^{99m}Tc]Tc-Disofenin (DISIDA) [^{99m}Tc]Tc-Mebrofenin (Br-IDA)
Renal cortical imaging	SPECT	^{99m}Tc	[^{99m}Tc]Tc-Succimer (DMSA)
Various (bladder, oesophageal transit, gastrointestinal bleeding…)	SPECT	^{99m}Tc	[^{99m}Tc]Tc-Sulfur Colloid (SC) [^{99m}Tc]Tc-Red Blood Cell (RBC) [^{99m}Tc]Tc-pertechnetate

Table 49: Gastrointestinal imaging radiopharmaceuticals summary table

[212] In some cases, the sources used refer to radionuclides and their associated radiopharmaceuticals that are only locally available, discontinued, or with a limited use and no expected growth in the future. They have been removed from the table for clarity purpose. Also, the usual public names for radiopharmaceuticals were used instead of the official IUPAC nomenclature, for the sake of simplicity and readability.
[213] ERNA - Equilibrium Radionuclide Angiocardiography / FPRNA - First-pass Radionuclide Angiography

Application & Imaging tool		Radionuclides and radiopharmaceuticals	
Amyloid plaque accumulation (Alzheimer)	PET	^{18}F	[^{18}F]F-Florbetaben (NeuraCeq™) [^{18}F]F-Florbetapir (Amyvid®) [^{18}F]F-Flutemetamol (Vizamyl™)
Brain metabolism	PET	^{18}F	[^{18}F]FDG
Brain perfusion	PET	^{15}O	H_2[^{15}O]O
Brain perfusion (incl. stroke)	SPECT	^{99m}Tc	[^{99m}Tc]Tc-Bicisate (ECD) [^{99m}Tc]Tc-Exametazime (HMPAO)
Cisternography and CSF leak	SPECT	^{111}In	[^{111}In]In-Pentetate (DTPA)
Parkinson's diseases (Presynaptic dopaminergic transporters)	SPECT	^{123}I	[^{123}I]I-Ioflupane
	PET	^{18}F	[^{18}F]-FDOPA

Table 50: Neurology imaging radiopharmaceuticals summary table

Application & Imaging tool		Radionuclides and radiopharmaceuticals	
Ciliary clearance	SPECT	^{99m}Tc	[^{99m}Tc]Tc-Human Albumin (Nanocolloids)
Lung perfusion imaging	SPECT	^{99m}Tc	[^{99m}Tc]Tc-Human Albumin (Macroaggregate)
Lung ventilation	SPECT	^{81m}Kr ^{99m}Tc	[^{81m}Kr]-Kr (gas) [^{99m}Tc]Tc-pentetate (DTPA) [^{99m}Tc]Tc-Technegas

Table 51: Pulmonary imaging radiopharmaceuticals summary table

Application & Imaging tool		Radionuclides and radiopharmaceuticals	
Adrenal scintigraphy	SPECT	^{123}I ^{131}I	[^{123}I]I-Iobenguane (MIBG) [^{131}I]I-Iobenguane (MIBG) [^{131}I]I-Adosterol (Norcholesterol)
Adrenal imaging	PET	^{18}F ^{11}C	[^{18}F]-FDOPA [^{11}C]C-Metomidate
Bone marrow	SPECT	^{99m}Tc	[^{99m}Tc]Tc-Human Albumin (Nanocolloids)
Bone scintigraphy	PET	^{18}F	Na[^{18}F]F (Sodium Fluoride)
Bone scintigraphy	SPECT	^{99m}Tc	[^{99m}Tc]Tc-DPD [^{99m}Tc]Tc-MDP/HDP/HEDP/HMDP
Brain & nervous systems tumours	PET	^{11}C	[^{11}C]C-Methionine
Brain tumours	PET	^{18}F	[^{18}F]-FDOPA [^{18}F]F-Fluoroethyltyrosine (FET) [^{18}F]-FMISO
Breast cancer	PET	^{18}F	[^{18}F]F-Fluoroestradiol (FES)
Breast cancer	SPECT	^{99m}Tc	[^{99m}Tc]Tc-sestamibi
Neuroendocrine tumours (NET)	SPECT	^{111}In ^{99m}Tc	[^{111}In]In-Pentetreotide (Octreoscan®) [^{99m}Tc]Tc-Octreotate [^{99m}Tc]Tc-Octreotide
Neuroendocrine tumours (NET)	PET	^{18}F ^{68}Ga	[^{18}F]FDOPA [^{68}Ga]Ga-DOTATATE (Octreotate) [^{68}Ga]Ga-DOTATOC (Octreotide) [^{68}Ga]Ga-DOTANOC
Non-hodgkin lymphoma (NHL)	SPECT	^{111}In	[^{111}In]In-Ibritumomab tiuxetan

Application & Imaging tool		Radionuclides and radiopharmaceuticals	
Parathyroid	PET	^{11}C	[^{11}C]C-Methionine
Prostate cancer	PET	^{68}Ga ^{11}C ^{18}F	[^{68}Ga]Ga-PSMA-11 [^{11}C]CH (Choline) [^{18}F]FCH (Fluorocholine) [^{18}F]FECH (or FEC)-Fluoroethylcholine
Sentinel node limphoscintigraphy	SPECT	^{99m}Tc	[^{99m}Tc]Tc-Human Albumin (Nanocolloids)
Thyroid and parathyroid imaging	SPECT	^{123}I ^{131}I ^{99m}Tc	Na[^{123}I]I (Sodium Iodide) Na[^{131}I]I (Sodium Iodide) [^{99m}Tc]Tc-pertechnetate [^{99m}Tc]Tc-sestamibi
Thyroid and parathyroid imaging	PET	^{18}F	[^{18}F]FCH (Choline)
Tumours detection and treatment efficiency measurement	PET	^{18}F ^{89}Zr ^{68}Ga	[^{18}F]FLT (Fluorothymidine) [^{18}F]FDG [^{89}Zr]Zr-atezolizumab [^{68}Ga]Ga-FAP
Lymphoma detection		^{68}Ga	[^{68}Ga]Ga-pentixafor
Tumours localisation (skeleton, brain…)	PET	^{18}F	[^{18}F]FDG

Table 52: Oncology imaging radiopharmaceuticals summary table

Application & Imaging tool		Radionuclides and radiopharmaceuticals	
Blood/platelet survival study	SPECT	^{111}In	[^{111}In]In-Oxyquinoline (Oxine)
Lymphoscintigraphic or sentinel lymph node mapping	SPECT	^{99m}Tc	[^{99m}Tc]Tc-human albumin (HSA)
Splenic function	SPECT	^{99m}Tc	[^{99m}Tc]Tc-heat-damaged RBC (HDRBC)
Infectious diseases	PET	^{18}F	[^{18}F]FDG
Infectious diseases	SPECT	^{99m}Tc	[^{99m}Tc]Tc-Exametazime (HMPAO) WBC
Imaging of the salivary glands and lachrymal tract	SPECT	^{99m}Tc	[^{99m}Tc]Tc-pertechnetate

Table 53: Other applications for imaging radiopharmaceuticals summary table

Application & Imaging tool	Radionuclides and radiopharmaceuticals	
Malignant neural crest tumours (pheochromocytoma) + paraganglioma	^{131}I	[^{131}I]I-Iobenguane (MIBG)
Neuroendocrine tumours	^{177}Lu ^{90}Y	[^{177}Lu]Lu-DOTATOC [^{177}Lu]Lu-Oxodotreotide [^{177}Lu]Lu-DOTATATE [^{90}Y]Y-DOTATATE [^{90}Y]Y-DOTATOC
Non-hodgkin lymphoma	^{90}Y	[^{90}Y]Y-Ibritumomab Tiuxetan (Zevalin®)
Polycythaemia and thrombocythaemia treatment	^{32}P	[^{32}P]P-Chromic Phosphate
Prostate cancer	^{177}Lu	[^{177}Lu]Lu-PSMA-ligands
Thyroid diseases therapy	^{131}I	Na[^{131}I]I (Sodium Iodide)
Palliative treatment bone metastases	^{153}Sm ^{186}Re	[^{153}Sm]Sm-Lexidronam (EDTMP) (Quadramet©)

Application & Imaging tool	Radionuclides and radiopharmaceuticals	
	^{223}Ra	[^{186}Re]Re-Etidronate (HEDP)
	^{89}Sr	[^{223}Ra]Ra-Dichloride (Xofigo©)
	^{177}Lu	[^{89}Sr]Sr-Chloride (Metastron©)
		[^{177}Lu]Lu-EDMTP
Radiosynovectomy - polyarthritis	^{169}Er	[^{169}Er]Er-Citrate
	^{186}Re	[^{186}Re]Re-Sulfide
	^{90}Y	[^{90}Y]Y-Citrate

Table 54: Therapeutic applications of radiopharmaceuticals

C. Nuclear Medicine statistics of use in the EU

The Swedish radionuclides situation

Most exhaustive information can be found within Swedish Radiation Safety Authority (SRSA), that publish on a yearly basis detailed statistic of use of radionuclides and radiopharmaceuticals (Isotopstatistik för nukleärmedicinsk verksamhet[214]). SRSA public database provide detailed statistics since 1999 of the nuclear medicine procedures performed, with emphasis on the type of radiopharmaceuticals used and the imaging or therapeutic objective. An excerpt of the most-used radiopharmaceuticals (26 radiopharmaceuticals products representing **~97.5% of total use** in Sweden in 2018) is given in the table below:

Radionuclides and radiopharmaceuticals		Number of procedures			
		2015	2016	2017	2018
^{99m}Tc	[^{99m}Tc]Tc-tetrofosmin	20 565	22 601	21 533	23 118
^{18}F	[^{18}F]FDG	14 821	16 897	19 515	20 814
^{99m}Tc	[^{99m}Tc]Tc-MDP/HDP	17 440	17 128	16 471	15 841
^{99m}Tc	[^{99m}Tc]Tc-Human Albumin (Nanocolloids)	8 343	8 286	7 837	6 912
^{99m}Tc	[^{99m}Tc]Tc-pertechnetate	5 555	5 269	5 707	5 417
^{99m}Tc	[^{99m}Tc]Tc-Human Albumin (Macroaggregate)	6 111	6 164	6 234	5 414
^{99m}Tc	[^{99m}Tc]Tc-Mertiatide (MAG3)	5 599	5 420	5 428	5 050
^{99m}Tc	[^{99m}Tc]Tc-sestamibi	6 286	5 900	5 464	4 988
^{99m}Tc	[^{99m}Tc]Tc-Technegas	3 781	4 163	5 081	4 687
^{131}I	Na[^{131}I]I (Sodium Iodide)	4 061	3 768	4 509	4 202
^{51}Cr	[^{51}Cr]Cr-Edetate (EDTA)	4 298	4 236	3 873	3 266
^{99m}Tc	[^{99m}Tc]Tc-Succimer (DMSA)	2 833	2 578	2 479	2 525
^{99m}Tc	[^{99m}Tc]Tc-human albumin (HSA)	446	505	518	1 470
^{223}Ra	[^{223}Ra]Ra-Dichloride (Xofigo©)	1 188	1 634	1 886	1 466
^{123}I	[^{123}I]I-Ioflupane (DATscan®)	1 234	1 242	1 306	1 348
^{68}Ga	[^{68}Ga]Ga-DOTATATE (Octreotate)			540	1 027
^{18}F	[^{18}F]FCH (Choline)	252	272	771	834
^{99m}Tc	[^{99m}Tc]Tc-Red Blood Cell (RBC)	758	589	597	563
^{75}Se	[^{75}Se]Se-Tauroselcholic acid (SeHCat)	528	536	535	523
^{18}F	[^{18}F]F-Flutemetamol (Vizamyl™)	107	126	171	452
^{68}Ga	[^{68}Ga]Ga-DOTATOC (Octreotide)			240	379
^{177}Lu	[^{177}Lu]Lu-Oxodotreotide				376
^{99m}Tc	[^{99m}Tc]Tc-Exametazime (HMPAO)	796	508	437	347
^{11}C	[^{11}C]C-Acetate	274	462	590	307
^{18}F	Na[^{18}F]F (Sodium Fluoride)	185	220	335	260
^{68}Ga	[^{68}Ga]Ga-PSMA		3	37	223

Table 55: Most-used radiopharmaceuticals in Sweden

[214] https://dosreg.ssm.se/Isotopstatistik/RegistreringPublik
The usual public names for radiopharmaceuticals were used instead of the official IUPAC nomenclature, for the sake of simplicity and readability.

The German radionuclides situation

Radiopharmaceuticals and radionuclides statistics are not directly collected by German statistics services. Nevertheless, a team from the "Klinik für Nuklearmedizin" (University of Regensburg) released an important publication[215] dealing with the practices of nuclear medicine in the country. They used in combination the statistics on the types of nuclear medicine procedures performed (Bone scintigraphy, myocardial perfusion…), the reimbursement paid by universal healthcare system (statutory or private health insurance), the German schedule of fees ("Einheitlicher Bewertungsmaßstab" – EBM, defining the reimbursement price of each medical procedure) and using data from public and private health players.

This team gathered data from the following national organizations to evaluate the number of procedures performed each year on the period 2009-2015:

- the German federal health report;
- the frequency statistics of the statutory health insurance for out-patients;
- the German medical association.

Details of radiopharmaceutical use in the private nuclear medicine sector for imaging application are provided in the table hereafter and cover roughly 80% of German diagnostic procedures.

Indication	Radiopharmaceutical	Number of procedures		
		2013	2014	2015
Thyroid imaging	[^{99m}Tc]Tc-pertechnetate	786 012	760 240	714 459
	Na[^{131}I]I (Sodium Iodide)	8 405	8 740	7 544
Bone imaging	[^{99m}Tc]Tc-MDP	361 954	358 839	344 452
	Na[^{18}F]F (Sodium Fluoride)	0	0	3
Heart imaging	[^{99m}Tc]Tc-sestamibi [^{99m}Tc]Tc-tetrofosmin	260 015	274 250	282 679
	[^{201}Tl]Tl-Thallous Chloride	4 758	3 560	2 710
	[^{99m}Tc]Tc-Red Blood Cell (RBC)	4 114	2 956	2 780
Renal imaging	[^{99m}Tc]Tc-Mertiatide (MAG3)	31 152	31 707	30 833
	[^{99m}Tc]Tc-Succimer (DMSA) [^{99m}Tc]Tc-pentetate (DTPA)	1 287	1 134	1 014
	[^{123}I]-Iodohippurate (OIH)	304	212	148
	[^{51}Cr]Cr-Edetate (EDTA)	0	2	1
Pulmonary imaging	[^{99m}Tc]Tc-Human Albumin (Macroaggregate)	10 193	11 081	11 524
	[^{99m}Tc]Tc-Technegas	4 713	5 562	6 004
	[^{81m}Kr]-Kr (gas)	934	958	1 017

[215] Nuklearmedizin in Deutschland - Aktualisierte Kennzahlen und Trends aus offiziellen Statistiken Dirk Hellwig; Jörg Marienhagen; Karin Menhart; Jirka Grosse - Klinik für Nuklearmedizin, Universitätsklinikum Regensburg, Regensburg - Nuklearmedizin 2017; 56(02): 55-68
DOI: 10.3413/Nukmed-0880-17-02

Indication	Radiopharmaceutical	Number of procedures		
		2013	2014	2015
Brain imaging	[^{99m}Tc]Tc-Bicisate (ECD) [^{99m}Tc]Tc-Exametazime (HMPAO)	1 371	1 217	1 145
	[^{99m}Tc]Tc-pentetate (DTPA)	16	21	30
	[^{123}I]I-Ioflupane (DATscan®)	8 636	9 315	10 074
	[^{111}In]In-pentetate (DTPA)	8	4	7
Lymphatic system	[^{99m}Tc]Tc-Human Albumin (Nanocolloids)	5 261	5 468	5 541
Tumours detection	[^{99m}Tc]Tc-marked tumour ligands	1 954	2 461	2 926
	[^{123}I]I-Iobenguane (MIBG)	391	372	395
	[^{111}In]In-Pentetreotide (Octreoscan®)	1 624	1 562	1 470
	[^{68}Ga]Ga-Citrate	2	3	3
	[^{111}In]In-Chloride	1	1	0
Immuno-scintigraphy	[^{99m}Tc]Tc-marked antibodies	2 442	2 091	1 878
Liver imaging	[^{99m}Tc]Tc-sulfur colloid (SC)	50	43	40
	[^{99m}Tc]Tc-Disofenin (DISIDA) [^{99m}Tc]Tc-Mebrofenin (Br-IDA)	121	98	87
Gastro-intestinal imaging	*Various RP based on ^{99m}Tc*	358	373	405
	[^{75}Se]Se-Tauroselcholic acid (SeHCat)	19	14	29
Haematology	[^{111}In]In-Oxyquinoline (Oxine)	38	35	29
	Na[^{51}Cr]Cr (Sodium Chromate)	5	0	0
	Total	1 496 138	1 482 319	1 429 227

Table 56: Imaging procedures performed in Germany on the period 2013-2015, in the private nuclear medicine sector – Source: see footnote

In the absence of detailed data for the public sector, it is assumed that it follows the same trends regarding the use of imaging radionuclides, with the exception of PET imaging which is much more developed in the public sector (~10% of public sector nuclear medicine imaging).

During the period, PET imaging only represented a small share of nuclear medicine procedures in Germany as compared to others EU countries, because of limited reimbursement mechanisms.

Due to country specificities, thyroid examinations and treatment are high in Germany. Thyroid treatments represented almost 90% of radionuclide use in therapeutic applications in 2015.

Some radionuclides which appeared only recently cannot be found in these statistics, such as ^{177}Lu.

	Radiopharmaceuticals	2013	2014	2015
Therapy	Na[^{131}I]I (Sodium Iodide)	17 846	17 320	16 138
	[^{153}Sm]Sm-Lexidronam (EDTMP)	274	245	302
	[^{131}I]I-Iobenguane (MIBG)	0	1	16
	RP based on ^{90}Y	23	22	22
	[^{223}Ra]Ra-Dichloride (Xofigo©)	0	126	1 938
Radio-synovectomy	[^{90}Y]Y-Citrate	17 843	18 573	19 330
	[^{186}Re]Re-Sulfide	11 585	11 744	11 605
	[^{169}Er]Er-Citrate	32 043	30 959	30 596
	Total	**79 614**	**78 990**	**79 947**

Table 57: Therapeutic procedures performed in the Germany on the period 2013-2015, in the private nuclear medicine sector - Source: see footnote

The Dutch radionuclides situation

In the Netherlands, RIVM (Rijksinstituut voor Volksgezondheid en Milieu – Health and Environment Ministry) publishes on a yearly basis a report focusing on Nuclear Medicine use in the country. Statistics regarding the use of radionuclides are not published on a yearly basis (no figures given in the 2019 & 2018 editions), but the report "Production and use of medical radio-isotopes in the Netherlands" includes an estimate of Dutch reactor-produced radionuclide use.

RN	Use	Procedures per year	Trend
^{99m}Tc	Diagnostic	220 000	Slight increase
Various	*PET Diagnostic*	*130 000*	/
^{82}Rb	Diagnostic	4200	increase
^{131}I	Therapy	1846	Slight increase
^{192}Ir	Brachytherapy	1 724	Stable
^{223}Ra	Pain management	1 100	Stable[216]
^{125}I	Brachytherapy	>1 000	Stable
^{177}Lu	Therapy	670	Large increase
^{90}Y	Therapy	225	Increase
^{153}Sm	Therapy	120	Stable
^{51}Cr	Diagnostic	100	Stable
^{188}Re	Therapy	100	Potential increase
^{166}Ho	Therapy	40	Increase
^{32}P	Therapy	22	Stable
^{89}Sr	Pain management	22	Decrease
^{169}Er	Pain management	10-15	Stable
^{186}Re	Therapy	10-15	Stable
^{133}Xe	Diagnostic	Unknown	-

Table 58: RIVM statistics on radionuclide use in Netherlands

No detailed statistics are provided for cyclotron-produced radionuclides, which represent roughly 130 000 procedures per year in Netherlands.

[216] Large increase is expected on the period 2017-2019, until reaching a stable value

D. Japanese industrial use of sealed radionuclides sources

The example of Japan can also be used to assess the most-used sealed sources radionuclides. The table below from the Japan RadioIsotopes Association (JRIA) gives the quantities supplied per year of each radionuclide[217], both in terms of MBq and pieces. It must be noted that the medical radionuclides used in brachytherapy are included in the table.

年度 Year / 核種 Nuclide	2014		2015		2016		2017		2018	
	数量 Activity (MBq)	個数 Piece	数量 Activity (MBq)	個数 Piece	数量 Activity (MBq)	個数 Piece	数量 Activity (MBq)	個数 Piece	数量 Activity (MBq)	個数 Piece
^{3}H Target	-	-	-	-	-	-	-	-	-	-
^{22}Na	2,178	21	57	16	1,508	10	76	21	1,547	16
^{55}Fe	3,857	8	37	1	37	1	3,700	1	-	-
^{57}Co	26,405	53	34,271	49	33,200	62	24,264	45	28,631	52
^{60}Co**	88,896,969,726	720	87,472,767,749	755	112,265,961,551	1,014	72,171,288,303	816	102,660,216,513	788
^{63}Ni	407,000	1,100	777,000	2,100	740,000	2,000	667,850	1,805	740,000	2,000
^{68}Ge	41,497	403	40,924	448	38,772	437	34,087	428	37,936	447
^{85}Kr	799,660	53	1,317,940	83	2,509,350	117	3,108,750	202	3,286,340	195
^{90}Sr	8,225	19	781	16	4,446	18	11,909	84	8,529	29
^{119m}Sn	-	-	740	2	555	1	740	2	740	1
^{125}I	2,680,782	210,916	3,060,447	242,233	2,808,093	223,422	2,537,082	200,961	2,476,129	197,704
^{137}Cs	141,948	271	11,921,384	260	3,553,124	315	3,349,725	226	3,076,679	168
^{147}Pm	555,185	42	299,185	26	373,730	26	735,675	61	506,960	42
^{153}Gd	-	-	18,500	2	-	-	-	-	-	-
^{169}Yb	1,110,000	3	1,110,000	3	1,110,000	3	1,110,000	3	1,110,000	3
^{192}Ir	624,557,820	1,697	668,256,300	1,813	684,869,300	1,856	691,255,240	1,853	708,280,420	1,904
^{198}Au	112,295	607	124,320	672	140,600	760	112,295	607	138,010	746
^{241}Am	166,783	5,113	148,500	6,208	37,925	8,250	203,646	4,436	111,478	8,049
^{241}Am+Be	-	-	-	-	185,000	1	-	-	-	-
^{252}Cf	12,681	371	2,149	457	16,506	504	3,273	373	635	352
その他 Others	20,261	15	1,985	25	1,656	36	2,416	31	2,383	33
合　計 Total	89,527,616,303	221,412	88,159,882,270	255,169	112,962,385,353	238,833	72,874,449,031	211,955	103,380,022,930	212,529

Figure 65: Amounts of major sealed radioisotopes supplied in fiscal years 2014-2018 (Source JRIA)

Based on 2018 supply statistics, the most-used sealed sources radionuclides are ^{192}Ir, ^{241}Am, ^{63}Ni, ^{60}Co. No major evolution can be seen over the years for the most widely used radionuclides.

The long half-life on some radionuclides drastically limits the need for regular supply (e.g. ^{137}Cs), thus it is also important to directly assess the number of sealed sources in use in the industry. The following table lists on Dec 31st, 2017 the different gamma-ray sealed sources in use in the Japanese industry and their different applications.

[217] https://www.jrias.or.jp/e/cat03/

機器 Appa-ratus / 核種 Nuclides	総数 Total	構成比 (Ratio%)	非破壊検査装置 Radio-graphy	厚さ計 Thickness Gauges	レベル計 Level Gauges	密度計 Density Gauges	水分計 Moisture Gauges	蛍光X線分析装置 X-ray Fluorescence Spectrometer	スラブ位置検出器 Slab Position Detector	ガスクロマトグラフ Gas Chromato-graph	硫黄分析計 Sulfur Meters	たばこ量目制御装置 Cigarette Weight controller	静電除去装置 Electric Static Eliminator	ガス検知器 Gas Detector	その他 Others
総数 Total	**30,800**	**100%**	**985**	**2,475**	**1,672**	**218**	**71**	**44**	**31**	**731**	**76**	**0**	**9**	**9**	**24,479**
^{3}H	7,117	23.1	–	–	–	–	–	–	–	8	–	–	–	–	7,109
^{55}Fe	165	0.5	–	4	–	–	–	25	–	–	–	–	–	–	136
^{57}Co	264	0.9	–	–	–	–	–	–	–	–	–	–	–	–	264
^{60}Co	1,029	3.3	130	–	401	1	–	–	20	–	–	–	–	–	477
^{63}Ni	783	2.5	–	–	–	–	–	–	–	723	–	–	–	9	51
^{68}Ge	103	0.3	–	–	–	–	–	–	–	–	–	–	–	–	103
^{85}Kr	11,138	36.2	–	1,271	–	–	–	–	–	–	–	–	–	–	9,867
^{90}Sr	127	0.4	–	126	–	1	–	–	–	–	–	–	–	–	–
^{119m}Sn	76	0.2	–	–	–	–	–	–	–	–	–	–	–	–	76
^{137}Cs	2,268	7.4	20	285	1,271	128	–	–	11	–	–	–	–	–	553
^{147}Pm	364	1.2	–	190	–	–	–	–	–	–	–	–	–	–	174
^{153}Gd	2	0.0	–	–	–	–	–	–	–	–	–	–	–	–	2
^{170}Tm	2	0.0	2	–	–	–	–	–	–	–	–	–	–	–	–
^{192}Ir	748	2.4	748	–	–	–	–	–	–	–	–	–	–	–	–
^{204}Tl	2	0.0	–	2	–	–	–	–	–	–	–	–	–	–	–
^{210}Po	14	0.0	–	–	–	–	–	–	–	–	–	–	5	–	9
^{241}Am	1,135	3.7	2	568	–	88	2	5	–	–	76	–	–	–	394
$^{241}Am/Be$	59	0.2	–	–	–	–	59	–	–	–	–	–	–	–	–
^{252}Cf	7	0.0	–	–	–	–	7	–	–	–	–	–	–	–	–
Others	5,397	17.5	83	29	–	–	3	14	–	–	–	–	4	–	5,264

Figure 66: Number of gamma-ray sources in use in the Industry in Japan in 2017 – Source JRIA

In addition to the previous radionuclides identified, ^{85}Kr (for thickness gauges) and ^{137}Cs (for level, density and thickness gauges) are also widely used.

E. Technology Readiness Level (TRL)

The following definitions are coming from the European Commission Horizon 2020 programme – General Annexes (https://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2018-2020/annexes/h2020-wp1820-annex-g-trl_en.pdf).

Where a topic description refers to a TRL, the following definitions apply, unless otherwise specified:

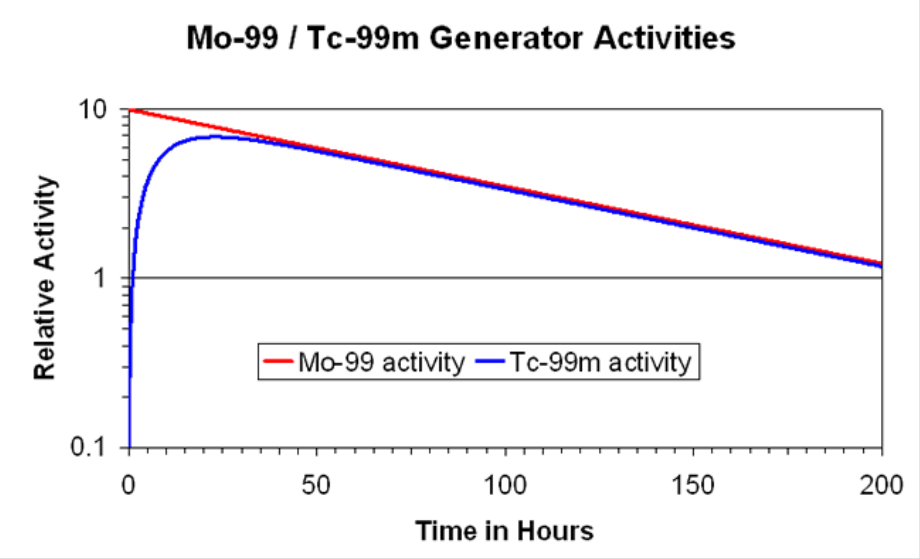
TRL 1	Basic principles observed
TRL 2	Technology concept formulated
TRL 3	Experimental proof of concept
TRL 4	Technology validated in lab
TRL 5	Technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies)
TRL 6	Technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies)
TRL 7	System prototype demonstration in operational environment
TRL 8	System complete and qualified
TRL 9	Actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space)

F. Principle of radionuclide generators

The content of this annex is an **extract from the IAEA online information resource of Human Health Campus – Radiopharmacy section**[218].

Radionuclide generators are made possible by the occurrence of radioactive decays where the daughter is also radioactive. Commonly a radioactive decay proceeds from a radioactive parent to a daughter that is stable. For example, when ^{32}P decays by beta emission the daughter is ^{32}S, which is not radioactive. In some decays however the daughter is itself radioactive and will undergo a decay process. There are many examples of this type of situation, and in some cases, useful generators can be constructed. In general, the generators will allow isolation and utilization of the radioactive daughter.

A **radionuclide generator** (these are sometimes referred to as "cows") will contain a long-lived radionuclide (also called "parent"), which then decays into a short-lived radionuclide (also known as "daughter") of interest. There are several useful isotopes that can be obtained from generator systems that have applications in medical diagnosis (imaging) and therapy as well as applications in radionuclide tracer work. There are generally two types of parent-daughter generator systems. The first one is "transient equilibrium generator" where the parent radionuclide half-life is somewhat greater than the daughter's. For example, the basic concept of the $^{99}Mo/^{99m}Tc$ generator relies on the availability of a relatively long-lived parent radionuclide that decays to a relatively short-lived daughter radionuclide that has useful physical and decay properties.



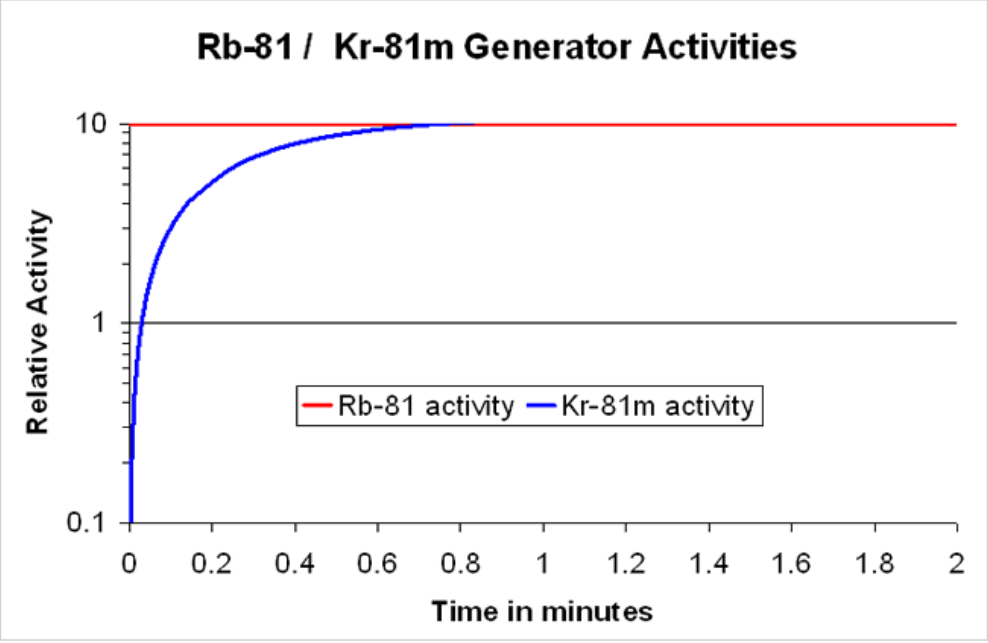
Transient equilibrium in the ^{99}Mo / ^{99m}Tc generator.

[218] https://humanhealth.iaea.org/HHW/Radiopharmacy/VirRad/Eluting_the_Generator/Generator_Module/Principles_of_radionuclide_generators/index.html

In a generator the parent is adsorbed on a suitable material; whereas the daughter will have different physical and chemical properties and can be eluted alone from the parent-daughter mixture. Although the $^{99}Mo \rightarrow {}^{99m}Tc$ radionuclide generator is the most common and best-known radionuclide generator, there are a variety of other examples of generators that fit this description.

The daughter radionuclide is a different element than the parent and will therefore often be in a quite different chemical form than the parent. With this difference in chemical characteristics between parent and daughter radionuclides, the latter can usually be separated by an elution method (this process is commonly called "milking" the generator or "cow"). The concept of "transient equilibrium" is described in equilibrium concepts and equations (This site is not yet available) but briefly we find that the daughter radionuclide after some time has passed will grow to a maximum and then appear to have a half-life that parallels the parent. Once the activity of the daughter is eluted there is a growth of the daughter until it again reaches a maximum and is again in equilibrium with the parent. This elution and regrowth can be continued as long as there are useful amounts of the parent radionuclide available. Elution may be performed before equilibrium is reached, and the amount of daughter activity eluted will depend on the time elapsed since the last elution.

Another type of generator is called the "secular equilibrium generator"; where the half-life of the parent is much longer than the half-live of the daughter. The parent will not decay noticeably during many daughter half-lives. This situation is called "secular equilibrium".



Secular equilibrium in the $^{81}Rb / {}^{81m}Kr$ generator.

This example of a secular equilibrium generator has the parent / daughter system $^{81}Rb \rightarrow {}^{81m}Kr$ (the rubidium / krypton generator) where the parent ^{81}Rb has a $T_{1/2}$ = 4.58 hours and the daughter ^{81m}Kr has a $T_{1/2}$ = 13 seconds. Like the transient equilibrium generator, the rate of daughter production initially is greater than its rate of decay and the daughter activity will continue to increase until it reaches a state where the rate of production equals the rate of decay. At this point the daughter appears to decay with the parent half-life. There are a wide variety of generator systems that have been developed or proposed as shown in GEN-11 but very few have been widely available due to the availability of the parent radionuclides and the technical complexity of most separation techniques.

G. US public support to radionuclides supply chain developments[219]

Legal frame

The American Medical Isotopes Production Act (AMIPA) legislation contained in the National Defense Authorization Act for Fiscal Year 2013, required the Secretary of Energy to establish a technology-neutral program to provide assistance to commercial entities to accelerate production of ^{99}Mo (aimed at ensuring a reliable domestic supply of the isotope ^{99}Mo) used to supply the medical diagnostic isotope ^{99m}Tc in the United States without the use of highly enriched uranium (HEU). This Act also called for an annual review of the NNSA 99Mo program by the NSAC. The National Nuclear Security Administration (NNSA) was given the responsibility for development of this program in 2009. Following an NNSA reorganization, the 99Mo program is now within NNSA's Office of Material Management and Minimization (NNSA-M^3).

The NNSA objective is NNSA is to bring online two U.S. producers, each capable of producing 3000 6-day Ci/week of ^{99}Mo, which corresponds to the US consumption (5000 6-day Ci/week, plus a reserve margin).

Status of the projects publicly supported

Besides local support (tax exemptions, land…), the selected projects are supported at the federal level by, as the case may be:

- "cooperative" agreements,
- support of US National laboratories,
- Uranium Lease and Take-Back agreements,
- the 10 US$/dose "FCR add-on" for non-HEU produced ^{99}Mo.

The next tables list the status of the different projects and the extent to which they are supported.

[219] Report to the Nuclear Science Advisory Committee. Annual Assessment of the NNSA-Material Management and Minimization (M3) 99Mo Program. February 24, 2020

					US FEDERAL SUPPORT		
NNSA/DOE AWARDS	**Company**	**Technology/Project**	**Time-to-market**	**Funding**	**DOE/NNSA support through direct Cooperative Agreements**	**DOE/NNSA support through National labs**	**DOE/NNSA support through Uranium Lease & Take back agreements**
New Funding Opportunity Announcement 2020 ongoing							
LAST AWARDS 2018-2019 (15 MUS$ each)	NorthStar (Beloit, WI)	LEU(n,γ)^{99}Mo irradiated in MURR Processing Facility in Beloit Extension of processing (enriched 98Mo) Low specific activity -> RADIOGENIX generator	Operating	unknown	Total : 65 MUS$	Since 2012, NNSA has provided over $100 million in non-proprietary technical support at the national laboratories to the 10 companies listed to accelerate the development of of a diverse set of Mo-99 production technologies NNSA/DOE appropriations in FY2019 and FY2020 : 25 MUS$ in total (see detailed table)	
		^{100}Mo(γ,n)^{99}Mo in Rhodotrons® (initially LINAC) Low specific activity -> RADIOGENIX generator	First 2 Rhodotron to be on-line in 2021, 6 other machines to follow. Production from 2022 ?	unknown			
	SHINE (Janesville, WI)	LEU(n,γ)99Mo in DT accelerator/neutron generator irradiating uranyl sulfate solution Online processing	5-day successful test of accelerator in Building 1 Janesville, WI (2019) Construction ongoing NRC operating licence to get. Forecast : 2022	Over 300 MUS$ raised to date (2019). AXA XL Insurance covering the commissioning and output of the facility (03/2020)	Total 40 MUS$		
	Northwest Medical Isotopes (Columbia, MO)	LEU(n,g)^{99}Mo Irradiation in Universities reactor network (targets : LEU microspheres) Radioisotope production facility (RPF) : Target fabrication, ^{99}Mo production, and uranium recycle and recovery (with Polish partners)	Complete RPF construction and initiate cold and hot startup by mid-2021 in concert with receiving NRC operating license	unknown $7million in tax abatments	15 MUS$?		
	NIOWAVE Inc. (Lansing, MI)	LINAC on uranium target ^{238}U(e$^-$,γ)^{99}Mo, but also ^{226}Ra(e$^-$,γ)^{225}Ac and other isotopes (priority to ^{99}Mo not obvious)	In 2021, β-emitters at 10 Ci/week		15 MUS$?		
Other companies supported	BWX Technologies						
	Coqui Radiopharmaceuticals						
	Global Medical Isotopes Systems						
	Magneto-Intertial Fusion Technologies						
	Eden Radioisotopes						
	Flibe Energy						

Table 59: Status of the publicly supported US Mo-99 production technologies (as of 2019)

None of the projects has yet attained the industrial production, except the NorthStar one based on irradiation in MURR (Missouri University Research Reactor).

Concerning the development of the technologies, the support of the US National labs is decisive, as can be seen from the next table.

Laboratory	Partner	Technology Area	Specific Support Objective (as of 2016)
ANL	SHINE	Separations	**Separation process development**
			Sorbent-based recovery of Mo
			Mo purification
			Cleanup of uranyl sulfate target solution
			Demonstration of Mo separation efficiency
			>97% recovery from uranyl sulfate solution
			High uranium recovery
			Production of demo product
			Demo runs have produced curie-quantities of Mo-99
			Product purity specification met for I-131, Ru-103, Te-132, and Sr-89/90 in 3 of 4 runs
ANL	SHINE	Irradiation physics	**Radiation stability and radiolysis effects**
			Thermal hydraulic effects of radiolytic gas formation
ANL/PNNL	SHINE		**Sample off-gas for volatile fission products (Xe, Kr, I)**
ANL/ORNL	NorthStar	Target design	**Optimization of sintered Mo disks for density and dissolution kinetics**
ANL	NorthStar	Irradiation	**Demonstrate accelerator-based production of Mo-99**
			100Mo(γ,n)99Mo reaction
			Radionuclide inventory
			Production modeling
ANL	NorthStar	Chemical processing	**Chemical processing of irradiated targets**
			Front-end purification of irradiated Mo
			Recycle process to recover enriched Mo
			Large-scale dissolution process demonstration
			Support to development and the FDA review of RadioGenix Mo-99 dispensing unit
LANL/ANL	NorthStar	Target design	**Target design and irradiation testing**
			Target thermal performance
			Subsystem development and testing
			Beam diagnostics
			Beam position monitor
			Target He cooling system
			Control systems
			Licensing of IP
LANL	NorthStar	Target design	**Production facility design support**
			Local target shielding
			Beam line design
			Target removal and conveyance
			Support to production and thermal tests at ANL
			Licensing of IP
LANL	SHINE	Analysis of nuclear system transient response Irradiation support Separations chemistry	**Simulation and modeling of accelerator-driven subcritical solution reactor** **Irradiations and separations chemistry**
			Uranium measurement and accounting methods
			Modeling of reaction vessel cooling systems
ORNL	GE Hitachi Nuclear Energy	Neutron capture technology	**Irradiation of Mo targets in HFIR**
			Assess impurities in Mo samples
			Explore methods to mitigate Mo target oxidation and sublimation. This included silicon coating using chemical vapor deposition.
ORNL	NorthStar Medical Radioisotopes	Accelerator target and production process	**Understand the requirements for and fabrication of Mo target disks**
			Develop a powder metallurgy process for fabricating accelerator target disks with a density of ≥90%
			Identify parameters that affect dissolution rate of the target disks
			Assist in developing recycle process for isotopically enriched Mo.
ORNL	Morgridge Institute for Research and SHINE	Accelerator technology with LEU fission	**Evaluation of candidate materials for the solution vessel**
			Irradiation testing
			Corrosion testing
			Stress-corrosion testing
			Flow-induced corrosion testing
			Gamma-induced corrosion testing
ORNL (Y-12/ANL)		High-density LEU target technology	**Testing of various target designs:**
			Acid and electrochemical dissolution concepts
			Planning was completed for HFIR irradiations but targets were not qualified for irradiation at the time the project ended.
SRNL		Tritium	**Thermal Cycling Absorption Process (TCAP)**
			Tritium purification system (TPS)
SRNL	SHINE	Tritium systems	**Design and fabrication of prototype cold-test TCAP unit**
			Design of TPS for transfer to architectural and engineering firm
			TPS automation studies
Y-12		High-density LEU target technology	**Testing of various target designs:**
			LEU-Foil Target Fabrication
			Nickel capsule with uranium foil and annular target and uranium foil
Y-12	SHINE	Technical consultation	
Y-12		Uranium Lease and Take-Back Program	**Support to the implementation of the supply portion of the Uranium Lease and Take-Back Program**

Table 60: US National Laboratories support to Mo-99 production technologies (Molybdenum-99 for Medical Imaging, NAS, 2016)

This table does not address the DOE actions for producing rarer isotopes (including the ORNL actions for enrichment, namely the future SIPF, evaluated to 150-200 MUS$), using the large US research installations (reactors, accelerators) or universities.

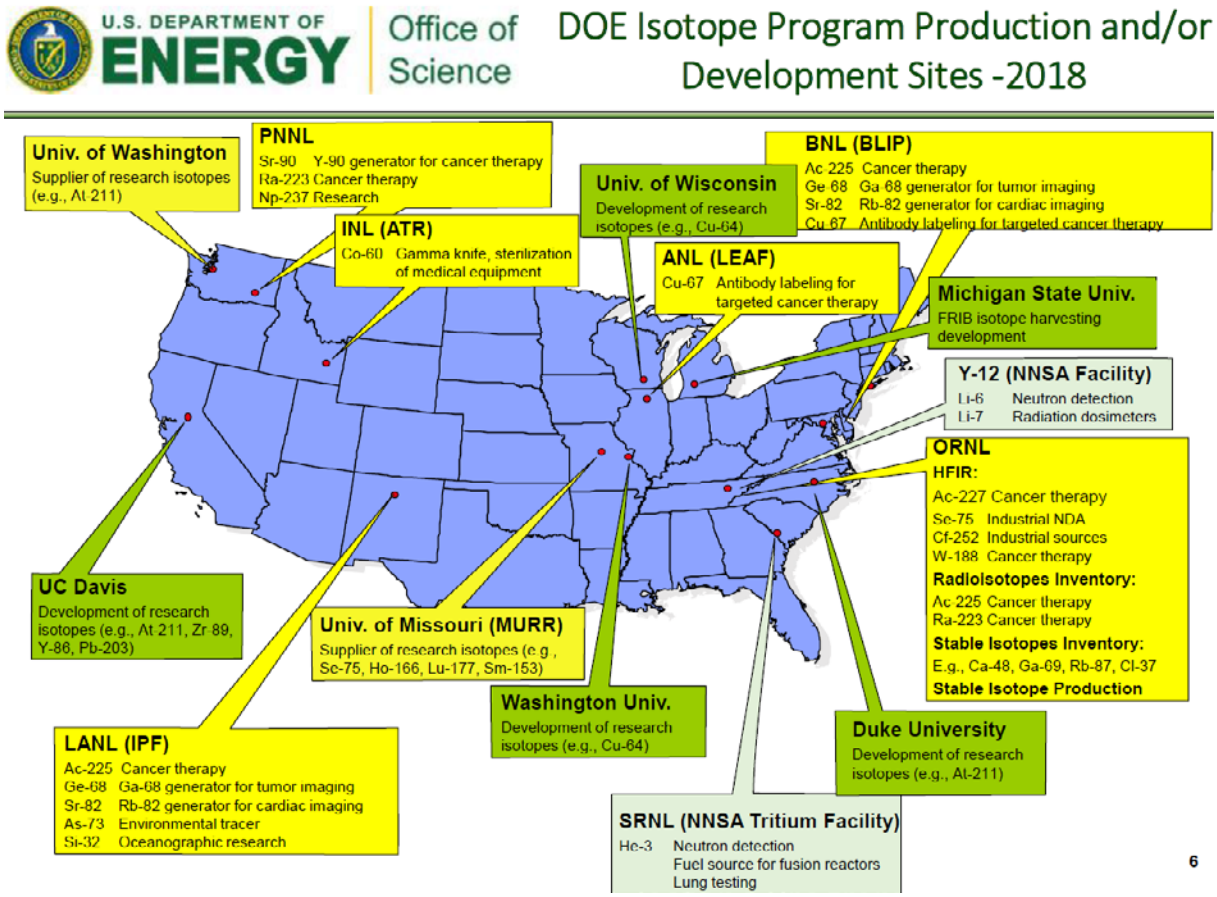


Figure 67: DOE Isotopes Program production and development sites

NSAC recommendations (Feb, 2020)[220]

NSAC acknowledges that longer term OECD projections point to the possibility of a significant ^{99}Mo overcapacity internationally as additional facilities come on-line. Such an overcapacity could threaten the sustained economic viability of the fledgling domestic (US) projects. NSAC also notes that "almost all projects, including conventional technologies and those supported by NNSA, have reported delays with variable impact on the current and future ^{99}Mo supply".

As of Feb,2020, the two main NSAC recommendations were:

[220] Report to the Nuclear Science Advisory Committee. Annual Assessment of the NNSA-Material Management and Minimization (M3) ^{99}Mo Program. February 24, 2020. Report of the NSAC 99Mo Subcommittee

Recommendation 1

The limitations of the ULTB[221] program continues to be one of the biggest risks to the program's success. The ULTB contract templates should be reviewed and revised as necessary; in particular, with respect to reducing the continuing significant uncertainties in the Take Back aspects of the DOE-EM (Environmental Management) program. The results of this review should be presented to the NSAC 99Mo Subcommittee at the next program assessment.

Recommendation 2

The NNSA stated during this (Feb, 2020) review that a program objective was to have at least two US producers, each capable of producing 3000 6-day Ci/week of ^{99}Mo. The third FOA[222] for this program is anticipated in 2020. After 10 years of significant investment in this program, the NNSA should focus their strategy on prioritizing future awards such that time-to-market, consistent with the stated objective, is considered as the most important review criteria. This strategy should be reflected in the approach to allocation of CA ("Cooperative agreements") funding and national laboratory resources.

Conclusions

The USA have continuously developed, from 2009 onwards, an ambitious self-reliance program, publicly heavily funded, for developing domestic production of ^{99}Mo, and for organising at the national level the production of stable and radioactive isotopes necessary to the Nuclear Medicine. NSAC advocates now for focusing the DOE/NNSA awards on the most promising projects, those with the shorter time-to-market.

The US example shows also that a decade is a very minimum timeframe for commencing to see the first results of such programs.

July 2020 NNSA update: The third FOA has been issued in July 2020. In a coherent manner with the NSAC recommendations above, criteria for the awards will now be focused on the ability to achieve Mo-99 production of at least 1,500 six-day curies per week by Dec. 31, 2023, and the capacity to increase the production to 3,000 six-day curies per week.

[221] ULTB: Uranium Lease and Take-Back program. The AMIPA Act requires DOE to retain responsibility for the final disposition of spent nuclear fuel (SNF) and to take title to and be responsible for the final disposition of radioactive waste that is created by the irradiation, processing, or purification of the leased uranium for which the (DOE) Secretary determines the producer does not have access to a disposal path. The Act also requires DOE to recover the costs associated with the ULTB Program. The limitations referred to above lie with the difficulties to set up contractual clauses concerning namely the costs for the contractors for transferring to DOE the responsibility of Greater-than-C category (GTCC) radioactive waste.
[222] FOA: Funding Opportunity Announcement

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