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FLIP OVER

Shaping Radionuclides for Nuclear Medicine

Requirements, Production Routes and Emerging Frontiers

By **Maria Letizia Terranova** [1,2]

SUMMARY

- Nuclear medicine is increasingly driven by next-generation tailored radionuclides enabling highly sensitive diagnostic imaging, precision targeted radiotherapy and innovative theranostic strategies
- This short review discusses the physical and radiochemical requirements of medical radionuclides, highlighting the main diagnostic and therapeutic nuclides currently used or under development.
- Current limitations in the availability and large-scale production of high-purity radionuclides are examined and discussed in the context of advanced projects and emerging technologies, including high-flux reactors, accelerator-driven systems and novel photon-based facilities.

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1. INTRODUCTION

Nuclear medicine is a clinical specialty that employs internally administered radionuclides, linked to specific vectors that selectively accumulate in biological sites, enabling the targeted delivery of ionizing radiation for both diagnostic imaging and targeted therapeutic procedures [1]. Radiodiagnostic techniques enable the identification and localization of diseases and can also monitor their temporal progression, while radiotherapeutic approaches selectively treat tumors or other pathological conditions in targeted regions of the body. Together, these complementary capabilities make nuclear medicine a key component of modern precision healthcare and are driving the rapid expansion of the sector, with the global market projected to rise from $9.3 billion in 2023 to over $42 billion by 2033, and therapeutics alone expected to grow at ~29% annually [2].

For each application in nuclear medicine, the selection of the most appropriate radionuclide from the wide range of potentially suitable candidates is primarily governed by the type of emitted radiation and the radionuclide half-life ($t_{1/2}$), which together determine the interactions between ionizing radiation and biological matter [3].

Regarding the type of radiation, diagnostic procedures usually employ highly penetrating radiation with a relatively long range, such as γ-rays, which can escape the body and be detected by external imaging systems. The primary diagnostic applications involve three-dimensional imaging techniques, namely positron emission tomography (PET) and single-photon emission computed tomography (SPECT) [4].

The PET technique exploits the interactions of positrons emitted by β^+-decaying isotopes with electrons, leading to annihilation events that produce two γ-photons of 511 keV emitted approximately 180° apart. The detection of these annihilation photons by the PET detector ring enables localization of the original positron emission site with millimetre-scale spatial resolution and,consequently, accurate 3-D reconstruction of the tracer distribution within the body.

In addition to a sufficiently short half-life and favorable chemical properties, PET relies on radionuclides that emit positrons with energies low enough to ensure that positron stopping and annihilation occur as close as possible to the emission site. Furthermore, the β^+-decay should not be accompanied by γ-emission. These stringent requirements limit the range of suitable radionuclides to a few well-established β^+-emitters, such as ^{18}F, ^{11}C, ^{13}N, ^{15}O, ^{68}Ga and ^{82}Rb, while ^{44}Sc, ^{64}Cu, ^{86}Y, ^{89}Zr and ^{124}I are considered promising candidates.

Conversely, SPECT imaging relies on the detection of individual γ-photons, typically in the 70–511 keV range, using γ-cameras equipped with appropriate collimators. Radionuclide physical properties, such as half-life, γ-ray energy and emission yield, photon attenuation and Compton scattering, strongly influence image quality, quantitative accuracy, patient dosimetry and practical aspects including acquisition time and radiopharmaceutical availability. While ^{123}I and ^{201}Tl are gaining ground for some specific clinical applications, the most widely used SPECT radionuclide is ^{99m}Tc, which accounts for approximately 85% of the 30 million nuclear medicine procedures performed worldwide each year. In 2025, it supported a global market valued abaut $7.5 billion, projected to reach about $11.5 billion by 2034 [5].

Unlike diagnostic procedures, therapeutic approaches require short-range emissions that deposit most of their energy within a confined area, making α- or β^- -emitting radionuclides with limited γ-emission the preferred choice [6]. Monoenergetic α-particles are particularly suitable due to their high linear energy transfer (LET) and short mean free path (40–100 μm), roughly spanning 2–6 cells, with maximum energy release occurring at the Bragg peak. This highly localized energy deposition induces DNA double-strand breaks at activities as low as 1×10^{-5} Ci , causing irreparable damage in cancer cells and tumor microenvironment while sparing surrounding healthy tissue [7]. In addition to the well-established ^{223}Ra, among the most widely used α-emitting therapeutic radionuclides are ^{211}At, ^{213}Bi and ^{225}Ac, selected for their suitable half-lives, high LET and short-range emissions. Other radionuclides under investigation, including ^{149}Tb, ^{212}Pb and ^{212}Bi, have also shown considerable potential in preclinical and early clinical studies.

Compared with α-particles, β^--particles have a longer penetration range in tissues (0.3–12 mm) and a lower LET (<1 keV/μm), therefore β^--emitting therapies typically require higher administered activities (≈ 0.1–1.0 Ci). However, the longer particle range, corresponding to several hundred cell diameters, allows effective irradiation of medium/large tumors as well as of extensive metastases [8]. Among the most commonly used β^--emitting radionuclides for therapeutic applications are ^{90}Y, ^{131}I, ^{177}Lu, ^{186}Re and ^{188}Re, whereas ^{47}Sc, ^{67}Cu, ^{161}Tb and ^{168}Ho are currently under investigation, the latter also enabling MRI due to its high paramagnetism.

Auger electrons, low-energy particles emitted during atomic relaxation following internal conversion (IC) or electron capture (EC), may also be exploited for therapy. Their extremely short range (nm–μm) and relatively high LET (4–26 keV/μm) enable highly localized DNA damage comparable to that produced by α-particles while sparing surrounding tissue [9]. Besides the classical Auger emitters ^{117m}Sn, $^{123/125}$I, ^{111}In and ^{99m}Tc, several additional radionuclides have been proposed . However, the lack of efficient DNA-targeting delivery systems has so far limited the clinical translation of Auger-based therapies .

A major milestone in nuclear medicine has been the emergence of "**radiation theranostics**", an integrated approach that combines targeted therapy with simultaneous imaging, allowing real-time monitoring of treatment response and representing a significant step toward personalized medicine [10]. This strategy couples diagnostic tracing and therapeutic intervention through the administration of a single pharmaceutical labeled with different radionuclides or, ideally, with a single multifunctional radionuclide.

In both diagnostic and therapeutic applications, selective delivery of radionuclides to target tissues is achieved via carrier systems, ranging from biomolecules to increasingly sophisticated micro- and nanostructures, including liposomes and nanozeolites. These systems form functional, biologically stable radioconjugates with high affinity and selectivity for specific cellular receptors [11]. More than 100 radiopharmaceuticals have been approved worldwide, and over 400 are currently in clinical trials [12].

Although substantial progress has been made in the design of delivery carriers, a major challenge remains the production of radionuclides with adequate chemical and isotopic purity and high specific activity. High isotopic purity prevents contamination by stable isotopes or undesired radioemitters, whereas high specific activity enables administration of minimal radioisotope amounts, thereby reducing toxicity risks and avoiding saturation of biological targets. These parameters are also critical for the implementation of accurate dosimetry and regulatory issues, whose assessment becomes increasingly complex with the introduction of new radionuclides and therapeutic strategies [13].

2. THE EVOLVING LANDSCAPE OF MEDICAL RADIONUCLIDE PRODUCTION

While worldwide efforts continue to address purity and dosimetric concerns, which are comparatively easier to manage, the principal limitation for the expansion of nuclear medicine remains the limited availability of many clinically important radionuclides . Addressing this supply challenge will require more than simply expanding existing production capacity. Many of the technologies needed to increase radionuclide availability, including high-power targets, advanced isotope separation methods, and reliable high-intensity beam systems, originate from developments in nuclear and high-energy physics and are now being adapted to meet the growing demands of nuclear medicine [14]. Nevertheless, current production still relies largely on conventional reactors, cyclotrons, and accelerators [15], which can produce only a limited number of radionuclides in sufficient quantities and at reasonable cost, thereby restricting their broader clinical adoption. This limitation is particularly critical for α-emitters , whose production often requires high-flux reactors or high-energy accelerators . For now, β-emitters are less affected by supply constraints, but the planned decommissioning of several aging reactors poses a significant threat even to these radioinuclides .

For PET applications , foreseen supply reductions could be offset by increasing the number of compact cyclotron in clinical centers, which can produce personalized doses on demand, including very short-lived β^+-emitters. Although cyclotron expansion has helped meet the demand for PET radionuclides, substantial limitations persist in the high-yield production of therapeutic β^-- and especially α-emitters .

This supply constraint is likewise observed in the United Kingdom, where, according to a recent House of Lords report [16], around 60% of the medical radioisotopes used by the NHS are currently imported. As discussed by Jane Sosabowski in her review of the UK radionuclide sector [17],following the decommissioning of national research reactors , domestic production is now limited to only a few radionuclides, including ^{11}C, ^{13}N, ^{15}O, ^{18}F and ^{81m}Kr, making the national medical isotope supply chain heavily reliant on cyclotron facilities. Additional capabilities are provided by the University of Manchester, which hosts cyclotrons and radiochemistry laboratories for both research and production of radiotracers.

Despite these facilities, the UK lacks a dedicated national reactor-based infrastructure for the large-scale production of medical radionuclides. To address this strategic gap, Project ARTHUR (Advanced Radioisotope Technology for Health Utility Reactor) has been launched as a publicsector initiative proposing the construction of a national nuclear medicine

laboratory equipped with a dedicated small research reactor [18]. Once operational, the facility is intended to provide a reliable and sustained domestic supply of key reactor-produced radionuclides currently imported into the UK. Based in northwest Wales , this laboratory is envisaged to operate for several decades and could become one of the few reactors worldwide primarily dedicated to the production of medical radionuclides . In parallel, several other radionuclide production projects are currently underway or under development in the United Kingdom [17].These include both upgrades to existing capabilities and innovative approaches, such as the extraction of medically valuable radionuclides from nuclear legacy materials. The UK National Nuclear Laboratory (UKNNL), within the Medical Radionuclide Innovation Programme (MRIP) funded by the U.K. Department for Energy Security and Net Zero, is developing advanced production and separation routes for therapeutic radionuclides through the recovery of valuable isotopes from legacy nuclear materials and recycled nuclear inventories. In addition to particular emphasis on ^{225}Ac, ^{90}Y and thorium-derived α-emitters, the MRIP programme also supports the development of radionuclides such as ^{211}At and ^{124}I, as well as theranostic pairs including ^{64}Cu/^{67}Cu and scandium-based radionuclides [19] .

Nevertheless, even with such initiatives, the limitations in production of medical radionuclide cannot be fully overcome without the development of next-generation facilities. Examples of innovative infrastructures, already operating, under construction or planned in Western countries include nuclear reactors with extremely high neutron fluxes, accelerator systems capable of delivering high-energy projectiles and superconducting synchrotrons generating intense γ-ray beams [20].

High-flux research reactors remain essential for medical radionuclides production [21]. The currently operating HFIR at ORNL (USA) and the ILLHFR (France) produce a wide range of clinically important isotopes, while the under-construction PALLAS reactor (Netherlands) and the multipurpose **RMB reactor** (Brasil), are expected to ensure a reliable supply of ^{99}Mo, ^{177}Lu and ^{161}Tb. Additionally, the JHR (France) , once fully operational, will provide high neutron fluxes for medical and scientific radionuclides production, including ^{99}Mo [14].

An alternative to nuclear reactors is offered by accelerator-driven neutron sources [22]. The Spallation Neutron Source (SNS, USA) and the Soreq Applied Research Accelerator Facility (SARAF, Israel) are operational facilities capable of generating intense neutron beams through high-energy proton or deuteron interactions with suitable targets, inducing spallation reactions. Beyond SNS and SARAF, additional installations are planned or already under construction, as the European Spallation Source (ESS,Sweden). Although primarily designed for fundamental research, these facilities will also support the production of medical isotopes, complementing conventional reactor- and cyclotron-based methods for some PET and α-emitting radionuclides.

Even more innovative are the accelerator-based facilities currently under-development : the Multi-purpose hYbrid Research Reactor for High-tech Applications (MYRRHA, Belgium) and the Sustainable Health-focused Isotope Production Enterprise (SHINE, USA). MYRRHA is an accelerator-driven subcritical system that combines a high-power proton accelerator with a nuclear reactor, where fission in the subcritical core (potentially containing a fertile isotope such as ^{232}Th) is sustained by an external intense flux of high-energy neutrons . This plant will enable advanced nuclear research, technology testing and production of medical radionuclides . Conversely, the SHINE project relies on a linear proton accelerator to generate thermal neutrons that induce fission in low-enriched uranium (LEU), producing ^{99}Mo and other medical isotopes. Unlike conventional fission reactors, SHINE, dedicated to radioisotope production, operates without a critical core, relying entirely on accelerator-driven neutrons.

Also high-energy photon sources are emerging as a promising approach [23]. Facilities such as ELI-NP (Romania) and HIγS (USA) already generate intense γ-ray beams via Compton backscattering or laser-based techniques, while the under development SMART/Lighthouse project (Belgium) will use a high-power superconducting electron Linac to irradiate enriched ^{100}Mo targets and produce ^{99}Mo via photonuclear reactions.Together with last-generation superconducting synchrotrons , these facilities allow γ-induced nuclear reactions to be exploited for the synthesis of medical radionuclides not readily accessible by conventional neutron or proton irradiation.

A practical alternative to reactor- or accelerator-based production is provided by “Radionuclides Generator” systems, which enable the recovery of daughter nuclides from the decay of their radioactive parents. A prominent example of such generator approach is the ^{99}Mo/^{99m}Tc system , which produces the widely used diagnostic radionuclide ^{99m}Tc ($t_{1/2}$ = 6.92 h) directly on site through the decay of the ^{99}Mo ($t_{1/2}$ = 65.9 h) .The central role of ^{99}Mo as the precursor of ^{99m}Tc explains why its production has become a primary international objective for many emerging radioisotope-producing infrastructures.

The radionuclide generator approach not only facilitates the use of short-lived isotopes, partially overcoming the complex logistical and distribution constraints, but also allows recycling of valuable medical radioisotopes from spent nuclear fuel [24]. Increasingly regarded as a key source of crucial radioisotopes rather than a waste, used fuel is stimulating recovery projects and the development of advanced radiochemical and physical separation techniques [25,26].

However, many daughter radionuclides originate from extremely long-lived parent nuclides, making their production through natural decay impractical. This is the case of the α-emitting ^{225}Ac, which could be obtained in larger amounts through the decay chain ^{233}U→ ^{229}Th → ^{225}Ra → ^{225}Ac from the inventory of ^{233}U ($t_{1/2}$ = 1.6 x 10^5 y) stored at ORNL, or of the ^{212}Pb, which could be extracted from its progenitor ^{232}Th ($t_{1/2}$ = 1.4 x 10^{10} y). To address this limitation, in 2023 DARPA (U.S.) launched the “Decay on Demand” Project, a fundamental research initiative investigating the use of high-energy lasers to accelerate the decay of α-emitting radionuclides by perturbing nuclear structure or lowering the Coulomb barrier [27].

3. FINAL REMARKS

The main steps discussed in this review are summarized in Fig. 1, which provides a schematic overview of the entire radionuclide pathway in nuclear medicine, from the production of radionuclides and the manufacturing of nuclide–vector compounds to patient administration and biological distribution.

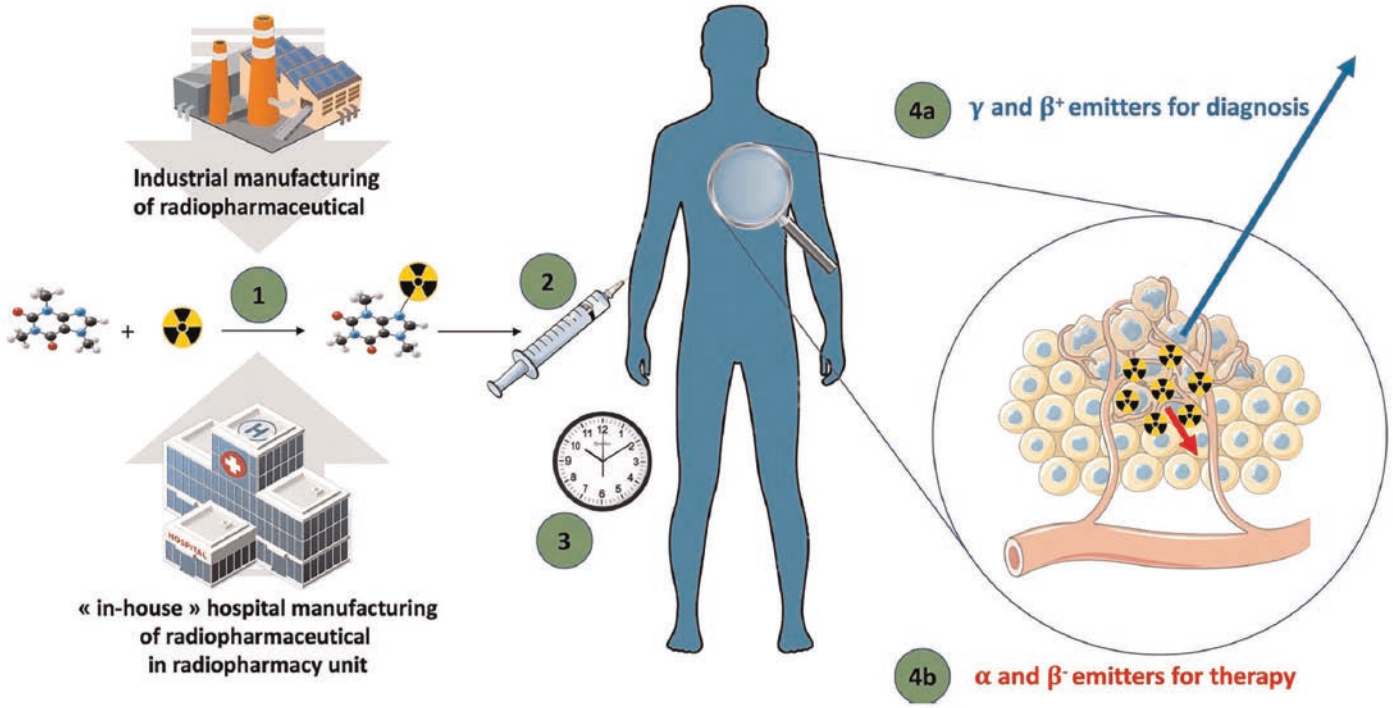

Fig.1 .The figure depicts the integration of production (1), clinical application (2–3) and the dual role of radionuclides in nuclear medicine : (4a) external emission for diagnostic imaging (γ or β^+ emitters) and (4b) targeted irradiation for therapy (α, β^-, or Auger emitters). From Ref. [28].

As highlighted throughout this brief review, the successful clinical application of both established radionuclides and emerging candidates relies on several stringent requirements, including high chemical and isotopic purity, appropriate delivery systems, and adequate specific activity. Although major advances have been achieved in radiopharmaceutical design and theranostic approaches, the reliable production and large-scale worldwide availability of high-purity medical radionuclides remain the principal bottlenecks hindering the widespread implementation of precision nuclear medicine. Emerging reactor-, accelerator- and photon-based technologies, together with innovative separation and recovery strategies , are expected to play a key role in overcoming these limitations . The convergence of next-generation infrastructures, with sustained advances in interdisciplinary research spanning nuclear physics, chemistry, radiochemistry and materials science, is now paving the way for a new era of rapid evolution in the field, ultimately unlocking the full potential of nuclear medicine.

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REFERENCES

[1] Mettler F. A., Guiberteau M. J., "Essentials of Nuclear Medicine and Molecular Imaging," Elsevier Health Sciences, 2019: ISBN 978-0-323-48319-3

[2] Veit-Haibach P. et al., "Green Nuclear Medicine and Radiotheranostics," J. Nucl. Med., 2025, 66: 340

[3] Terranova M. L., "Radioisotopes for nuclear medicine: an overview," Nuclear Technology, 2026: 1–28 ; https://doi.org/10.1080/00295450.2025.2588983

[4] Hussain S. et al., "Modern Diagnostic Imaging Technique Applications and Risk Factors in the Medical Field: A Review," Biomed. Res. Int., 2022, 2022: 5164970; https://doi.org/10.1155/2022/5164970

[5] Precedence Research, Technetium-99m Market Size and Forecast 2025–2034, Report 6310, 2025

[6] Dash A. et al., "Targeted radionuclide therapy—an overview," Curr. Radiopharm., 2013, 6: 152–180; doi: 10.2174/18744710113066660023

[7] Kim Y.-S., Brechbiel M. W., "An Overview of Targeted Alpha Therapy," Tumor Biol., 2012, 33: 573; https://doi.org/10.1007/s13277-011-0286-y

[8] Parus J. L., Mikolajczak R., "Beta-emitting radionuclides for peptide receptor radionuclide therapy," Curr. Top. Med. Chem., 2012, 12: 2686–2693; doi: 10.2174/1568026611212230006

[9] Bolcaen J. et al., "Marshalling the Potential of Auger Electron Radiopharmaceutical Therapy," J. Nucl. Med., 2023, 64: 1344; https://doi.org/10.2967/jnumed.122.265039

[10] Herrmann K. et al., "Radiotheranostics: A Roadmap for Future Development," Lancet Oncol., 2020, 21: 146

[11] Zhang S. et al., "Radiopharmaceuticals and Their Applications in Medicine," Signal Transduct. Target Ther., 2025, 10: 1; https://doi.org/10.1038/s41392-024-02041-6

[12] WORLD NUCLEAR ASSOCIATION, "Radioisotopes in Medicine," 2026; https://world-nuclear.org/information-library/non-power-nuclear-applications/radioisotopes-research/radioisotopes-in-medicine

[13] Giammarile F. et al., "Production and regulatory issues for theranostics" Lancet Oncol., 2024, 25: e260–e269; https://doi.org/10.1016/S1470-2045(24)00041-X

[14] Stora T. , "The age of the blockbuster-scale radiopharmaceutical," CERN Courier (2 June 2026) ; https://cerncourier.com/a/the-age-of-the-blockbuster-scale-radiopharmaceutical

[15] Köster U., Cantone M.-C., "Radioisotope Production," in Azaiez F. et al., Nuclear Physics for Medicine, European Science Foundation–NuPECC, Strasbourg, France, 2014: 97–143; ISBN 978-2-36873-008-937

[16] House of Lords Library, Domestic Manufacture of Medical Nuclear Radioisotopes, LLN-2025-0017, UK Parliament, London, UK (2025) https://lordslibrary.parliament.uk/domestic-manufacture-of-medical-nuclear-radioisotopes/

[17] Sosabowski J. " The UK medical radionuclide supply conundrum" Nuclear Future (Mar/Apr 2026, pp. 22–25) ; https://www.nuclearinst.com/resources/nuclear-future/nuclear-future-march-april-2026-magazine

[18] WORLD NUCLEAR NEWS, "Welsh plan for new nuclear medicine laboratory," 2023; https://www.world-nuclear-news.org/Articles/Welsh-plan-for-new-nuclear-medicine-laboratory-%281%29

[19] Department for Energy Security and Net Zero, "Medical Radionuclide Innovation Programme (MRIP): Selected Projects," UK Government, October 18, 2023 ; https://www.gov.uk/government/publications/medical-radionuclide-innovation-programme/mrip-selected-projects]

[20] OECD/NEA, Supply of Medical Radioisotopes: Challenges and Perspectives, NEA 7743, 2025

[21] Hoffman I., Berg R., "Medical isotope production, research reactors and their contribution to the global xenon background," J. Radioanal. Nucl. Chem., 2018, 318: 165–173; https://doi.org/10.1007/s10967-018-6128-2

[22] Zakalek P. et al., "Neutron sources for large scale user facilities: The potential of high current accelerator-driven neutron sources," Prog. Part. Nucl. Phys., 2025, 142: 104163; https://doi.org/10.1016/j.ppnp.2025.104163

[23] INTERNATIONAL ATOMIC ENERGY AGENCY, Photonuclear Production of Radioisotopes, IAEA TECDOC 2051, 2024; ISBN 978 92 0 116424 7

[24] Terranova M. L., Tavares O. A. P., "Trends and Perspectives on Nuclear Waste Management: Recovering, Recycling, and Reusing," J. Nucl. Eng., 2024, 5: 299; https://doi.org/10.3390/jne5030020

[25] Baker, A.et al ., "The development of centifugal contactors: Next generation solvent extraction equipment for advanced reprocessing of nuclear fuels ." Nuclear Future, 2022, 18(5), 38–50 ; ISSN: 1745-2058

[26] Taylor, R. et al., "The development of future options for aqueous recycling of spent nuclear fuels," Progress in Nuclear Energy, 2023 , 164,104837, https://doi.org/10.1016/j.pnucene.2023.104837]

[27] AMERICAN NUCLEAR SOCIETY, "Decay on Demand: DARPA's Bid to Disrupt Isotope Production," Am. Nucl. Soc. News, 2025; https://www.ans.org/news/article-6171

[28] Faivre-Chauvet A. et al., "Radiopharmaceutical good practices: Regulation between hospital and industry," Front. Nucl. Med., 2022, 7:2:990330; doi: 10.3389/fnume.2022.990330.