SMART

Source of MedicAl RadioisoTopes

MKT-077

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IRE'S LEADERSHIP IN NUCLEAR MEDICINE

IRE is one of the leaders in the production of molybdenum-99 (^{99}Mo) enabling the manufacturing of technetium-99 (^{99m}Tc) generators.

1. The ^{99}Mo/^{99m}Tc combination

Nuclear medicine uses specialised scans to detect diseases of the bones, heart, lungs, kidneys, liver, thyroid, brain, gastrointestinal system, etc.
These examinations make it possible to give an appropriate diagnosis of numerous diseases such as cancers, cardiac arrests, infections and inflammations, respiratory problems, degenerative diseases of the brain such as Alzheimer's, and endocrine disorders. In the case of cancer, analysis of this image is primarily used to scale out the magnitude of the disease.

One of the most important radioisotopes produced on the IRE site is ^{99}Mo, the "parent" isotope of the metastable ^{99m}Tc, which is used in more than 80% of diagnoses. This ^{99m}Tc isotope can reach a target organ and can be visualised with the use of a detection system (SPECT camera). The radiation from the ^{99m}TC isotop is caught by the SPECT camera and converted to an image that is used by specialist doctors to make a reliable diagnosis.

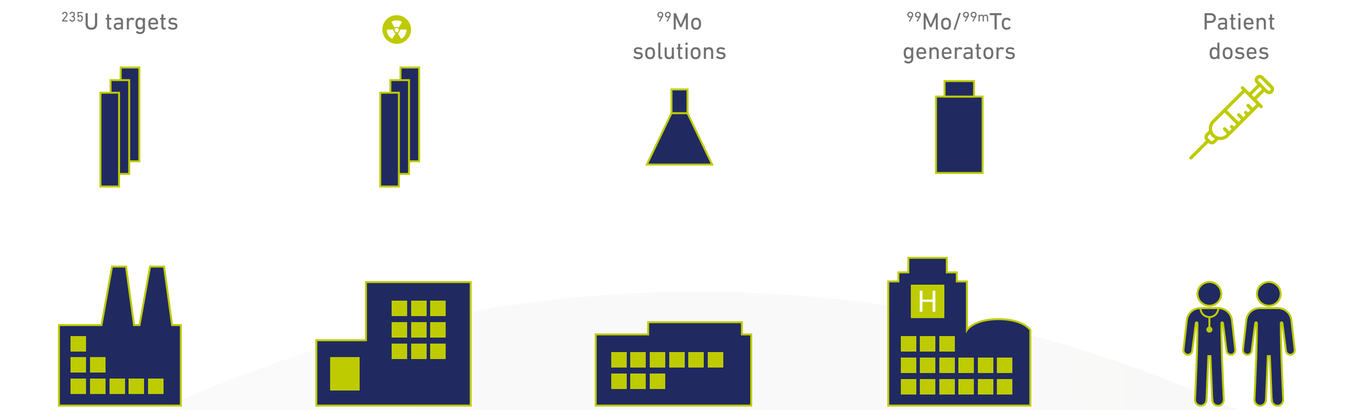
The "parent" isotope, ^{99}Mo, is placed on a sorbent, the generator, and then distributed to the different hospitals. By decay, ^{99}Mo evolves to radioactive ^{99m}Tc, that will be used in the hospitals.

2. The current ^{99}Mo production process

The raw material consists of uranium targets that are irradiated in research reactors and then sent to processors' such as IRE to extract and purify the relevant radioisotopes. The ^{99}Mo is then harvested from fission products, purified and sent to the pharmaceutical companies, which will load it into the ^{99m}Tc generators.

The radioactivity of the radioisotopes decreases very rapidly. The time required for the radioactivity to decrease by half is called the “half-life”. In the case of medical radioisotopes, this period can vary from a few hours to a few days. In the case of Mo-99, the half-life is reached in 66 hours, and in just 6 hours for Tc-99m.

If the activity of these medical radioisotopes is to be preserved, it is essential for the production time and the time of transport time from the producer to the user to be reduced to the absolute minimum. IRE extracts, purifies and dispatches the molybdenum in 12 hours.



Nuclear reactors

The uranium targets are irradiated in a reactor creating different types of isotopes

Medical radioisotope processors

We dissolve the radioactive targets using a chemical process to extract and purify medical radioisotopes

Pharmaceutical manufacturers

The solutions are sent to pharmaceutical companies for the production of ^{99m}Tc generators

Radiopharmacies and hospitals

The generators are supplied to radiopharmacies and nuclear medicine departments in hospitals

Doctors and patients

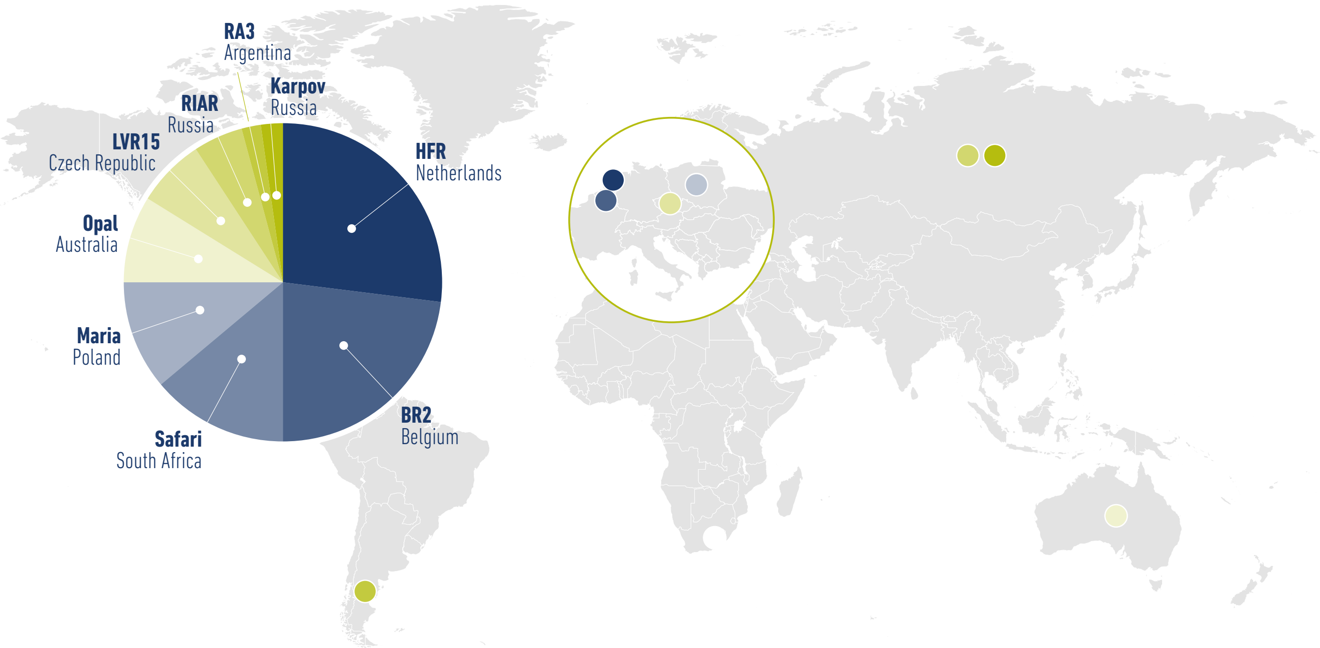
The radiopharmaceuticals prepared with the ^{99m}Tc are injected into patients to perform diagnostic tests

3. The ^{99}Mo market

Today, four producers supply the ^{99}Mo market.

IRE has a strategic position on this market, irradiating uranium thanks to three reactors: BR2 in Mol (Belgium), HFR (Netherlands) and LVR15 (Czech Republic).

OVERALL CAPACITY OF THE REACTORS FOR MO-99



Global capacity of the reactors currently available for medical isotopes (OCDE-AEN)

NB: The reactors in Russia and Argentina only produce isotopes for local use.

CHALLENGES FOR THE FUTURE

Technological | non-renewal of the reactor fleet

Risk of non-renewal of the European research reactors is one of the issues with this production method, as the dependence on reactors that are often more than 50 years old represents a risk for production.

Environmental | management of irradiated materials

The chemical production process creates by-products containing uranium that must be stored, transported and then treated to be disposed of or recycled.

The objective of the **RECUMO** partnership signed between **IRE** and **SCK•CEN** in December 2018 is to convert these irradiated materials into low-enriched uranium and then to purify them in Mol to obtain a high-quality recyclable material. It is an industrial structural solution for the management of these materials, but it does not reduce the volume.

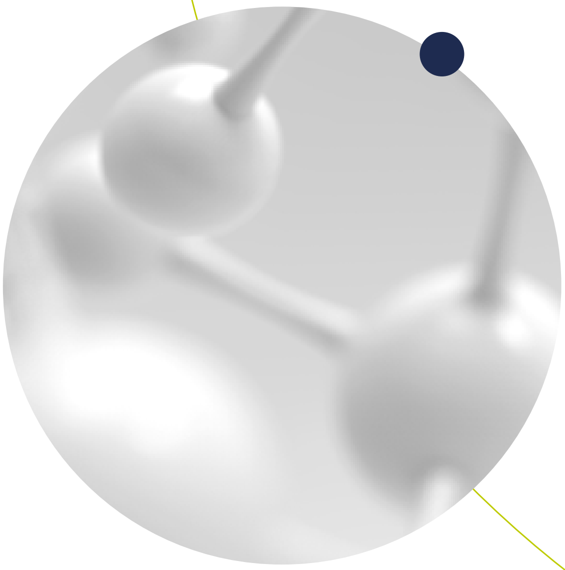
In addition to the uranium by-products, the isotope extraction and purification process generates radioactive waste that also has to be scrupulously managed in the short and long term so that it can be disposed of.

Geopolitical | non-proliferation

The geopolitical context and the stances adopted by Belgium in regard to nuclear non-proliferation also make access to uranium increasingly difficult. Although the LEU (Low Enriched Uranium) conversion of the processes improves the situation, supplying uranium remains sensitive, with significant constraints in terms of traceability.

Regulatory

The transport and handling of irradiating materials on our site must be closely supervised to ensure maximum protection of the population, the workers and the environment during their lifetime, generating substantial and therefore resource-intensive constraints throughout the production chain.



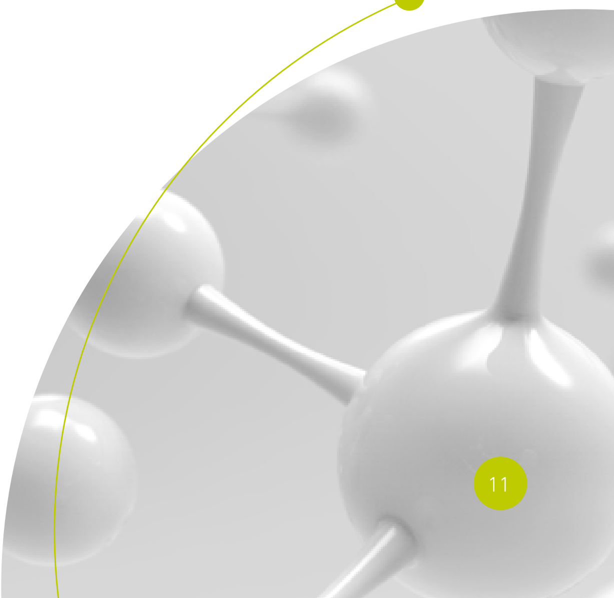
SMART

AN INNOVATIVE PARTNERSHIP BASED ON REVOLUTIONARY TECHNOLOGY FOR THE PRODUCTION OF ^{99}MO

1. An innovative partnership with ASML, a Dutch manufacturer of lithography machines for the semiconductor industry

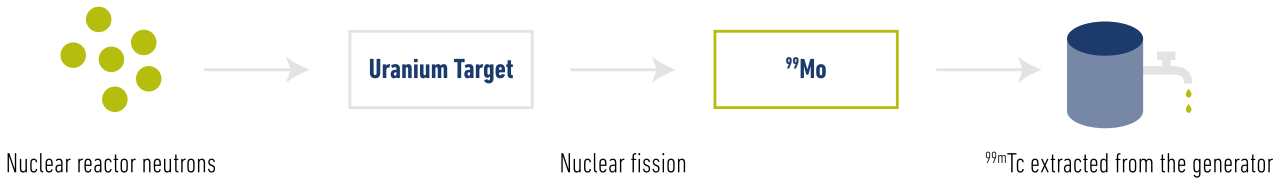
ASML is a Dutch company, the world's largest supplier of lithography systems for the semiconductor sector. The lithography equipment manufactured by ASML is used in the production of computer chips. Created in 1984, the company operates in 60 countries, with its headquarters in Veldhoven in the Netherlands. The company employs more than 24,500 people, over 9,000 in the research and development department.

ASML has developed a free-electron laser as part of a study on a potential light source for its future lithography systems. The origin of this electron laser is a high-energy electron beam. In 2015, ASML discovered that this new development could be adapted to produce the radioisotope ^{99}Mo. They created LightHouse to continue the development of the project outside of ASML.

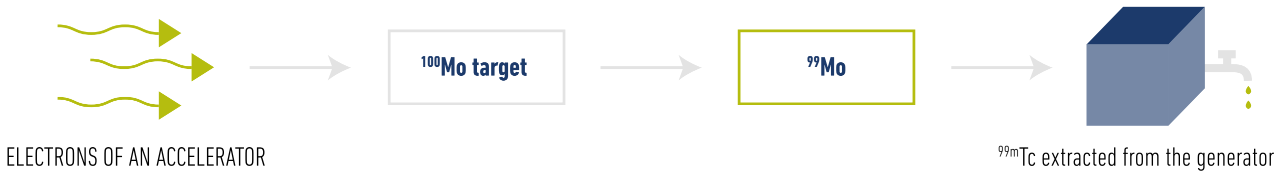


2. The Lighthouse principle: a new method of ^{99}Mo production

CURRENT METHOD USING THE NUCLEAR REACTORS



LIGHTHOUSE METHOD USING AN ELECTRON ACCELERATOR



The electron accelerators are already used to produce small quantities of low specific activity ^{99}Mo, but this does not meet the specifications for the large-scale production of usable ^{99}Mo for the nuclear medicine industry.

One of the major challenges of the Lighthouse technology and the whole issue of the SMART project was to be able to supply large volumes of high specific activity ^{99}Mo to serve the industry and the ^{99}Mo market.

SMART must therefore enable the use of the Lighthouse technology via a superconductive, high-power linear electron accelerator. The innovation lies in its ability to produce large volumes of high specific activity ^{99}Mo.

The production begins with the irradiation of ^{100}Mo, targets, without any nuclear fission operation. This innovative accelerator produces a high-energy electron beam (to exceed the energy needed for the reaction of ^{100}Mo to ^{99}Mo) with a high current (to produce the required quantity of ^{99}Mo). Technically, this beam is divided and then used to expose both sides of a target composed of Mo enriched in ^{100}Mo. The high-energy electrons are stopped in the target and produce rays that transform the ^{100}Mo into ^{99}Mo.

IRE was looking for an alternative and durable production method for ^{99}Mo, while ASML, for its part, was looking for a partner to fully develop the technology for use in the nuclear medicine industry: these two parties came together to create the partnership and the SMART project.

3. Distribution of responsibilities in SMART

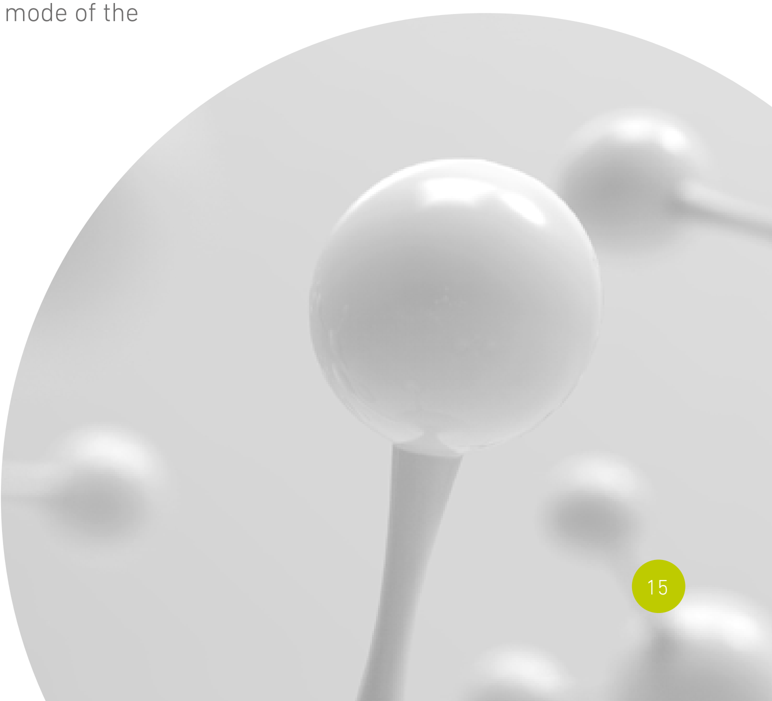
As a result of its expertise in the production of radioisotopes and its historical knowledge of the nuclear medicine market, IRE is in charge of the development and deployment of the SMART technology at the Fleurus site (Belgium), and ASML will assist IRE with this development through the expertise of its Lighthouse technology, the ability to adapt it to the development of the accelerator, the ^{100}Mo target and its cooling.

IRE, leader of the development, will be responsible for:

- Project management
- Developing the chemical treatment of the ^{100}Mo targets
- Evaluating the current generators and the final products
- Developing the building
- The various authorisation processes

4. Benefits of this production method

- Long-term security of supply without any dependence on the research reactors
- No longer using uranium as a raw material, eliminating the risk of proliferation
- A process that generates minimum waste
- A process resulting in ^{99}Mo with greater purity
- The possibility to use the current ^{99m}Tc generators as is or modified without any consequence for the end users, especially their size or the operating mode of the generators

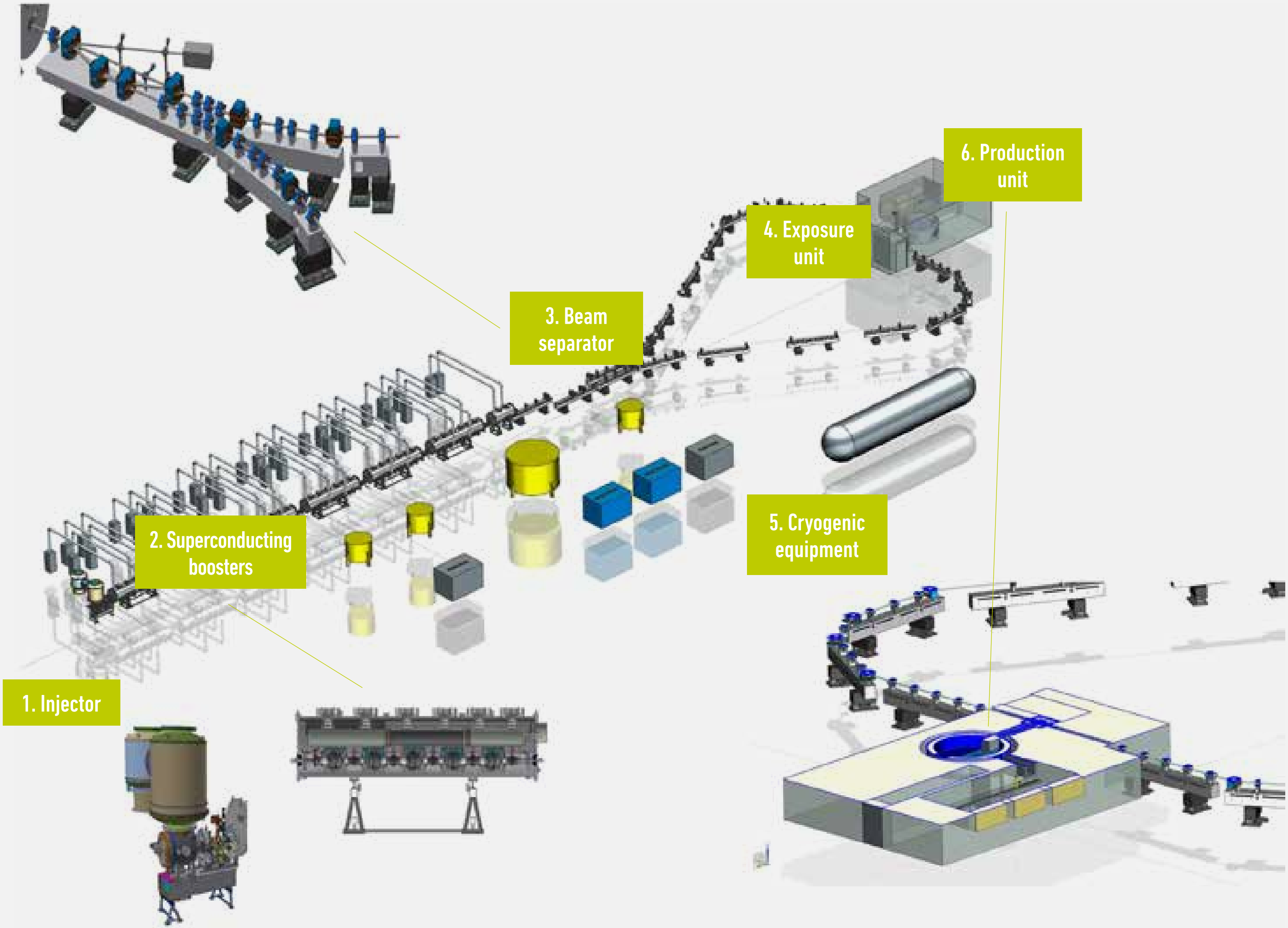


THE DESIGN OF THE PROJECT

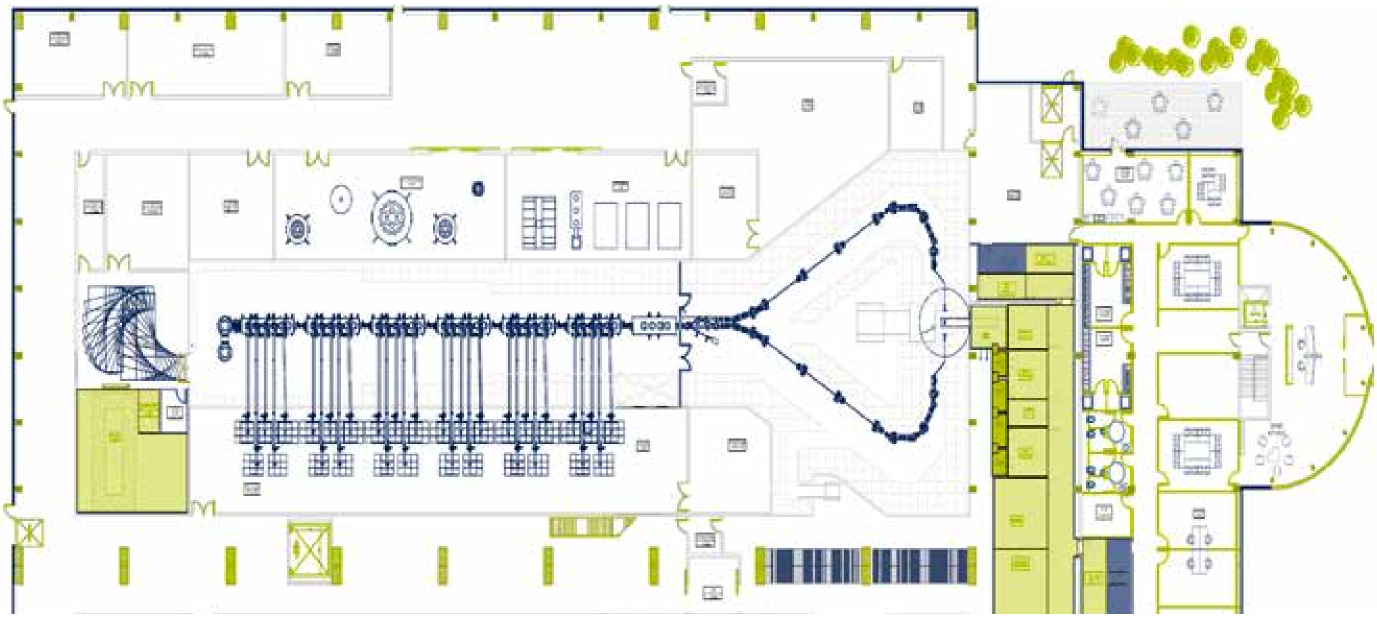
1.One production line will be installed at the Fleurus site

This is the blueprint of the line and the “journey of an electron from the injector at the start of the line to the ^{100}Mo target” in the production cell at the end of the line.

1. The electrons are released in the injector
2. They are accelerated to 75 MeV in the superconducting boosters
3. The beam is divided to reach both sides of the target
4. In the exposure unit, the high-energy electrons are stopped in the ^{100}Mo target and produce a Bremsstrahlung (gamma rays or X rays) which transforms the ^{100}Mo into ^{99}Mo
5. The target is cooled as the electrons also create a high thermal load on the target
6. After the target has been exposed for about one week, part of the target is harvested and treated to produce the active pharmaceutical ingredient (API) ^{99}Mo


6. Production unit
4. Exposure unit
3. Beam separator
5. Cryogenic equipment
2. Superconducting boosters
1. Injector

2. Project to set up the future SMART factory, the surface of the building will be slightly smaller than a soccer field



SOCIO-ECONOMIC IMPACTS

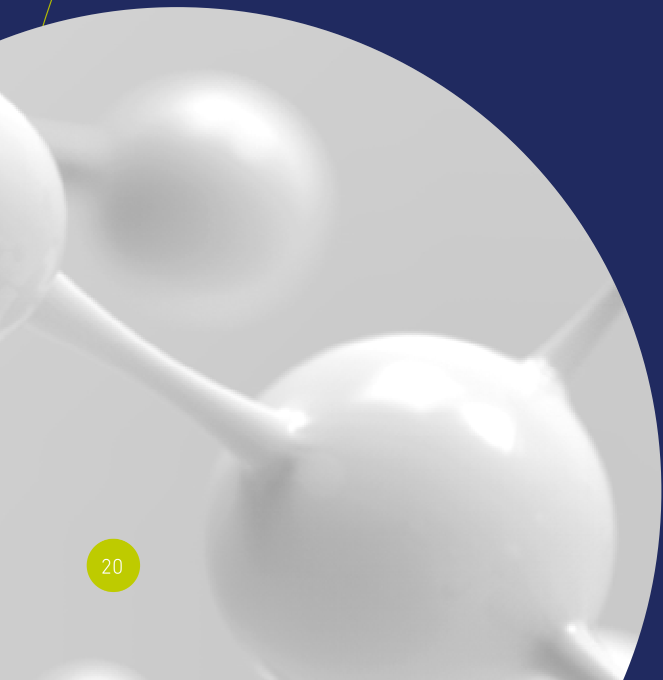
1. Enhanced security, reassured public

Although an electron accelerator always requires a high level of safety with regard to the installations, this is nothing compared to the requirements in and around nuclear installations. SMART uses non-radioactive targets, which makes the entire process intrinsically safe.

Neighbouring municipalities, local residents and, more generally, public opinion will also be reassured with installations of this type.

2. Employment support in Belgium

IRE, which currently employs more than 240 people and has increased its workforce by over 50% since 2010, is a leading employer that creates, and will continue to create, jobs in Belgium, especially with SMART, which calls on a wide range of competencies and qualifications. From the transfer of technology upstream with Research and Development and Business Developer teams, to the construction of the factory with more operational field teams. Routine operation and sales will be taken care of by the Production, Quality Assurance, Safety, Sales and Marketing teams.



3. Non-proliferation commitments

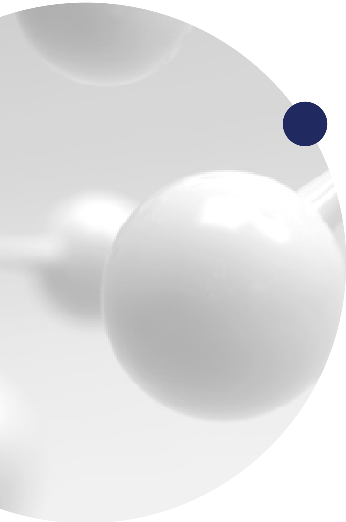
As mentioned before, supplying uranium is still sensitive, as it can be used for civil as well as for defence purposes. In Belgium, it is therefore subject to strict controls. At the European Union level, the European Commission carries out the controls within the framework of chapter VII of the Euratom Treaty to make sure that nuclear material, such as uranium, is used for the authorised purposes.

The International Atomic Energy Agency (IAEA) carries out non-proliferation controls on a global level to ensure the international community of a peaceful use of these materials.

With SMART and avoiding the use of uranium, Belgium is ready to move in the direction of the international non-proliferation commitments.

4. Limited waste management costs

The SMART technology generates minimum waste throughout - about 100 times less waste generated than with current technology - which reduces the costs related to the management of these irradiated materials at the IRE site as well as the costs associated with the radioactive waste from the reactors.



PLANNING & BUDGET

IRE invested €4M to complete the feasibility study, while the Belgian public authorities provided €52 million to support the design and engineering phase. This phase will be completed in 2022 with the definition of the technical specifications to start the construction of the factory. The first production is expected in 2028.

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