

Actineer: Building a Sustainable Actinium-225 Supply for Targeted Alpha Therapy

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Actineer

Abstract

The growing clinical assessment of targeted alpha therapies (TAT) is creating an urgent need for reliable and scalable actinium-225 (Ac-225) supply. This report evaluates the leading Ac-225 production routes, including the thorium-229 (Th-229) generator, photonuclear production from radium-226 (Ra-226), and the Ra-226(p,2n)Ac-225 pathway, discussing their scalability, maturity, and long-term supply potential. The Ra-226(p,2n) route is specifically highlighted for its long-term supply potential, addressing the high yields, high product purity, and efficient utilization of valuable Ra-226 resources capable through this production methodology. This report further highlights selected strategic and technological achievements of Actineer, including the development of an integrated closed-loop production platform, and demonstrates how effective Ra-226 management, supply-chain resilience, and scalable manufacturing will support the development of a reliable and sustainable long-term Ac-225 supply for the growing TAT market.

Introduction

Actinium-225 (Ac-225, T½ = 9.92 d) is widely considered one of the most promising alpha-emitting radionuclides applicable for targeted alpha therapy (TAT) in nuclear medicine today [1]. With four alpha- and two beta-decays in its decay chain **(Figure 1A)**, Ac-225 has a high cytotoxic potential which makes it an attractive radionuclide for applications in radiopharmaceutical therapy (RPT), Early uncontrolled studies with Ac-225-labelled RPTs targeting somatostatin receptors (SSTR) or prostate-specific membrane antigen (PSMA) suggest antitumour activity in patients with advanced gastroenteropancreatic-neuroendocrine tumours (GEP-NET) or metastatic castration-resistant prostate cancer (mCRPC), respectively [2, 3]. Pioneering pre-clinical and clinical studies highlighted the potential of Ac-225, whose high linear energy transfer (<100 KeV/µm) of the emitted alpha-particles (5.8 – 8.4 MeV) creates dense ionization tracks across tumour cell DNA **(Figure 1B)**, potentially leading to superior antitumour activity over radionuclide β-emitters [4-6]. Although

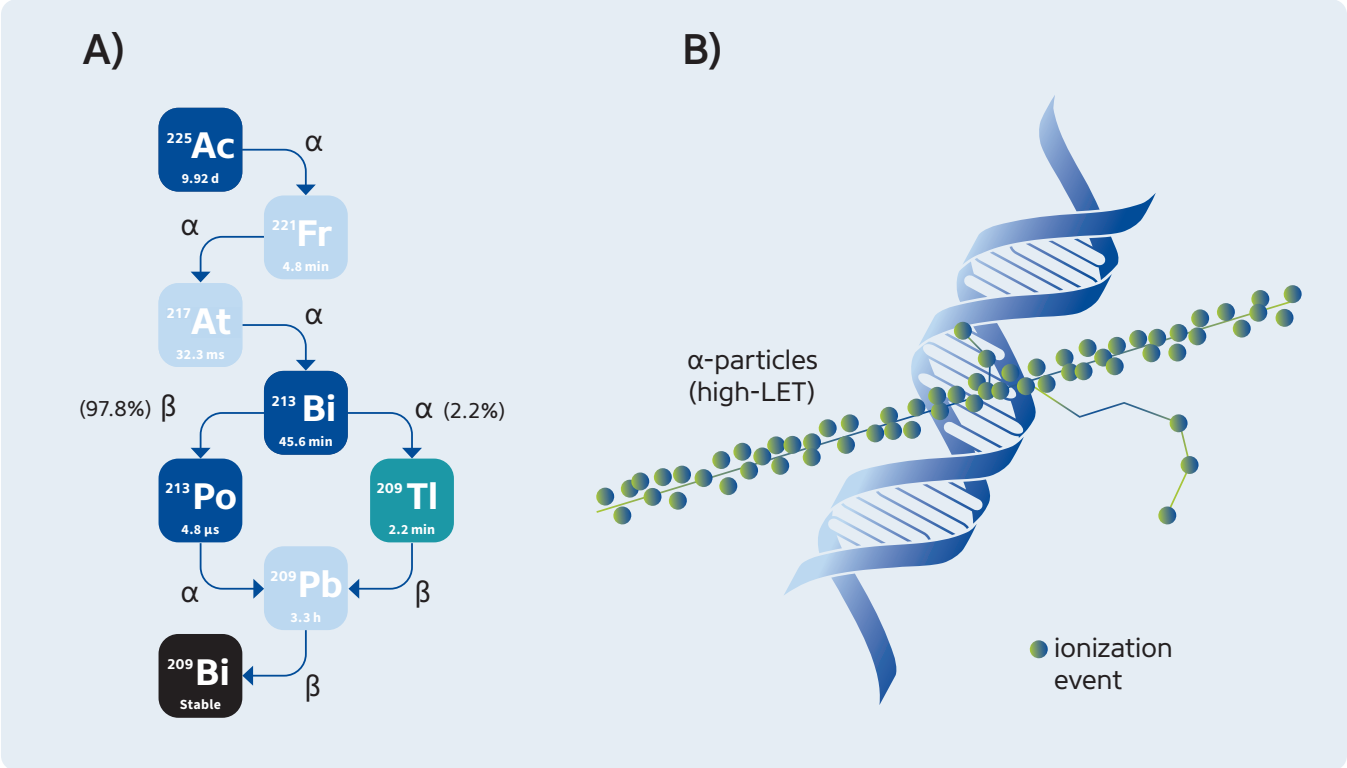

Figure 1: A) Decay chain of Ac-225 B) Demonstration of the ionization track resulting from an alpha-particle traversing across nuclear DNA [8].

no Ac-225 RPT products have yet received marketing authorization, clinical interest in Ac-225 remains high, as evidenced by >35 active clinical trials registered on ClinicalTrials.gov (as of August 2026) [7]. However, the clinical development of Ac-225 has been constrained by the limited availability of Ac-225 [1].

The primary source of Ac-225 for many decades has been from thorium-229 (Th-229, T½ = 7,917 y) generators, which were estimated to produce 60 – 75 GBq Ac-225 per year from approximately 1.6 g Th-229 [9, 10]. Through ongoing uranium-233 (U-233, T½ = 1.6×10^5 y) extraction campaigns, the inventory of Th-229 has increased significantly in recent years [11]. However, the quantity of Th-229 currently available in the purity and specifications required for medical isotope generator systems has not been publicly disclosed. Conservative estimates suggest that 3,000 GBq of Ac-225 must be produced annually to treat 100,000 patients [12]. This estimate assumes that 10 MBq Ac-225 must be produced per administered dose, based on a therapeutic activity of 100 kBq/kg and factoring in radioactive decay losses and radiolabelling yields. It further assumes that each patient receives three treatment cycles.

Current Ac-225 clinical trials are including, but also expanding beyond the established RPT indications of GEP-NET and mCRPC to include several highly prevalent and lethal cancers, such as those of the lung, breast, pancreas and colorectal organs [1, 7, 13]. The United States alone has approximately 1 million estimated new cases of prostate, breast, lung and colorectal cancers (combined, both sexes) each year [13]. Additionally, RPTs are showing positive outcomes in earlier treatment lines and differentiated biological targets [14, 15]. As RPT & Ac-225 TAT are broadening to wider clinical applications, scalable manufacturing and reliable radionuclide supply are critical to maintain growth and adoption [7]. **Figure 2** illustrates with a growing demand of Ac-225, new production technologies will be needed to treat growing patient numbers.

There are currently several emerging technologies and activities to improve Ac-225 supply, varying in their starting material (Th-229 or radium-226 (Ra-226, T½ = 1600 y)), production methodology (generator vs irradiation) and irradiation types (proton, gamma or neutron). Independent of the underlying technology, the most sustainable Ac-225 production route will be

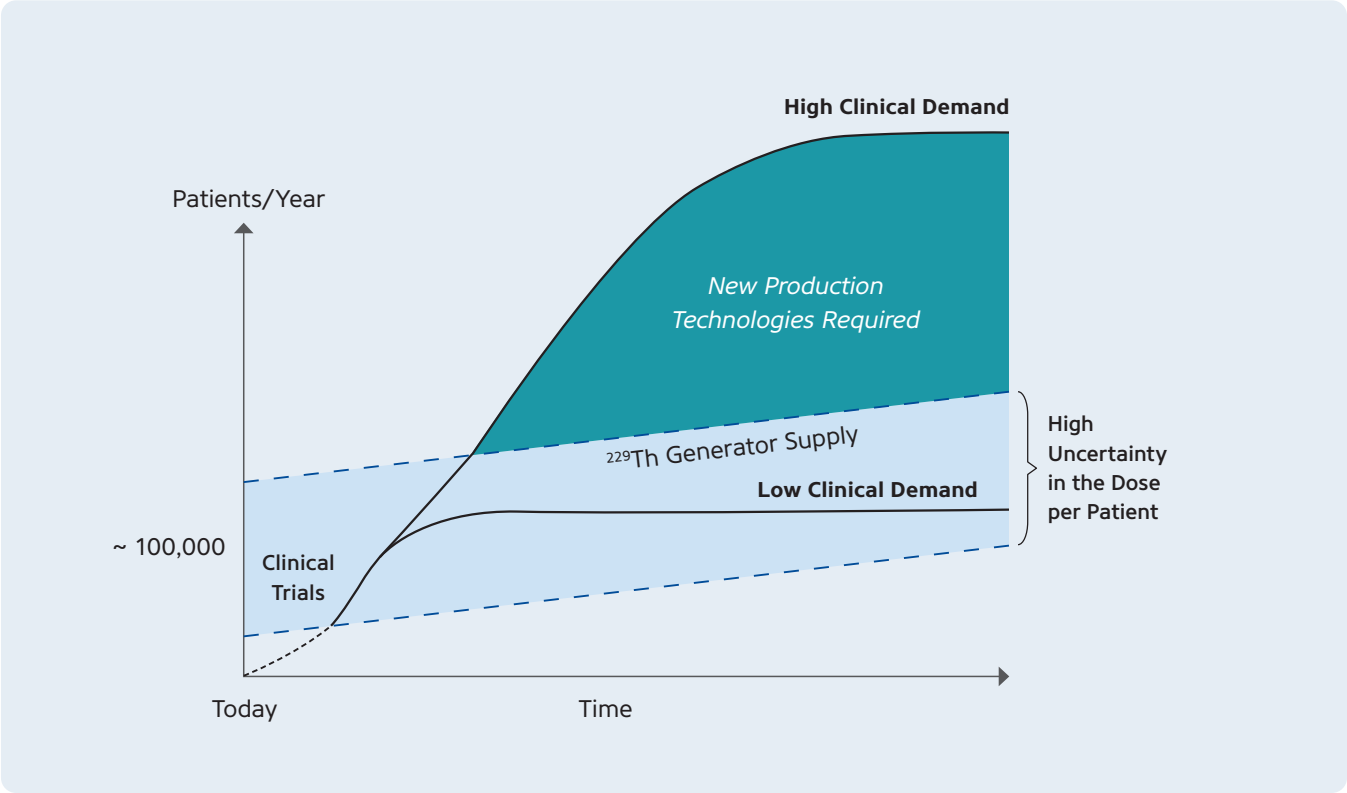

Figure 2: Illustrative projection in the predicted increase in the relative need of Ac-225 over time and availability from U-233/Th-229 stockpiles [16]. The Ac-225 supply quantities shown assume the availability of 45 g of Th-229, derived from U-233 inventories held by the U.S. Department of Energy (DOE) [17]. The wide activity corridor for how much Ac-225 is needed to treat 100,000 patients is based on uncertainties in what a single dose per patient will be, the number of cycles per patient and decay losses from production site to patient.

one that can reliably scale to meet the needs of global multicentre trials and marketed therapies. It must also address key user concerns, including supply reliability and supply-chain security, to support long-term confidence and adoption. Widespread adoption will also depend on consistently delivering the chemical and radionuclidic purity required for radiolabelling, clinical use, and waste management restrictions by manufacturers, hospitals, and treatment centres. Maintaining economic viability by maximizing production efficiency and minimizing costs through activity decay losses and disposal of nuclear waste byproducts will also be essential.

Production of Ac-225 through the high-energy (>100 MeV) proton spallation of thorium-232 (Th-232, T½ = 1.4 × 10^{10} y) is applied today to produce Ac-225 through a Th-232(p, x)Ac-225 pathway, or alternatively to produce radium-225 (Ra-225) (T½ = 14.9 d) by Th-232(p, x)Ra-225 to create Ra-225/Ac-225 generators [18]. The long-term application of this route is hindered by several key limitations, such as the substantial amount of radioactive waste generation, limited available production infrastructure, and significant co-production of actinium-227 (Ac-227, T½ = 21.7 y) in the Th-232(p, x)Ac-225 pathway (0.1 – 0.3% Ac-227 activity to Ac-225) [18]. Producing Ac-225 through Th-232 (p, x)Ra-225 $\xrightarrow{\beta^-}$ Ac-225 can avoid Ac-227 contamination but produces considerably lower Ac-225 activities. Due to these reasons, the high-energy proton spallation of Th-232 to produce Ac-225 is widely regarded as neither a medium- or long-term viable supply route of Ac-225. Producing Ac-225 using high-energy neutron (>6.4 MeV) irradiation is also possible through a Ra-226 (n, 2n)Ra-225 $\xrightarrow{\beta^-}$ Ac-225 reaction but co-production of significant amounts of Ac-227 is expected, creating high waste disposal costs and limiting clinical application [19].

This report focuses on the Th-229 generator, photonuclear production from Ra-226, and proton irradiation of Ra-226 via the (p,2n) reaction, as these routes currently represent the most viable options for sustainable long-term Ac-225 supply and have reached either a sufficient level of technical maturity or method feasibility.

Production Routes Overview

Thorium-229 Generators

Ac-225 is produced from a Th-229 generator through the decay chain Th-229 (T½ = 7,917 y) $\xrightarrow{\alpha}$ Ra-225 (T½ = 14.9 d) $\xrightarrow{\beta^-}$ Ac-225. In this system, Ac-225 is produced as a decay product and approaches the activity of the parent Th-229 through secular equilibrium. Ac-225 is periodically separated from the Th-229/Ra-225 generator to provide a “first-pass” Ac-225 product, while the recovered Ra-225 can be retained in a secondary generator to produce additional Ac-225 in a “second-pass process”. The production and decay profiles of these systems are shown in **Figure 3**.

Ac-225 production in these generators is ultimately constrained by the production and decay of Ra-225 derived from Th-229. Although secular equilibrium for Ac-225 in this system would require approximately 100 days to be reached, it is not necessary to wait for equilibrium before harvesting Ac-225. More frequent separations can increase Ac-225 availability, albeit at the expense of greater operational complexity and higher manufacturing costs [20]. For practical and economic reasons, Ac-225 is typically separated from the Th-229 generator every 30 – 60 days, corresponding to approximately 50 – 85% Ac-225 ingrowth relative to the Th-229 activity. The retained Ra-225 can then be used in a secondary generator, from which Ac-225 is harvested 14 – 21 days later, providing an additional ~33% Ac-225 relative to parent Th-229 activity [10, 20, 21]. The secondary Ra-225/Ac-225 generator may be eluted multiple times; however, each subsequent elution yields less Ac-225, resulting in diminishing returns and increased production costs.

Using the 215 mg Th-229 generator at the Institute for Transuranium Elements (ITU) at Karlsruhe, Germany as a reference and rounding to 200 mg for simplification, a 200 mg Th-229 generator could provide Ac-225 on a biweekly cadence producing approximately 1 GBq of Ac-225 per month [21]. This is achievable by eluting ~0.61 GBq Ac-225 from the primary generator every 30 days and ~0.40 GBq Ac-225 from the secondary Ra-225/Ac-225 generator 14 days later [21, 22]. This yield assumes a 95% recovery yield for both separations, complete Ra-225 recovery, and a 3-day processing time [21].

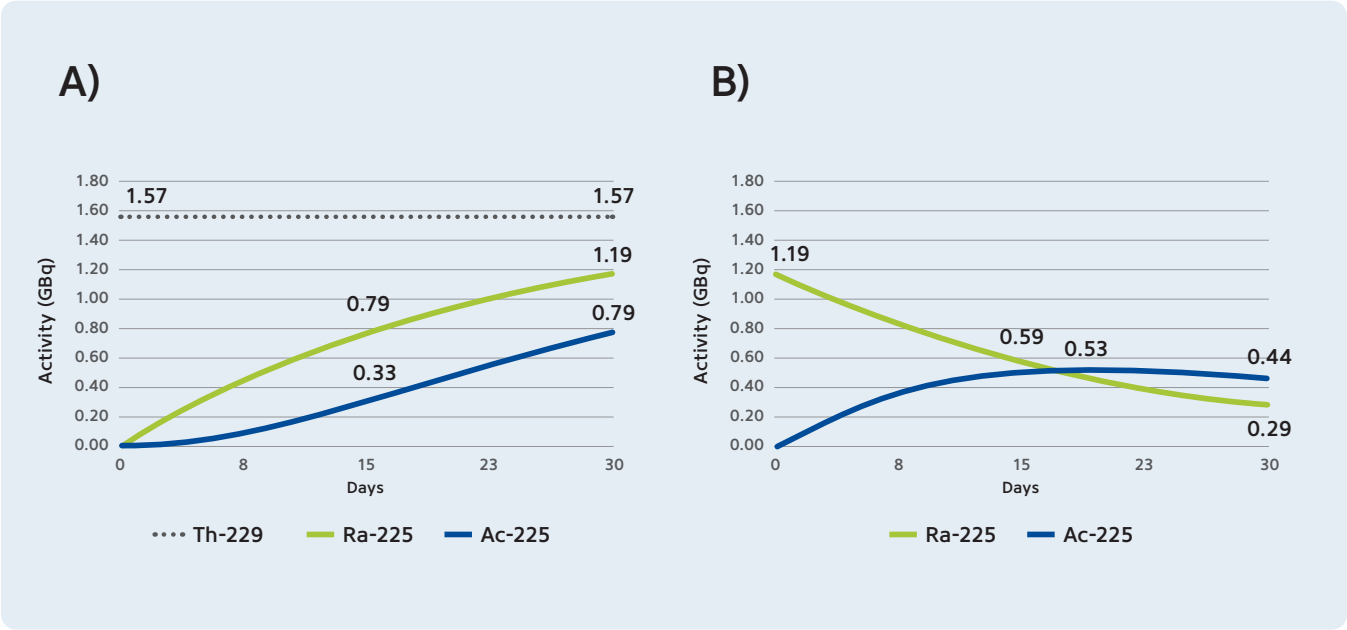

Figure 3: Theoretical ingrowth and decay of Ra-225 and Ac-225 from 200 mg Th-229 over 30-day production cycles. A) First-pass system showing accumulation of Ra-225 (1.19 GBq) and Ac-225 (0.79 GBq) after 30 days. B) Second-pass Ra-225/Ac-225 generator, assuming complete Ra-225 recovery, with Ac-225 peaking at 0.53 GBq after 17 days. Activities reflect decay-generated inventories only and exclude process yields and recovery losses.

The Th-229 generator route is a mature and well-established method for Ac-225 production, having been routinely employed by multiple institutions for decades. Despite reported thorium-228 (Th-228, T½ = 1.9 y) and radium-224 (Ra-224, T½ = 3.6 d) contaminations in some DOE/ORNL Th-229 inventories, Ac-225 can be produced with high radionuclidic purity [22]. However, Ac-225 production through this route is fundamentally constrained by the natural decay of Th-229 and Ra-225. While this provides a reliable and predictable supply, it limits production flexibility and scalability. More frequent generator elution's can increase Ac-225 availability but result in lower yields per harvest and higher manufacturing costs. Additional Th-229 generators can also be established to improve supply availability and flexibility, i.e. 2 × 100 mg Th-229 generators rather 1 × 200 mg generator. Operating 2 generators in parallel could offer weekly Ac-225 availability but have higher operating costs and contribute to manufacturing complexity. Increasing the number of Th-229 generators is also limited by facility and infrastructure constraints, including hot-cell capacity and critical equipment availability.

The principal limitation of this production route is the scarcity of Th-229, which is derived largely from legacy U-233 inventories. Increasing Th-229 stockpiles can also be achieved through prolonged neutron irradiation of Ra-226 via a sequence of neutron-capture reactions and β^- decays leading ultimately to Th-229, where reported production yields were low (74 MBq Th-229 / g Ra-226, 26 d irradiation), also utilising the very high-flux HFIR reactor (2.0×10^{15} n $cm^{-2} \cdot s^{-1}$), indicating very long irradiations (multiple years) using very large Ra-226 masses would be needed to produce meaningful quantities of Th-229 [23]. The produced Th-229 would also be heavily contaminated with Th-228, requiring significant decay to occur before Th-229 generator establishment.

Currently, the rate at which Th-229 can be extracted from U-233 stockpiles is not publicly disclosed, nor is the extent to which "significant" amounts of accumulated Th-228 influences the continuous Th-229 refinement [22]. This Th-228 contamination constrains Th-229 processing throughput due to the generation of hazardous decay-chain products, including radon-220 (Rn-220, T½ = 55 s) and thallium-208 (Tl-208, T½ = 3 m). Even with full utilization of the DOE's >45 g Th-229 inventory, this would be insufficient to meet projected long-term clinical demand for Ac-225, underscoring the need for additional large-scale production technologies.

Photonuclear Production of Ac-225 through Ra-226

Irradiating Ra-226 with high-energy photons (>6.4 MeV) produces Ac-225 through the Ra-226(ɣ,n) Ra-225 $\xrightarrow{\beta^-}$ Ac-225 pathway, which has a maximum cross-section of 266 mb at 12 MeV [24-26]. The photonuclear production of Ac-225 has been experimentally reported, while published yields remain low (<3 MBq), recent announcements suggest that substantially higher rates may be achievable through modern dedicated, high-power photon irradiation systems [25, 27-31]. The generation of bremsstrahlung photons is one such method to produce Ac-225 through the photonuclear pathway. Bremsstrahlung photons are generated by directing high-energy electrons (typically 20 – 40 MeV) onto converter targets such as tungsten or tantalum, producing a broad-spectrum photon field, which contribute to by-product production through additional (ɣ, x) reactions. This approach generates Ra-225, which serves as a Ra-225/Ac-225 generator system that can be eluted multiple times **(Figure 4)**. As the photonuclear reaction is based on establishing Ra-225/Ac-225 generators, multiple generator systems can be operated in parallel, enabling a higher Ac-225 supply cadence than is achievable for a single generator system.

With photon energies exceeding 11 MeV, the desired Ra-226(ɣ,n)Ra-225 reaction competes with the Ra-226 (ɣ,2n)Ra-224 and with Ra-226(ɣ,3n)radium-223 (Ra-223, T½ = 11.4 d) at gamma energies exceeding 19 MeV, respectively **(Figure 5)**. As photon energy increases, the (ɣ,2n) reaction becomes increasingly significant, reaching cross-sections of 122 mb at 12 MeV and 515 mb at 14 MeV. Diehl et al. observed close agreement between measured and TENDL-predicted values, reporting a Ra-225:Ra-224 production ratio of 1:3 [27]. The co-production of Ra-224 creates operational and environmental challenges, notably from Rn-220 and Tl-208, which can limit processing capacity. If the radium fraction (Ra-223, Ra-224, Ra-225, and Ra-226) cannot be effectively separated from Ac-225, it also creates radiation protection challenges for receiving sites and patient therapy.

Ac-227 is generated through neutron capture on Ra-226 via the Ra-226(n,ɣ)radium-227(Ra-227) $\xrightarrow{\beta^-}$ Ac-227 reaction. Ac-227 content can be mitigated by allowing Ra-227 (T½ = 42.2 m) to decay fully before processing, discarding the resulting Ac-225/Ac-227 fraction, and retaining the radium fraction for subsequent Ac-225 ingrowth. The consequence of discarding the Ac-225/Ac-227 fraction is naturally a lower quantity of Ac 225 per irradiation in favour of removing the Ac-227.

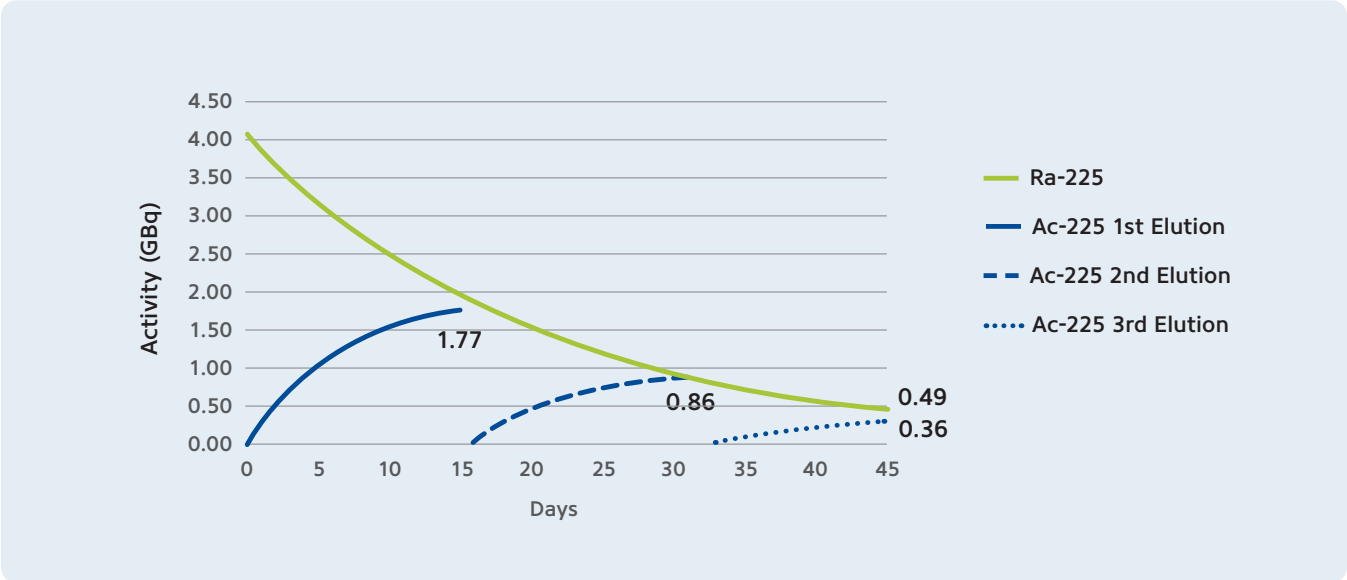

Figure 4: Decay of Ra-225 and in-growth of Ac-225 in a Ra-225/Ac-225 system. As an example, 4 GBq Ra-225 could be eluted three times to produce ~3 GBq Ac-225. Ac-225 production from Ra-225 generators follows the same principles in both the Th-229 and photonuclear routes. The feasible number of generator elutions depends on the available Ra-225 activity and the diminishing benefits of repeated elutions.

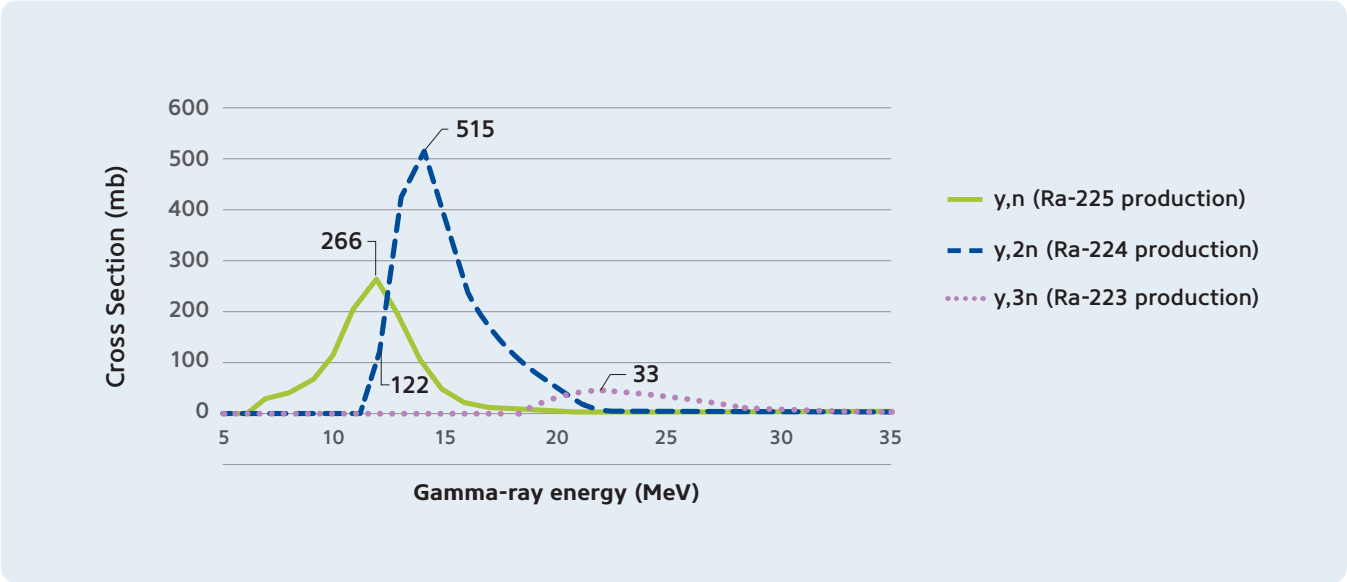

Figure 5: TENDL 2017 cross-sections for the photonuclear production of Ra-225, Ra-224 and Ra-223 from Ra-226 using highly energetic photons [26]. Selected cross-section values are highlighted due to their relevance to the production of Ra-225 and key unwanted by-products, Ra-224 and Ra-223.

Photonuclear reactions generally have lower cross-sections and production yields than neutron- or proton-induced production routes [32]. To improve yield, Ra-226 targets can be stacked or shaped to fit within the photon field, while converter designs and photon generating apparatus can be tailored to maximize photon flux within the target mass [33, 34]. However, generating sufficient photon flux for large-scale Ra-225/Ac-225 yields requires prolonged high-power irradiation of the converter, creating substantial thermal and engineering challenges. Maslov et al. experimentally measured Ac-225 production rates of approximately 550 Bq/mg Ra-226/μAh using electron-induced photonuclear reactions on Ra-226 targets [29]. Independent FLUKA simulations performed by Diamond and Ross found production rates of 415-456 Bq/mg Ra-226/μAh, which show consistency with the experimental measurements [24]. These results demonstrate that substantial Ac-225 activities may be achievable through the photonuclear route when paired with gram-scale Ra-226 target masses [27]. In contrast, lower production rates have been reported for less optimized irradiation arrangements [27, 28]. For example, Melville et al. produced <2.4 MBq of Ac-225 from a 40 mg Ra-226 target using an 18 MeV medical linear accelerator, although the equipment used was not specifically designed or optimized for isotope production [28].

Scaling Ra-226 target mass can significantly increase Ac-225 production, but it also increases the challenge of achieving the high Ra/Ac separation factors required for product purification. Based on the results of Diehl et al., production of 0.127 kBq Ac-225 from 12.8 kBq Ra-226 implies that a separation factor of >1 × 10^7 is needed to limit residual Ra-226 to <0.001% of the final product [27]. As Ac-225 and Ra-225 decay in the generator system, increasingly higher separation factors are required to maintain <0.001% Ra-226 radionuclidic purity relative to Ac-225.

Proposed photonuclear production concepts suggest 1 – 10 g Ra-226 targets are feasible, however, with larger Ra-226 mass, radiolysis and processing complexity will increase, which intensify the challenges in maintaining sufficient separation efficiencies [24, 35]. While Ac-227 is often considered the principal long-lived impurity of concern in Ac-225 production, residual Ra-226 represents a greater radiological concern due to its T½ = 1600 y and hazardous decay chain. Consequently, any Ra-226-based Ac-225 production route must demonstrate exceptionally efficient Ra-226/Ac-225 separation to achieve acceptable radionuclidic purity. While the photonuclear route offers a theoretically scalable approach to Ac-225 production, there is currently limited experimental evidence demonstrating performance at the gram Ra-226 scale which is suggested as necessary for large Ac-225 yields. As a result, the achievable long-term supply capacity remains uncertain and will depend on successful validation of production yields, target technologies, and high-efficiency Ra-226 decontamination processes.

Cyclotron Irradiation, the Ra-226(p,2n)Ac-225 Route

The Ra-226(p,2n)Ac-225 reaction is produced using medium-energy cyclotrons, utilizing proton energies in the 15 – 18 MeV range. In the 16 – 16.8 MeV range, the reaction has a cross-section of 698 – 710 mb **(Figure 6)** and has been demonstrated to produce large yields, exceeding 2 GBq [36, 37]. Minor quantities of actinium-224 (Ac-224, T½ = 2.8 h) & actinium-226 (Ac-226, T½ = 29.4 h) are co-produced through the Ra-226(p,3n)Ac-224 and Ra-226(p,n)Ac-226 reaction pathways, respectively [36]. Ac-224, Ac-225, and Ac-226 are all isotopes of the same element, and therefore cannot be separated through standard chemistry or chromatography methods. Instead, impurity control relies on proton-energy optimization, target design, and post-irradiation decay management. Although Ra-226(p,3n)Ac-224 has a relatively high cross-section of 294 mb at 16 MeV **(Figure 6)**, the short half-life of Ac-224 allows it to decay to neglible activities before the final product processing steps, making its contribution negligible. In contrast, Ac-226 has a very small cross-section of 34 mb at 16 MeV **(Figure 6)** but the longer half-life necessitates careful management, as this is typically the defining impurity for the Ac-225 radionuclide purity value. As Ac-225 has a substantially longer half-life than Ac-226 (9.92 d vs. 29.4 h), the Ac-226 content generally determines the earliest release date of the product rather than the length of its shelf-life. Through appropriate irradiation condition management, decay and chemical processing, high radionuclidic purities can be achieved, with Nagatsu et al. reporting >99% Ac-225 purity [38].

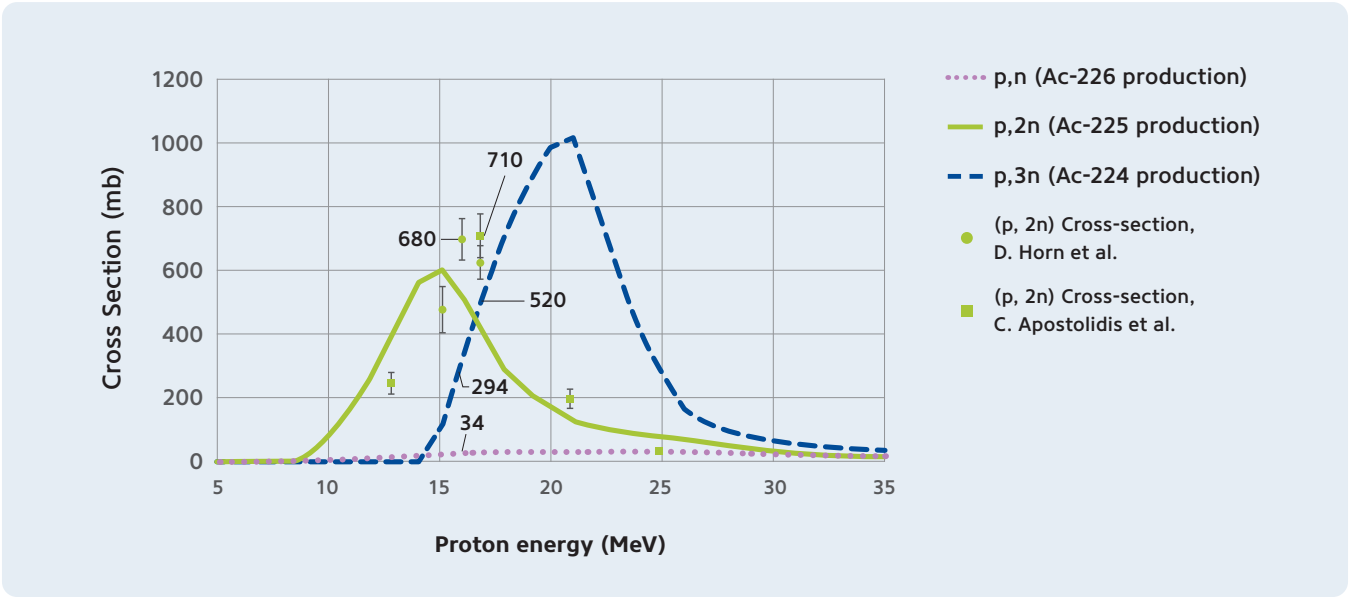

Figure 6: TENDL 2017 cross-sections for the proton-activation production of Ac-225, Ac-224 and Ac-226 from Ra-226 using medium-energy protons, including experimentally determined measurements [26, 36, 39]. Relevant cross-section values are highlighted to illustrate the production pathways of Ac-225, and the Ac-224 and Ac-226 by-products. Error bars are shown only for the data reported by Horn et al. and Apostolidis et al., as uncertainties were not provided for the Tendl dataset.

Control of Ac-227 co-production is critical in the Ra-226(p,2n)Ac-225 production route, as Ac-227 cannot be chemically separated from Ac-225 and its much longer half-life prevents removal through decay management. Ac-227 can be generated via both the Ra-226(p,γ)Ac-227 reaction and a secondary-neutron capture through the Ra-226(n,γ)Ra-227 $\xrightarrow{\beta^-}$ Ac-227 pathway. Minimizing its formation requires careful consideration of irradiation conditions and targetry. These parameters are equally important for target stability, as Ra-226 targets must safely withstand high fluence while maintaining structural integrity and containing Ra-226 and its activation and decay products. Reliable, efficient production of high-quality product is key to commercial scale-up and viability.

This route is not constrained by the ingrowth

of Ac-225 from Ra-225, enabling a short production timeline from irradiation to shipment. This minimizes decay losses and maximizes the amount of Ac-225 delivered per milligram of irradiated Ra-226. Combined with its high reaction cross-section and the large stopping power of protons in solid Ra-226 targets, the p,2n route offers a large Ac-225 production efficiency relative to the Ra-226 target mass. There is currently no commercial-scale production of Ra-226, and global supplies remain limited to material recovered from legacy sources. Consequently, the efficient preparation, irradiation, recovery and recycling of Ra-226 targets, are critical to the long-term sustainability of this production route, and any that utilize Ra-226 as a target material.

The technology underlying this production route is relatively mature and approaching large-scale commercialization. There are a number of commercial cyclotrons manufacturers producing cyclotrons with multiple beam lines, with sufficient proton energies and beam power to produce massive Ac-225 activities, therefore irradiation capacity is unlikely to be a limiting constraint in the Ra-226(p,2n)Ac-225 route. The remaining challenges lie in developing robust target systems capable of withstanding prolonged high-power irradiation, together with scalable chemistry processes for Ra-226 target preparation, Ra-226/Ac-225 separation and recycling, and final-step production of large quantities of high-purity Ac-225.

Actineer's Innovations Driving Next-Generation Ac-225 Manufacturing

Actineer has advanced the Ra-226(p,2n)Ac-225 route from laboratory demonstration to routine manufacturing through a series of technological innovations. Stable Ra-226 targets were reproducibly prepared, achieving a substantial scale-up to double-digit mg Ra-226 target masses, with further increases in development. The developed Ra-226 solid-target design demonstrated reliable performance under high fluence conditions, maintaining its integrity throughout production operations and subsequent processing steps. Throughout Actineer's irradiation campaigns, zero targets failed during irradiation, reflecting on the robust target design. High-yield Ac-225 production has been achieved, producing several GBq's per irradiation. The Actineer production yield is consistent with the high cross-section (~700 mb) of the Ra-226(p,2n)Ac-225 route reported by Apostolidis et al. and Horn et al. [36, 39]. Qualification testing beyond the current production envelope has demonstrated stable operation at higher beam currents, longer irradiation times and greater target masses, providing a clear pathway to further increases in output per irradiation.

The end-to-end process was designed to recover high yields of Ac-225 whilst separating and retaining a maximum amount Ra-226 for future irradiations. Additionally, decay products of Ra-226, Ac-224 and Ac-226, and activation products from trace constituents or proton-fission products are removed in a multi-step automated chromatographic process. Development of this process has been supported by the extensive Ac-225 chemistry, manufacturing, and quality control expertise established within Isotope Technologies Munich SE (ITM) and Canadian Nuclear Laboratories (CNL) through years of working with Ac-225 and medical radioisotopes. The irradiation conditions were designed not only to maximize Ac-225 production, but also to favour the Ra-226(p,2n)Ac-225 reaction over adjacent reaction channels producing Ac-226 or Ac-227. The results of these efforts have translated to an Ac-225 product with consistent ≥99.9% radionuclidic purity at customer calibrated activities.

Ac-227 is commonly regarded as a concerning waste product of Ac-225 production due to the large amount of Ac-227 that is produced in the Th-232 spallation production route of Ac-225 [18]. During the Actineer scale-up campaign, we frequently observed the Ac-227 content to be below the minimum detectable activity (MDA) with a maximum observed value of $\leq 9.2 \times 10^{-4}$% at the end of shelf-life of our product. Ra-226 was always below the MDA in our purified Ac-225, further highlighting the efficacy of the targetry system and production processes. The Ra-226 separation processes have achieved an

outstanding separation of Ra-226 from Ac-225, resulting in a decontamination factor exceeding multiple orders of magnitude. This will facilitate target scale-up without concern for Ra-226 impurities in the Actineer final product.

The consistently high radionuclidic purity (≥99.9%) of our Ac-225 across increasing Ra-226 target masses and Ra-226/Ac-225 separation factor demonstrates the robustness, reliability, and radiolytic stability of our irradiation and production processes. This is further supported by the satisfactory radiolabelling performance of Ac-225 produced using our recently scaled-up process, achieving radiolabelling yields ≥99% (1 MBq Ac-225 /10 µg of DOTATOC). The desirable radiolabelling performance is attributable to the favourable chemical purity profile of the Ac-225 product.

Ra-226 recovered from irradiated targets was successfully purified, reintroduced into the production process, and re-irradiated to again produce Ac-225, demonstrating the completion of a closed-loop production cycle [40]. Each step in this cycle is supported by high-yield & high-recovery manufacturing processes which add to the sustainability of Actineer's Ac-225 production. An overview of the major steps in the production cycle are illustrated in **Figure 7**. The recycled Ra-226 was able to maintain consistent product quality and yield across the different production cycles. Actineer's current and future supply of Ra-226 is secure, supported by a large existing inventory of Ra-226 through CNL together with highly efficient and demonstrated processes [40].

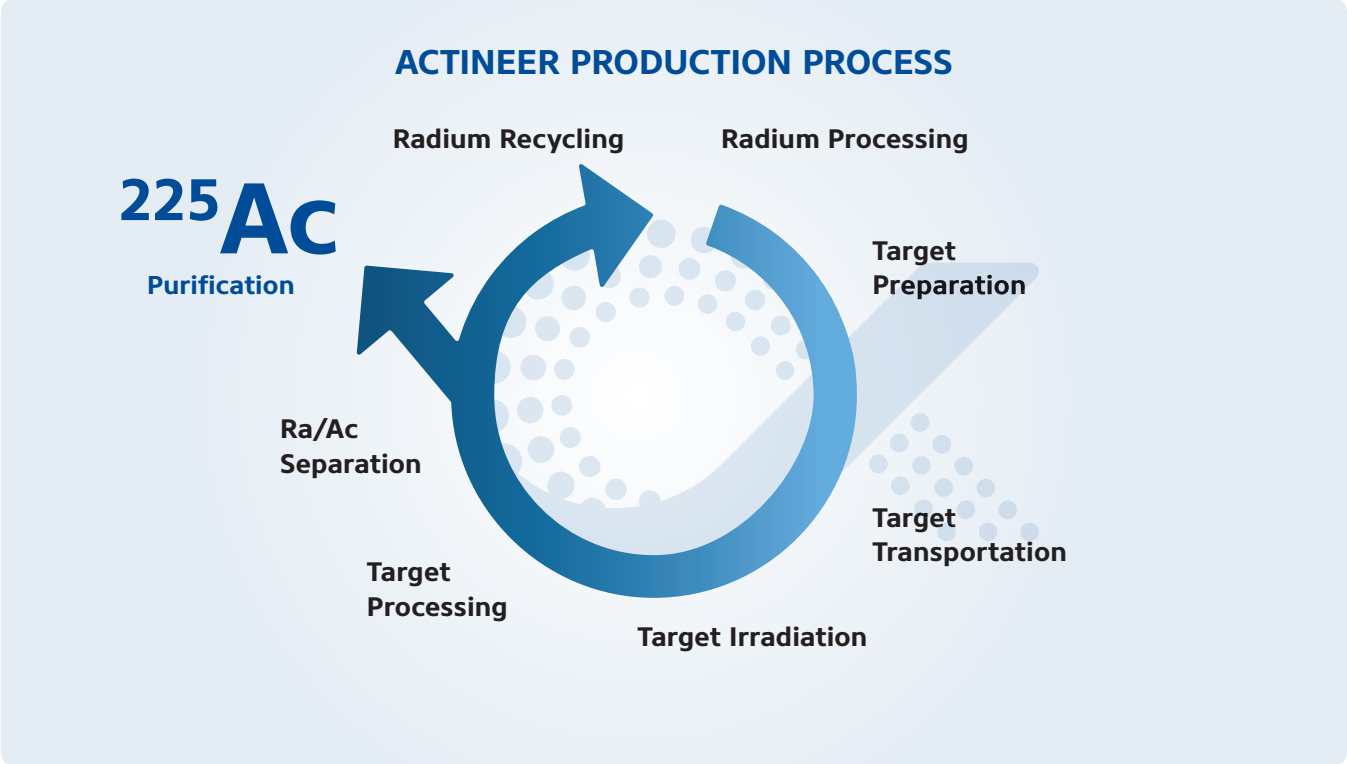

Figure 7: Overview of the major steps in the Actineer Ac-225 production process. Actineer has developed and implemented a closed production cycle that enhances supply chain security and supports scalable manufacturing across the entire production process.

Actineer benefits from a resilient supply chain. Through access to the facilities, technical expertise, and resources of ITM and CNL, Actineer is well positioned to scale manufacturing capacity and expand the global availability of Ac-225 [41]. Irradiation capacity is secured and can be expanded quickly, while additional beamline and production capacity are available through CNL and the Sylvia Fedoruk Canadian Centre for Nuclear Innovation, Inc. (SFC) laboratories in Canada [42]. Actineer also benefits from ITM's established manufacturing, quality control, and regulatory expertise, facilitating the short-term Ac-225 production capabilities while working long-term towards a dedicated Actinium Production Facility (APF) [41].

	Ra-226(p,2n)Ac-225	Th-229 Generator	Ra-226(y,n) Ra-225 $\xrightarrow{\beta^-}$ Ac-225
Availability of Starting Materials	**Medium** Limited supply of natural Ra-226 from legacy stocks or mining	**Low** Th-229 coming only from U-233 legacy stocks, structurally capped	**Low** Limited Ra-226 availability and larger inventories needed than (p, 2n) route
Technological Maturity	**Medium-High** Proven route. Relatively mature and approaching large-scale commercialization	**High** Well-established and robust process.	**Low-Medium** Theoretically able to supply but never proven at meaningful scale
Product Quality	**High** Negligible Ac-227 impurities and excellent Ra-226/Ac-225 separation achieved with effective management of long-lived contaminants	**High** Virtually no impurities from Th-229 natural decay	**Medium-High** Ac-227 can be eliminated during processing; Ra-226/Ac-225 separation factors >1 × 10^7 needed to avoid Ra-226 breakthrough
Route Sustainability	**High** High-yield Ac-225 production enabled by demonstrated closed-loop manufacturing process, effective Ra-226 recycling and minimal waste generation	**High** Long Th-229 T½ (7,917 y) supports ongoing Ac-225 production; Th-229 is recovered and retained across cycles.	**Medium** Large Ra-226 target processing present significant chemistry challenges, and high-purity separations at scale are unproven. Minimizing Ra-226 losses across production cycles is critical
Scalability	**High**	**Low-Medium**	**Medium**
Viability	**Proven route already demonstrated. Effective Ra-226 inventory management and technology achievements provide clear pathway to further production scaling**	Well-established methodology with robust chemistry demonstrated. Structurally limited supply potential.	High theoretically capacity with limited experimental evidence. Large Ra-226 targets will add process complexity and residual Ra-226 is major radiobiological concern.

Conclusion

The growing demand for Ac-225 is driving the need for robust, scalable, and sustainable production technologies. Existing production methodologies are unable to supply the current and future clinical and market needs, underpinning the need for new production technologies to emerge. While each route offers distinct advantages, the Ra-226(p,2n)Ac-225 pathway stands out for its ability to produce large quantities of high-purity Ac-225, offering scalability beyond Th-229 generators while maximizing Ra-226 utilization through high production rates and short production process lengths. Efficient recovery and recycling of Ra-226 are critical to long-term supply sustainability, enabling repeated production campaigns, reducing material losses and costs, and consistently delivering high-purity Ac-225 without Ra-226 contamination.

Actineer's approach to Ac-225 production is built around a fully integrated, closed-loop production cycle designed for both scalability and operational resilience. By integrating Ra-226 management, isotope production, product purification, and Ra-226 recovery within a single platform, Actineer maximizes the utilization of a critical raw material while minimizing waste, supply-chain dependencies, and production risks. This approach is further strengthened by access to the established expertise, infrastructure, and operational capabilities of ITM and CNL, enabling the efficient development and scale-up of Ac-225 manufacturing.

Furthermore, each step in the manufacturing process can be expanded independently and incorporates redundancy, enabling the manufacturing platform to scale efficiently in response to growing market demand. By combining innovation, quality, and supply-chain resilience, Actineer is establishing itself as a trusted isotope supplier, enabling a reliable long-term supply of Ac-225 and to support the continued advancement of research and development of TAT.

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About Actineer, Inc.

Actineer™ Inc. is a joint venture company between Canadian Nuclear Laboratories (CNL) and ITM Isotope Technologies Munich SE (ITM) dedicated to advancing Ac-225 technologies, quickly securing supply, and producing industrial-scale quantities of this valuable, rare medical radioisotope for the treatment of cancer. Founded in October 2023, Actineer™ Inc. together with its strong supply chain collaborators seeks to progress Ac-225 development, production, and processing technologies. It has established short-term production capabilities that are expected to lead to significantly boosting international supplies, while working long-term towards the construction of a new Actinium Production Facility (APF) in Canada. The joint venture's mission is to fulfil the unmet global manufacturing and production needs of this coveted radioisotope with significant potential in the fight against cancer.

For sales requests or to receive technical assistance

If you require actinium-225 or have any sales related questions, please contact ITM's sales team. The team is more than happy to answer any questions you might have and advise you regarding your intended use of actinium-225.

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