

MEDICAL USES OF NUCLEAR TECHNOLOGY ROLE, CHALLENGES & PERSPECTIVES



FACTS

9 Mn

Patients in Europe who benefit from nuclear medicine every year

1.5 Mn

Radiotherapy procedures for cancer therapy in Europe every year

100

Different nuclear medicine procedures approved by health regulators

4 out of 6

Research reactors providing 95% of the world's Mo-99 or Lu-177 production, are based in the EU

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EXECUTIVE SUMMARY

Overview

Nuclear energy plays an essential role in the European Union's (EU) energy mix – particularly when it comes to complying with the Paris Agreement signed during the 21 Conference of the Parties (COP21) and its commitment of decarbonising the bloc's electricity system by 2050. Currently, thanks to 106 nuclear reactors operating in 13 EU Member States, 26% of the electricity produced in the EU comes from nuclear energy which remains the largest source of low-carbon electricity (almost 50%). Apart from being a stable source of low-carbon electricity, nuclear technology offers many other essential features as it can provide clean water through desalination and produce district heating by using direct or waste heat from nuclear power plants. It can also be used for industrial processes such as the chemicals, paper and pulp industries and for agricultural applications.

Nuclear technology also plays a significant role in the medical sector. Medical applications, which include production of medical isotopes and the development of therapeutic and diagnostic procedures, help save thousands of lives each day. Thanks to nuclear applications, Europe's citizens have access to life saving treatments and diagnostic technologies. Every year, more than 9 million patients in Europe benefit from nuclear medicine in the diagnosis and treatment of illnesses such as cancer, cardiovascular or neurological disorders.

Nuclear technology's contribution to saving lives in Europe is significant, partly thanks to the fact that several nuclear facilities, which provide a continuous supply of required medical products, are based in the EU. For example, medical radioisotopes are produced in several EU based nuclear research reactors, such as: HFR (Petten in the Netherlands), BR-2 (Mol in Belgium), MARIA (Świerk in Poland), FRM-2 (Garching in Germany) or LVR-15 (Rez in the Czech Republic). Investments are also being made in new reactors which will replace ageing ones, including, amongst others, CEA in Cadarache, France, (Jules Horowitz Reactor - JHR) and PALLAS (Petten in the Netherlands) to ensure that European demand can be met in the years to come. This is key as future demand for nuclear medicine will grow significantly as more and more highly targeted therapeutic medicines reach the market. The global nuclear medicine business in 2019 was estimated at €4 billion and is expected to grow to €7-10 billion by 2024. The therapy part of the overall business is poised to grow from a 12% to a 31% share of the total value¹ within the same timeframe.

The market growth over the next decade will predominantly come from Positron Emission Tomography (PET) and Therapy with a sustained growth in Single-Photon Emission Computerized Tomography (SPECT) resulting in the need to ensure resilience in the Mo99 (SPECT) infrastructure but also PET/Therapy which has vast R&D and advanced stage clinical trial pipeline.

The EU is involved in the nuclear medicine sector and its developments. The nuclear medicine sector collaborates with the EU through many projects, which seek to identify opportunities and challenges for the use and development of ionising radiation and in order to discuss potential solutions to address challenges in areas where the EU can add value. In one of the recent documents on this topic, the Council of the EU has highlighted that "nuclear and radiological technologies play an important role outside the nuclear energy sector in vital areas, such as medicine, industry, research and environment, providing numerous benefits to the EU citizens"². In addition, it was underlined that "Euratom legislation requires that non-power use of nuclear and radiation technologies is appropriately justified, the radiation protection of the public, patients and staff is adequately optimised and that non-power radioactive waste and spent fuel are safely disposed". The document also mentioned the importance of "ensuring additional radioisotopes production capacity and launching or advancing projects for new production facilities, including research reactors and alternative technologies" as the "production of source materials for the supply chain of medical radioisotopes is important to increase the resilience of the European supply chain and to reduce the dependence on foreign actors".

¹ Nuclear Medicine Europe data.

² <https://data.consilium.europa.eu/doc/document/ST-9437-2019-INIT/en/pdf>
Council of the European Union (2019, 24 May), [Non-power nuclear and radiological technologies and applications-Adoption of Council Conclusions](#) (Item Note 9437/19)

In addition, the European Commission's SAMIRA (Strategic Agenda for Medical Ionising Radiation Applications) Action Plan³, adopted in February 2021, emphasises the importance of securing the supply of medical radioisotopes in the EU, in order to ensure that European patients reap their full benefits in battling cancer and other diseases. The action plan expresses directly that "there is significant scope for further action to secure and develop the radioisotope supply for the coming decades".

Challenges

The European nuclear medicine sector, while doing its best to provide Europeans with the required medical services, is currently facing a number of challenges. These may have a significant impact on its future role in the EU if no changes are implemented. A number of key issues must be addressed in order to maintain the edge that the EU enjoys today in this field globally, the current level of medical radioisotopes supply as well as to address the increasing demand which is foreseen in the future. These challenges roughly fall into two categories: supply chain investment needs and regulatory framework.

Supply chain investment needs

1. Insufficient funds for investment in new capacity which may have an impact on supplying demand in the years to come as well as the EU's dependence on reactors in other parts of the world.
2. Market failures – including disincentives to private investment, lack of harmonization which hinders the operation of the sector, as well as the ability to monitor and anticipate the need for public investment in order to help assure security of supply in the absence of commercial production.
3. Nuclear medicine supply chain challenges – including aging of research reactors (need for new investment and long-term operation).
4. Need for investment in – and implementation of – additional innovative solutions for the management of spent nuclear fuel and radioactive waste produced by research reactors, which is important for the future of nuclear technology in the EU and its perception by key stakeholders.
5. Production of some radioisotopes requires High-Assay Low Enriched Uranium (HALEU), which is currently delivered from limited stocks available in either the US or from Russia.

Regulatory framework

1. No clear level-playing field conditions for investment in nuclear technology at EU level.
2. Differences in approach towards internationally agreed policies by EU Member States.
3. A complicated regulatory environment across the 27 Member States which impacts innovation in this field.
4. Market access and reimbursement of nuclear medicine applications across different countries and the big variation in the age of nuclear medicine diagnostic equipment imposes a massive access inequality to European citizens according to where they live. Access to radiopharmaceuticals that are not currently licensed in certain Member States along with medicine regulations for each country can also increase inequalities between countries. For example, compassionate use of radiopharmaceuticals is easier in Germany than in France, therefore driving inequalities in access.
5. Highly radioactive irradiated targets have to be transported across different European countries. Closer coordination among the national licensing authorities for such transports should be part of the sustainable and diverse supply scenario for Europe.
6. In addition to these technical challenges, there is also the challenge of perception. Negative attitudes towards the nuclear sector (primarily power generation) in some EU Member States and the lack of education or misinformation have an impact on the future of nuclear medicine in the EU and the benefits it can offer to patients.

³ https://ec.europa.eu/energy/sites/default/files/swd_strategic_agenda_for_medical_ionising_radiation_applications_samira.pdf
European Commission (2021), COMMISSION STAFF WORKING DOCUMENT on a Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) (SWD(2021) 14 final)

Recommendations

Taking into account the challenges mentioned – which have to be addressed at EU level in order to ensure that the supply of medical isotopes produced using nuclear technology will be continued and, by doing so, will keep contributing to saving the lives of Europeans – FORATOM and Nuclear Medicine Europe recommend the following:

Supply chain investment needs

1. The EU should promote new research reactor capacity along with innovation in the sector and the design modification of the current fleet to enable the production of some radioisotopes like Co-60 or Lu-177.
2. The EU should reconsider reimbursement systems and levels for radiopharmaceutical products to ensure that irradiation sites are fully remunerated for the costs incurred.
3. The EU needs to develop a robust supply chain which goes beyond irradiation and includes the supply of target material and processing capabilities.
4. EU should reconsider and adapt clinical R&D of new radiopharmaceutical compounds as well as for application marketing authorisations or variations to authorized medical products.

Regulatory framework

1. The role of nuclear technology and its non-power applications should be better recognised and supported at EU level and relevant policies and legislation.
2. A quick implementation of the action identified in the SAMIRA Action plan 'Research roadmap for medical applications of ionising radiation technologies.
3. EU should support the implementation and use of Low Enriched Uranium for radioisotopes production (HEU – HALEU).
4. Market access, regulatory framework for the development of new medicines and reimbursement models for nuclear medicine applications should be homogenized across all Member States. The concept of an "equal access to treatment among EU citizens" should be promoted.
5. Renovate the nuclear medicine equipment especially in EU periphery countries in order to allow similar levels of diagnoses across the entire EU.
6. Regarding power applications, the EU should secure a level-playing field for the development of low-carbon technologies.
7. Nuclear should be included, amongst others, in the [EU NextGeneration Recovery Plan](#) & [Industrial Strategy](#).

The mentioned above challenges and recommendations are explained in detail in the position paper.

CONTEXT

The following position paper **“Medical Uses of Nuclear Technology – Role, Challenges & Perspectives”**, which has been prepared jointly by [FORATOM](#) and [Nuclear Medicine Europe](#), aims to present the full scope of how nuclear technology is being used in medicine, what its contribution at EU level is and what the current situation at EU and Member State level looks like. In addition, the position paper aims to show the main challenges that the nuclear medicine sector currently faces in the EU, what the potential risks of the current situation are and their potential effects. Lastly, the paper highlights a list of detailed policy recommendations of what could be done at EU level to ensure that a stable supply of nuclear medicine produced using nuclear technology can be guaranteed and maintained in the EU.

The position paper aims to fit into the currently ongoing discussions at EU level regarding health issues as nuclear radioisotopes are used for the diagnosis and treatment of many severe diseases, including cancer, which – as underlined by the European Commission – is the second leading cause of mortality in the EU. Therefore, it comes as no surprise that the current Commission decided to prioritise policy relating to the diagnosis and treatment of cancer during its 5-year term. Commission President Ursula von der Leyen keeps underlining the fact that cancer is one of her main priorities in the health domain. Her political guidelines refer to “a European plan to fight cancer, to support Member States in improving cancer control and care, to reduce the suffering caused by this disease and for Europe to take the lead in the fight against cancer”. In order to do so, a special program entitled “Europe Beating Cancer” has been announced and it focuses on four pillars: (1) prevention, (2) early diagnosis, (3) treatment, and (4) follow-up care. In addition, cancer is one of the European research and innovation missions and part of the Horizon Europe framework beginning in 2021. Nuclear technologies definitely play an important role in this undertaking. Also considering that the Euratom programme includes the non-power applications of nuclear technology (with priority given to nuclear medicine in the first 2 years of the work programme).

In early 2021, the Commission adopted the SAMIRA Action Plan, which focuses on securing the supply of medical radioisotopes in the EU, in order to ensure that European patients reap their full benefits in battling cancer and other diseases. The plan stresses that there is significant scope for further action to secure and develop radioisotope supply for the coming decades.

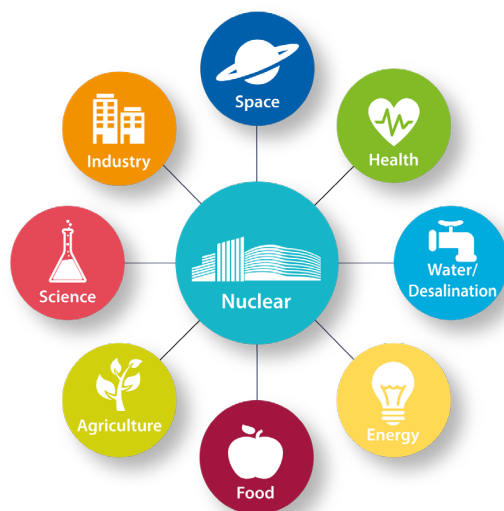
Finally, apart from the direct impact of nuclear technology on the EU’s health agenda, the nuclear medicine sector – among others, thanks to its scale – fits within other current EU policy files and can help the EU achieve various goals, which are explained later in the position paper.

VARIOUS USES OF NUCLEAR ENERGY

Nuclear energy plays an essential role in the EU's energy mix – particularly when it comes to complying with the COP (Conference of the Parties) 21 Paris Agreement commitment of decarbonising the bloc's electricity system by 2050. In its "[Clean Planet for all](#)" strategy, published on 28 November 2018, the Commission confirmed that nuclear will form the backbone of a carbon-free European power system, together with renewables. This announcement came just after the publication of the latest United Nations' Intergovernmental Panel on Climate Change (IPCC) report (Global Warming of 1.5°C) which also recognises that nuclear power is essential if the world is to keep global warming to below 1.5 degrees. According to one of the IPCC scenarios, a six-fold increase in global nuclear capacity is needed if we want to achieve our climate goals. Not only is nuclear low-carbon, but it also has one of the lowest total energy costs and goes hand in hand with variable renewable sources.

Currently, thanks to 106 nuclear reactors operating in 13 EU Member States, **26% of the electricity produced in the EU comes from nuclear energy, which remains the largest source of low-carbon electricity (almost 50%)⁴.**

What is important, apart from being a stable source of low-carbon electricity, is that nuclear technology offers many other essential features:



Currently nuclear energy

- can provide clean water through desalination,
- can produce district heating by using direct or waste heat from nuclear power plants,
- can be used for industrial processes such as the chemicals industry, paper and pulp,
- can be also used for agricultural applications.

In addition, in the future it could also

- help produce hydrogen for hard-to-decarbonise sectors (industry and transport),
- produce synthetic fuels that could be used in sectors such as aviation.

But nuclear technology is also playing a significant role in the medical sector. As highlighted in an [open letter](#) signed by the European nuclear industry's leaders in mid-2020, nuclear technologies play an indispensable role in the medical sector as they help diagnose and treat various severe diseases, such as different forms of cancer, heart conditions, dementia and movement disorders. Furthermore, new therapeutic applications of nuclear medicine can target and kill cancer cells, thanks to the radiation of medical isotopes, without the side effects⁵ of other traditional, non-targeted therapies. Treatments involving different forms of radiation can be carried out both externally (radiation therapy) or by targeted radionuclide therapy (or radioligand therapy).

The following chapters offer an in-depth analysis and summary of nuclear technology's role related to health issues and their treatment as well as an overview of the whole nuclear medicine sector.

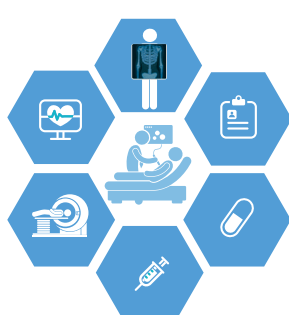
⁴https://ec.europa.eu/eurostat/statistics-explained/index.php/Electricity_production_consumption_and_market_overview
Eurostat (2020) [Electricity production, consumption and market overview](#)

⁵ Reference: Jackson et al. EJNMMI Radiopharmacy and Chemistry (2020) 5:24 <https://doi.org/10.1186/s41181-020-00110-z> Jackson, I.M. et al. (2020), [Use of 55 PET radiotracers under approval of a Radioactive Drug Research Committee \(RDRC\)](#). EJNMMI radiopharm. chem. 5, 24

NUCLEAR MEDICINE (RADIATION & RADIOISOTOPES)

Nuclear medicine is one of the key nuclear technology applications. Medical applications, which include production of medical isotopes and the development of therapeutic and diagnostic procedures, help save thousands of lives each day. Thanks to nuclear applications, Europe's citizens have access to life saving treatments and diagnostic technologies. Every year, more than 9 million patients in Europe benefit from nuclear medicine in the diagnosis and treatment of illnesses such as cancer, cardiovascular or neurological disorders. There are about 100 different nuclear medicine procedures approved by health regulators.

Medical isotopes which are used in nuclear medicine are produced in nuclear research reactors or using accelerators such as cyclotrons. These isotopes emit radiation which is employed to diagnose patients through imaging or as therapeutic drugs for treatment. Nuclear medicine – in particular radioligand therapy – helps to treat various medical conditions, such as cancer, by killing precisely targeted cancer cells in the human body. The European nuclear industry, including research facilities, is a leading supplier of radioisotopes, helping 30 million patients worldwide every year.



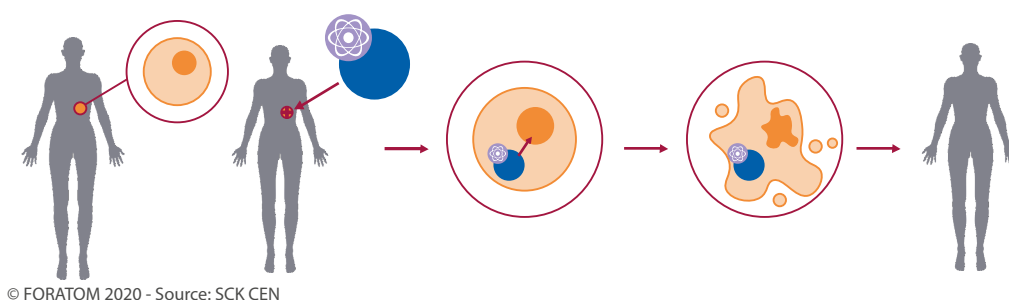
Radioisotopes

Radioisotopes - a radioactive form of elements, with unstable nuclei, which undergo radioactive decay to stable forms, emitting characteristic alpha, beta, or gamma radiation - are used frequently in medicine for diagnostic (identification) and therapeutic (treatment) purposes.

Treatment of cancer

The radioisotope is attached to a carrier molecule, which becomes a therapeutic radiopharmaceutical. It targets the tumour after being administered to the patient. Once the molecule is attached to the cancerous cell, the radioisotope irradiates it and eventually kills the tumour by disrupting its DNA.

Such a targeted approach has a clear benefit over external radiotherapy (irradiation) as it limits the damage to healthy tissue around the tumour.



Cancer treatment constitutes an important part of the entire nuclear medicine sector. More than 80% of all nuclear-medicine therapies are related to cancer treatment – and it is still growing steadily.

Radioisotopes

Nuclear medicine utilizes radioactive isotopes (called radioisotopes) which are atoms with unstable nuclei, thanks to which radiation is emitted. As far as the technicalities of nuclear medicine are concerned, nuclear medicine uses radiation to achieve two objectives:

- provide information via imaging procedures about selected human organs (verifying their function, early identification of possible diseases), which accounts for 90% of nuclear medicine procedures,
- treat diseased organs, accounting for 10% of nuclear medicine procedures (although this share is growing).

The most frequently used radioisotope is Technetium-99m (Tc-99m) and the most frequently used radioisotope in therapeutic procedures is iodine-131 (I-131). Compared with other parts of the world, **Europe is considered to be the second largest consumer of Tc-99m (20% of global consumption). As far as the production of Tc-99m is concerned, Europe is the largest producer (>60% of the global production).**

Tc-99m is produced through a process combining irradiation of uranium targets in nuclear research reactors which produce Molybdenum-99 (Mo-99) followed by extraction and purification of Mo-99 in dedicated facilities and, finally, production of Tc-99m generators. It is worth noting that the amount of Mo-99, and consequently Tc-99m, depends on a number of production research reactors operating in the EU – which is currently quite low and most of them are reaching the end of their operating licence. **Maintaining the current level of Mo-99 production will require new investment to avoid any severe disruption in this field.** Demand for Mo-99 is estimated at 9,500 6-day Ci-EOP (End of Production) per week. To ensure sufficient supply, production capacity must at least be equal to demand, plus an additional 35% of so-called Outage Reserve Capacity, which may be needed in case one of the production reactors encounter an unexpected outage. According to the available data, if there is not new investment in research reactors, over the next 5-10 years there will be a risk of disruption as the closure of current research reactors which have reached their maximum life will mean a significant loss in supply, particularly when taking into account the expected growth in consumption.

The market growth over the next decade will predominantly come from Positron Emission Tomography (PET) and Therapy with a sustained growth in Single Photon Emission Computed Tomography (SPECT) resulting in the need to ensure resilience in the Mo-99 (SPECT) infrastructure as well as PET/Therapy which has vast R&D and advanced stage clinical trials in the pipeline.

Diagnosis using radioisotopes

Nuclear medicine is a specialized field of medicine covering all aspects of the use of radioactive substances that are injected into people with the aim of diagnosing or treating a disease. **The vast majority of nuclear medicine procedures (about 90%) are today of diagnostic nature.** Imaging of tissues or organs can be obtained through the particular properties of radioactivity that produces highly energetic radiation (such as gamma rays). Radioactive substances concentrate in specific cells and tissues as a consequence of the grafting of radioactive atoms (radionuclides) to drugs that have the property to recognize and therefore remain, in these specific cells. In general, cells undertaking transformation, growing or dying, such as tumor cells or ischemic tissues in the heart, can easily be differentiated from normal neighboring cells, as their biology is altered. Special cameras able to detect the radiation that is emitted from these zones where the drug is concentrated provide accurate / images of this area. The physician can therefore easily evaluate the extension of the affected area, recognize the disease and provide a diagnosis.

As very small, infinitesimal quantities of radionuclides are used, there are no side effects due to the radioactivity, which has a very short life due to its physical half-life and biological clearance. Depending on the type of radiation, detection equipment must be adapted. Thus, SPECT or PET will be used depending on whether a hospital has a PET or SPECT camera, as well as whether it has the best radiopharmaceutical available for the particular indication. Imaging methods in nuclear medicine are ideal tools for evaluating the extension of a heart infarction, identifying and localizing tumors and metastases or estimating the degree of development of neurodegenerative diseases. They are now also used to follow the efficacy of a therapy. Due to its sensitivity, nuclear medicine detects very faint sources of radioactivity and is therefore ideal for early detection of very small lesions.

DIAGNOSIS & THERAPY

Nuclear Medicine for Your Health

Over the years, Nuclear Medicine became a technology of high significance in the **detection and diagnosis** of diseases of almost any kind and is now proposing additional solutions for **therapy**.

Left Side (Diagnostic/Imaging):

- Brain imaging
 - Stroke imaging
 - Epilepsy
 - Alzheimer's disease
 - Parkinson disease
- Leukaemia
- Non-Hodgkin Lymphoma
- Lung ventilation
- Lung perfusion imaging
- Whole body : primary tumours and metastases
- Liver imaging
- Liver cancer
- Gastro-intestinal absorption
- Neuroendocrine tumours
- Kidney diseases
- Adrenal imaging
- Bladder imaging
- Prostate cancer
- Infectious diseases

Right Side (Therapeutic/Treatment):

- Salivary glands and the lachrymal tract imaging
- Thyroid diseases
- Thyroid imaging
- Blood studies
- Cardiac diseases
- Breast cancer
- Spleen diseases - Biliary function
- Palliative treatment
- Bone imaging
- Bone metastases
- Cervix cancer
- Deep vein thrombosis
- Non-cancerous blood cell diseases treatments
- Radiosynovectomy - Polyarthritits (knee, hand, shoulder, hip)

NUCLEAR MEDICINE EUROPE
the industry association

To learn more about nuclear medicine animations, brochures and leaflets are available at : whatisnuclearmedicine.com

Therapy using medical isotopes

Another form of radioactivity is expressed by the emission of particles instead of gamma rays. These alpha or beta minus radiations destroy cells using strong local ionization and can therefore be used to kill unwanted, harmful cells. I-131 alone has been used in therapy since the early 50s and has no substitute to treat certain thyroid cancers. More recently, when based on the same principle as imaging agents, the radionuclides are being linked to vectors that bring them specifically to these areas. This simplified description of the process is the basis of vectorised or metabolic radiotherapy, in other words, of nuclear medicine for therapy. This efficient therapeutic technology is mainly used to cure cancer patients but also shows promise for some applications in the field of rheumatology.

In addition, targeted radionuclide therapy or radioligand therapy can also be used as palliative treatment, focusing on pain management. Patients receive a medical isotope that slows down the disease process, thereby reducing pain and improving quality of life. The radiation dose administered during therapy is much higher and of a different nature than the dose used for diagnostic procedures. In most of such cases the patient can be considered radioactive for a period of time and, depending on the country, s/he either needs to stay in a specific ward in the hospital or stay at home for a few days. The most used radioisotopes in radioligand therapy are lutetium-177 (Lu-177) or I-131.

Another possible therapy is brachytherapy. It is a procedure which uses temporary irradiation close to the area of disease by means of sealed radioactive sources, seeds, such as in prostate cancer. The radioactive source often used in the seeds is Iodine-125. Another important isotope produced in reactors is iridium-192 (Ir-192), which is used for brachytherapy.

Nuclear Medicines' radiation impact on health

It is important to underline that nuclear medicines, and radioligand therapies in particular, do not have a negative impact on patients' health or on the environment as their radiation level is very low and short-lived. In addition, the radiation doses and their placement are selected very carefully in order to avoid any impact on the surrounding and healthy cells.

Each time and for each patient:

- a treatment plan is precisely developed and agreed in advance,
- the used dose is precisely calculated,
- the target is well-known,
- the duration of the procedure is short.

The procedure itself does not cause any pain or harm as it is non-invasive.

EUROPEAN NUCLEAR MEDICINE SECTOR'S LANDSCAPE

Europe' competitive advantage in Nuclear Medicine

Nuclear technology's contribution to beating cancer in Europe is significant partly thanks to the fact that several nuclear facilities are based in the EU, providing a continuous supply of required products. For example, in the EU, medical radioisotopes are produced in several nuclear research reactors.

Many key facilities are located in the EU contributing significantly to the current level of medical radioisotope production, such as:

- **uranium research reactor fuel and medical isotope target manufacturers:**
 - Framatome-CERCA in France
 - URENCO in the Netherlands, Germany and the United Kingdom
- **research reactors which irradiate targets for Mo-99, Lu-177, etc.:**
 - BR2 in Belgium
 - HFR in The Netherlands
 - MARIA in Poland
 - LVR15 in the Czech Republic
 - FRM-II in Germany
 - ILL in France [small volume]
- **irradiated uranium targets processing facilities:**
 - Curium in The Netherlands
 - IRE in Belgium
- **Tc-99m generators manufacturing sites in the Netherlands, France and Poland.**

The above translate into almost a 100% self-sufficiency in the Mo-99/Tc-99m supply chain for the EU.

There are also many ongoing projects (such as, for example, the Jules Horowitz Reactor), which, once finished, will allow the EU to boost its capacity at a global level in this field. These include the PALLAS reactor, a new medical isotopes reactor that is expected to replace the currently operating HFR in Petten.

Furthermore, the EU is home to some of the biggest radiopharmaceutical companies working in tandem with strong academic medical centres and universities to develop novel "tracing" molecules that carry and guide the diagnostic/therapeutic radioisotopes ("radiotracers") to their target.

In addition, Europe has a long-standing tradition in the development of detection technologies applicable also to nuclear medicine. Since the beginning of this medical modality European institutions and companies, in collaboration with US counterparts, have developed technologies in the field of radiation detection, image formation and interpretation which are extensively used today in nuclear medicine.

The EU plays an essential role in the international nuclear medicine supply chain as well as in international research and development efforts. It is one of the leading suppliers of medical radioisotopes on the global market (e.g., +60% of Mo-99/Tc-99m production).

Due to the short half-life of the main products, Mo-99 and Tc-99m (66 hours and 6 hours respectively), the production of this radioisotope requires continuous processing and complex logistics, as they cannot be stockpiled or inventoried.

Processing targets from multiple nuclear research reactors allows the European nuclear medicine sector to provide and coordinate the steady and reliable supply of the required radioisotopes. Unexpected outage of either the HFR or BR2 would lead to shortages. The fact that there are only four large processors globally is even more critical. In 2019 global shortages were recorded as NTP (South Africa) was out of service for several extended periods and ANSTO (Australia) was in the process of commissioning a new Mo-99 facility. In addition, Europe hosts many highly developed medical facilities which are frontrunners in the field of medical radioisotopes research and development (both in diagnosis and therapy).

According to the experts, in the future, demand for nuclear medicine will grow significantly as more and more highly targeted radioisotope-based therapeutic medicines reach the market. The global nuclear medicine business was estimated at €4 billion in 2019 and is expected to grow to €7-10 billion by 2024. The therapy part of the overall business is poised to grow from a 12% to a 31% share of the total value⁶ within that same time frame.

The future of the market will directly depend also on the many innovative and breakthrough technologies that are currently being developed in different parts of the EU and in other parts of the world (and which will eventually be introduced in the EU). Projects include SMART, NorthStar and the SHINE initiative.

Over the next 15-20 years, the development of the market will be also driven thanks to the growing importance of PET (Positron Emission Tomography).

Scope of the market

The global nuclear medicine sector – and in particular the European one – is a significant and important contributor to the global economy. Below are some key figures:

- Global Turnover: €8.5 Bn (pharma €4.5 Bn + equipment €2 Bn + services €2 Bn)
- Transport – 2.5 million packages containing radioactive material are being shipped across the EU every year – about 2% of all “sensitive” packages in the EU – most of these packages (almost 90%) contain relatively small quantities of radioactive material for medical purposes, including radioisotopes.
- Tc-99m demand is rising worldwide due to the aging population of Europe and North America – the predicted annual growth rate in “developed countries” is 3%.
- Only six nuclear research reactors provide about 95% of the world’s **Mo-99 or Lu-177 production**. In the EU, it is the HFR reactor in the Netherlands, the BR2 reactor in Belgium, the MARIA reactor in Poland and the REZ reactor in the Czech Republic. Almost all of these reactors are over 40 years old and are approaching the end of their originally intended life span, although all have been refurbished.

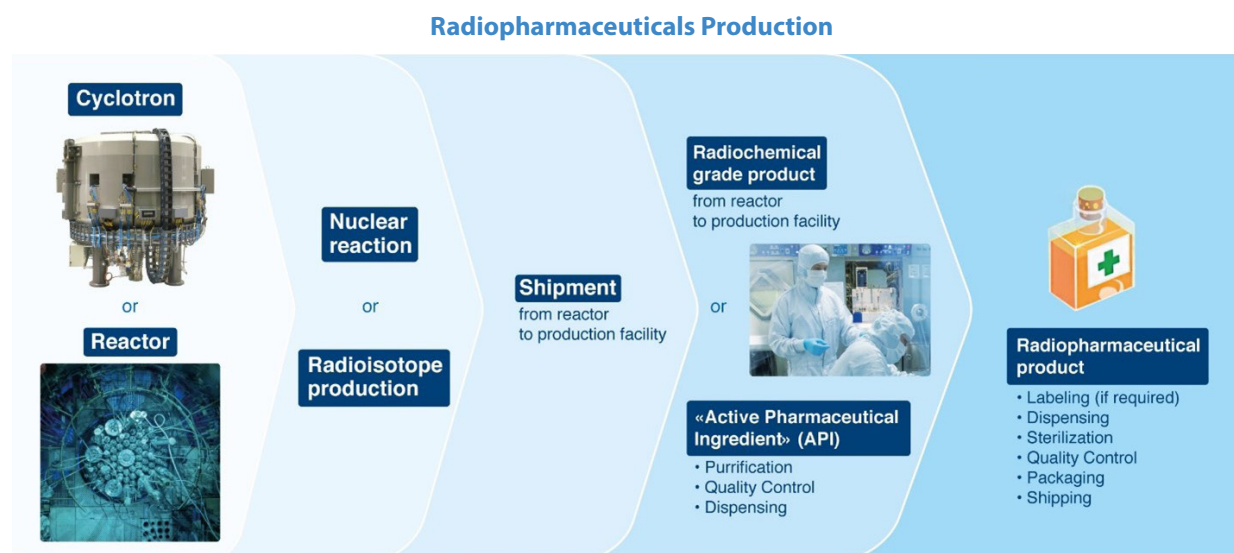
Major current Mo-99 producing reactors in the EU

Reactor name	Location	Annual operating days	Normal production per week	Weekly % of world demand	Date of commissioning	Estimated end of operation
BR-2	Belgium	140	5 200	25-65	1961	2036
HFR	Netherlands	300	4 680	35-70	1961	2024
LVR-15	Czech Republic	-	+600	-	1957	2028
MARIA	Poland	-	700 – 1 500	-	1974	2035

⁶Nuclear Medicine Europe data

How does the nuclear medicine supply chain work?

The irradiation of raw materials (either in a reactor or in an accelerator) is only a small part of the production process of medical isotopes. A series of processing, separation, and purification steps in laboratories designed for handling radioactive material follows the irradiation. Reactors play an important role in the production of medical isotopes, however it is the pharmaceutical industry that carry out additional steps utilizing the radioisotopes and by quickly transporting the irradiated materials to manufacturing facilities and finally to clinics/hospitals. Sophisticated logistics are extremely important due to the short life of the isotopes.



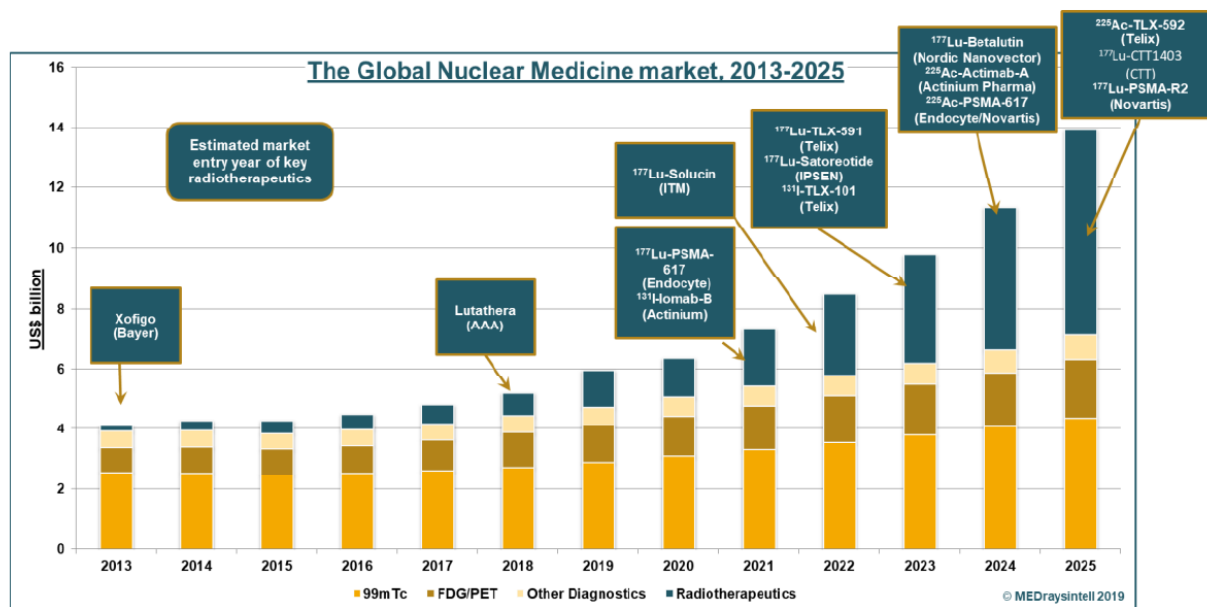
The radioisotope market includes the following players

1. Irradiation providers: primarily research reactors (but may also include commercial nuclear power plants in the future) which generate the radionuclides.
2. Isotope producers: sometimes research reactors have their own capabilities to process irradiated targets into radionuclides. In other instances, separate processing facilities have dedicated facilities that processes targets into usable radiochemicals.
3. Radiopharmaceutical companies develop the end-products and distribute them to the nuclear medicine departments.
4. End users, such as hospitals, etc.
5. Patients

Growth of therapeutic applications in nuclear medicine

The development of radiotherapeutics accelerated between 2015-2018. A kind of 'natural selection' led to a list of radionuclides of highest interest in terms of medical applications and industrial availability. Also, the aim of almost any new radiotherapeutic project is to treat a sub-group of well identified patients with almost 100% chances of success. Therefore, in order to identify the potential positive responders for a certain therapy, it became obvious that any single radiotherapeutic has to be accompanied by efficient radiodiagnostics leading to the obvious development of pairs of radiotheranostics. Within the next 10 years all new radiotherapeutics will be centered on pairs of either Tc-99m, Ga-68 or Zr-89 based diagnostics together with Lu-177 therapeutic analogues, or F-18 or I-123 based diagnostics together with I-131 analogues. Very recently it appeared that alphanuclide therapy will have to play a major role as its efficiency has proven to be superior to beta therapy in relapse cases. However, as access to the radionuclides will be of highest priority, it seems that only At-211, Pb-212 and Ac-225 could play a real role in the short term⁷.

FIGURE 10: THE GLOBAL NUCLEAR MEDICINE MARKET 2013-2025 AND NEW RADIOTHERAPEUTICS



Source: MEDraysintell (<http://medraysintell.com/>)

⁷ MEDraysintell

ACTIVITIES AT EU LEVEL

The EU is involved in the nuclear medicine sector by, for example, monitoring all the latest developments. The nuclear medicine sector collaborates with the EU through a variety of projects, which seek to identify opportunities and challenges for the use and development of ionising radiation and in order to discuss potential solutions to address challenges in areas where the EU can add value. In one of the recent documents on this topic, the Council of the EU⁸ highlighted that “nuclear and radiological technologies play an important role outside the nuclear energy sector in vital areas, such as medicine, industry, research and environment, providing numerous benefits to the EU citizens and AWARE OF the significant contribution that nuclear science can make to addressing societal challenges”. In addition, it was underlined that “Euratom legislation requires that non-power use of nuclear and radiation technologies is appropriately justified, the radiation protection of the public, patients and staff is adequately optimised and that non-power radioactive waste and spent fuel are safely disposed”. The document also mentioned the importance of “ensuring additional radioisotopes production capacity and launching or advancing projects for new production facilities, including research reactors and alternative technologies” as the “production of source materials for the supply chain of medical radioisotopes is important to increase the resilience of the European supply chain and to reduce the dependence on foreign actors”.

Nuclear medicine-related programmes conducted at EU level

- SAMIRA & SAMIRA Action Plan
- SMER-1 & SMER-2
- European Observatory on the Supply of Medical Radioisotopes
- Euratom Supply Agency
- HEU to HALEU conversion of targets used for Mo-99 production



“Courtesy of Siemens Healthcare GmbH”

The mentioned programmes are explained in detail in the PP’s annex.

⁸ <https://data.consilium.europa.eu/doc/document/ST-9437-2019-INIT/en/pdf> Council of the European Union (2019), op. cit.

CHALLENGES

The European nuclear medicine sector, while doing its best to provide Europeans with the required medical services, is currently facing a number of challenges. These may have a significant impact on its future role in the EU if no changes are implemented. A number of key issues must be addressed in order to maintain the edge that the EU enjoys today in this field globally, the current level of medical radioisotopes supply as well as to address the increasing demand which is foreseen in the future. These challenges roughly fall into two categories: supply chain investment needs and regulatory framework.

Supply chain investment needs

1. Insufficient funds for investment in research reactors

New reactor capacity is needed to support the predicted growth in demand. Supply of radioisotopes from the current reactor base is limited and most likely not sufficient in the future. Many of the existing reactors are bound to shut down in the coming 15 years, and there are only a few new reactor initiatives. Current radioisotopes supply relies on a small number of aging production reactors and due to the aging fleet of reactors, demand for radioisotopes in the near future may be not met by EU-based companies which can lead to a growing dependence on external (non-EU) suppliers of certain radioisotopes. The issue of aging fleet refers also to nuclear medicine's equipment in hospitals in certain parts of Europe.

2. Market failures – disincentives to private sector investment and lack of harmonization

The public and private sector need to have a better dialogue to understand where disincentives exist to private sector investment in various parts of the radiopharmaceutical supply chain, and where public sector investment may be required to ensure that key infrastructure is in place to meet emerging requirements. This challenge may refer to issues such as: development of medicine as well as the transport of radiopharmaceutical products (such as international rules for radioactive compounds, available flights in normal or "crisis" conditions).

3. Nuclear medicine supply chain challenges

Time constraints in the production and transport of isotopes, and having access to transportation hubs (e.g., airports) that understand the need for quick and swift handling and processing is key.

4. Management of nuclear waste

Stakeholders and opinion leaders have questions and concerns regarding nuclear waste which is also produced by the nuclear medicine sector.

5. Production of some of radioisotopes requires High-Assay Low Enriched Uranium (HALEU), which is currently delivered from limited stocks available in the US or from Russia.

Regulatory framework**1. No clear level-playing field conditions**

By promoting in their files certain low-carbon technologies (renewables) over others (nuclear), the EU is making any future investments in nuclear less feasible.

2. Differences in approach towards internationally agreed policies

Lack of consistency between countries in terms of internationally agreed policies which results in different approaches among countries in obeying and implementing internationally agreed policies which have an impact on the operation of the sector at international level.

3. A complicated and fragmented regulatory environment across the 27 Member States impacts innovation in the nuclear medicine field**4. Reimbursement of nuclear medicine applications across different countries and the big variation on the age of nuclear medicine diagnostic equipment imposes a massive access inequality to European citizen according to where they live.****5. Highly radioactive irradiated targets have to be transported within European countries.**

Closer coordination among the national licensing authorities for these transports should be part of the sustainable and diverse supply scenario for Europe.

6. Negative attitudes towards the nuclear sector (power production) in various EU files pushed by some EU Member States and the lack of education or miseducation on radiation.

A negative approach towards nuclear energy in general among some EU Member States, which is later reflected in EU files, has a negative impact on the current and future nuclear-related sectors, including the nuclear medicine sector.



"Courtesy of Siemens Healthcare GmbH"

POLICY RECOMMENDATIONS

Taking into account the abovementioned challenges – which have to be addressed at EU level in order to ensure that the supply of medical isotopes produced using nuclear technology will be continued and by doing so will keep contributing to saving lives of Europeans – FORATOM and NMEu recommend discussing and implementing the following policy recommendations:

Supply chain investment needs

1. The EU should promote new research reactor capacity along with innovation in the sector

To maintain the lead and to enable development and broad availability of life-saving medicines, new reactor capacity must be added in the EU. Incentives are needed to support investment in nuclear research reactors and the design modification of the current fleet that could enable the production of some radioisotopes like Co-60 or Lu-177 in the EU.

2. Reconsider reimbursement systems and levels for radiopharmaceutical products to ensure that irradiation sites are fully remunerated for the costs incurred.

Several national governments in Europe collaborate in realizing a joint market for pharmaceuticals, partly to ensure proper market dynamics by strengthening the procurement of scarce and/or expensive pharmaceuticals, and partly to ensure early access to new pharmaceutical products. Moreover, several countries have taken the initiative to reconsider their reimbursement systems for radiopharmaceutical products⁹.

3. The EU needs to develop a robust supply chain which goes beyond irradiation and includes the supply of target material and processing capabilities.

4. Reconsider and adapt clinical R&D of new radiopharmaceutical compounds

To unleash the potential of molecular imaging and radioligand therapy, the European regulatory authorities must review, adapt and, if needed, create specific clinical guidance to facilitate the development and access to highly efficient treatment.

⁹<http://www.oecd-nea.org/med-radio/>: The supply of medical radioisotopes the path to reliability 2011 P25 Exec Summary OECD/NEA (2011), [The supply of medical radioisotopes: The path to reliability, p.25](#)

Regulatory framework**1. The role of nuclear technology and its non-power applications should be better recognised and supported at EU level**

Support for nuclear medicine can mean, for example, integrating nuclear technology and its role in the EU cancer action plan. Nuclear medicine is an important part of the whole nuclear ecosystem that deserves more attention from EU institutions and should be considered as a strategic sector. FORATOM and Nuclear Medicine Europe call for a quick implementation of the SAMIRA Action plan

A quick implementation of the action identified in the SAMIRA Action plan 'Research roadmap for medical applications of ionising radiation technologies. There is strong demand for a multiyear, multi-lateral R&D programme that supports the various stages of the development of nuclear medicines. Synergies between Euratom R&T and Horizon Europe should be enabled, ensuring access to cross sectorial innovation projects and missions, as well as vibrant education, training and mobility opportunities for scientists and engineers.

2. Support of the implementation of the use of Low Enriched Uranium

Fully implement and enforce the conversion to the use of Low Enriched Uranium as for many years the international agreement on nonproliferation has included policies to ban the use of High Enriched Uranium (HEU) / HALEU for the production of medical isotopes in the future.

3. Market access and reimbursement models for nuclear medicine applications should be homogenized across all Member States.

Market access of novel diagnostics and therapeutic radiopharmaceuticals should be streamlined across the EU. The EU should adopt the OECD's recommendation stating that in cooperation with healthcare providers and private health insurance companies, countries should monitor radiopharmaceutical price changes in order to support the transparency of costs. Payment rates and payment policies should be periodically reviewed with the objective of determining if they are sufficient to ensure an adequate supply of Tc-99m to the medical community. Countries should also consider moving towards separating reimbursement for isotopes from the radiopharmaceutical products as well as from the diagnostic imaging procedures¹⁰.

4. Renovate nuclear medicine equipment especially in EU periphery countries in order to allow similar levels of diagnoses across the entire EU.

The 2019 COCIR report¹¹ describes the current install base of PET and PET/CT equipment, amongst other radiological devices. Almost one fifth of the PET and PET/CT systems in Europe were already more than ten years old. For SPECT and SPECT/CT systems anecdotal information describes a much more ageing fleet. Considering the tremendous improvements in the technological and radiopharmaceuticals area that allow new protocols with substantially lower radiation doses and heightened diagnostic accuracy, such aged systems may not provide the full picture of a patient's disease spread and certainly not at the lowest achievable radiation dose.

5. Securing a level-playing field for low-carbon technologies

The EU should create a level-playing field for all low-carbon technologies, addressing major hurdles which are currently blocking investment in the development of nuclear-related projects and initiatives at EU level.

6. Nuclear to be included in EU NextGeneration Recovery Plan & Industrial Strategy

Nuclear technology (including nuclear medicine) and its contribution should be included in the EU's Industrial Strategy as well the bloc's post-COVID19 recovery plan as its importance and contribution to achieving the bloc's key objectives cannot be overlooked. These actions should include, for example, the creation of an industrial alliance to deal with the objectives of the European Radioisotopes Valley Initiative or – in line with the SAMIRA action plan – launching the actions mentioned in the SAMIRA action plan.

¹⁰ <http://www.oecd-nea.org/med-radio/>: The supply of medical radioisotopes the path to reliability 2011 (P25 Exec Summ. Top of the page)

Ibid

¹¹ https://www.cocir.org/fileadmin/Publications_2019/19076_COC_AGE_PROFILE_web.pdf

COCIR (2019) Medical Imaging Equipment Age Profile & Density

List of abbreviations

Ac-225	Actinium-225
ANTSO	Australian Nuclear Science and Technology Organisation
API	Active Pharmaceutical Ingredient
At-211	Astatine-211
BR-2	Belgian Reactor 2
Co-60	Cobalt-60
CMO	Contract Manufacturing Organisation
COP	Conference of the Parties
CRO	Contract Research Organization
EANM	European Association of Nuclear Medicine
ENER	Directorate-General for Energy
ENTR	Directorate-General for Enterprise and Industry
EOP	Emergency Operating Procedure
ERVI	European Radioisotope Valley Initiative
ESA	Euratom Supply Agency
F-18	Fluorine-18
FRM	Forschungs-Neutronenquelle Heinz Maier-Leibnitz
Ga-68	Gallium-68
Ge-68	Germanium-68
HALEU	High-Assay Low Enriched Uranium
HEU	Highly Enriched Uranium
HFR	Petten High Flux Reactor
HLG-MR	High-Level Group on Medical Radioisotopes
HTA	Health Technology Assessment
I-125	Iodine-125
I-131	Iodine-131
ILL	Institut Laue Langevin
IPCC	United Nations' Intergovernmental Panel on Climate Change
Ir-192	Iridium-192
IRE	Institut National des Radioelements
JHR	Jules Horowitz Reactor
JRC	Joint Research Centre
Lu-177	Lutetium-177
Mo-99	Molybdenum-99
PET	Positron Emission Tomography
RTD	Directorate-General for Research and Innovation
SAMIRA	Strategic Agenda for Medical Ionising Radiation Applications
SANTE	Directorate-General for Health and Food Safety
SMART	System-integrated Modular Advanced Reactor
SMER	Sustainable and Resilient Supply of Medical Radioisotopes
SPECT	Single-Photon Emission Computerized Tomography
TAT	Targeted Alpha Therapies
Tc-99m	Technetium-99m
Zr-89	Zirconium-89

About us

The European Atomic Forum (FORATOM) is the Brussels-based trade association for the nuclear energy industry in Europe. The membership of FORATOM is made up of 15 national nuclear associations and through these associations, FORATOM represents nearly 3,000 European companies working in the industry and supporting around 1.1 million jobs.

Nuclear Medicine Europe (ex AIPES) is a European Industrial Association working on promotion, awareness and defence of Nuclear Medicine and Molecular Healthcare in Europe. We are active in the field of Imaging and Therapy with Molecular and Radioactive Tracers. The main objective of our association in this field is to ensure the promotion of the economic and/or commercial interests of its Members, in particular, by all means allowing to increase the awareness to the benefits of the products and services they offer.



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