

Actinium Pharmaceuticals, Inc.

(ATNM: NYSE American)

ATNM: Introduction to Radiopharmaceuticals

Research Note - Radiopharmaceuticals

Following our recent [initiation of coverage](#) for Actinium Pharmaceuticals, Inc. (NYSE American: ATNM), this research note provides life sciences investors with an introduction to the radiopharmaceutical industry. We examine the science, clinical applications and manufacturing requirements shaping the sector, highlighting both its therapeutic potential and the challenges of development and commercialization. The following pages complement our company-specific research and provide a foundation for evaluating Actinium and other radiopharmaceutical companies.

Radiopharmaceuticals are radioactive medicines or radioisotopes that are used to diagnose and/or treat disease. They are used to image a variety of conditions from cancer to cardiovascular disease to kidney dysfunction and neurodegenerative disease. They have also shown promise in conditioning prior to a stem cell transplant due to the precise delivery of radiation. In the treatment realm, this class of drug is predominantly used in cancer. Imaging has broader applications in oncology, neurology and cardiology. Radionuclides are radioactive forms of elements that can either occur naturally or be manufactured. The radioactive element contains an unstable nucleus which emits radiation as it decays. The particles and rays that it emits can either be detected by a variety of diagnostic devices or bombard tumors which causes DNA strand breaks and cancer cell death.

The agents can be further categorized depending upon what type of radiation they produce. These include products that release alpha (α) particles, beta (β) particles, gamma (γ) radiation, positrons and neutrons among other emissions. The emissions support applications in medicine, scientific research, industrial processes and energy production. Some of the most common radionuclides, which are also known as radioisotopes, are listed below.

Exhibit I – Common Isotopes Used in Radiomedicine

Actinium-225	Thallium-201	Indium-111	Yttrium-90
Samarium-153	Radium-223	Gallium-68	Carbon-11
Lutetium-177	Fluorine-18	Iodine-131	Cobalt-60

Compiled by Zacks Analyst

The physical half-life¹ of a radioactive isotope is a critical consideration in the use, safety, and efficacy of radiopharmaceuticals. It determines which facilities can accommodate a given product and constrains which clinical applications are feasible. For diagnostic use, an isotope must have a half-life short enough to decay away soon after imaging is completed, whereas for therapeutic applications, the physical half-life must be long enough to fatally damage the cancer cells it seeks to eradicate. The biological half-life is another vital consideration. It is the time required for the body to eliminate half the agent through metabolism, excretion, and other physiological processes. Together, the physical and biological half-lives combine to yield the effective half-life, calculated as $T_e = (T_p \times T_b) / (T_p + T_b)$,² which governs the elimination of radioactivity from the body. When estimating residual activity or performing radiation dosimetry calculations, the effective half-life is the most important value, as it accounts for both radioactive decay and biological clearance.

¹ The half-life is the time it takes for half of any given amount of a radioactive isotope to decay into its daughter products. This rate remains constant regardless of the sample size.

² T_e is effective half-life, T_p is physical half-life and T_b is biological half-life.

Radiopharmaceuticals undergo rapid decay and often must be prepared immediately before administration, placing operational demands on manufacturers, hospital pharmacies and nuclear medicine departments. This requires providers to balance limits on distribution range and scheduling flexibility against exposure to unnecessary radiation beyond the diagnostic or therapeutic window. From a patient safety standpoint, the radionuclide half-life of a diagnostic agent should ideally be as short as possible, since any radioactivity remaining after a scan has no diagnostic value and contributes only to patient radiation exposure. Radionuclide selection must be tailored to the specific clinical application, the logistics of delivery and the imperative to minimize patient risk.

Other features important to success include low cost and availability. The agent must specifically target the desired tissue but must either not accumulate in or clear quickly from non-target tissues in order to minimize background noise and organ exposure. The radionuclide should emit the proper type of radiation for its purpose, such as gamma rays for imaging and alpha or beta particles for therapy. Favorable pharmacokinetic properties are also essential such as effective targeting, stable labeling, predictable biodistribution, rapid clearance from non-target tissue and chemical stability.

Types of Radiation

Radiomedicine is associated with many types of radiation including X-rays, gamma radiation, alpha and beta particles, positrons and Auger electrons. The most widely used type of radiation in modern medicine is the X-ray. It is used for body imaging, mammography, dental imaging and fluoroscopy. Gamma rays are important for their role in imaging, positron emission tomography (PET) scans and stereotactic radiosurgery (SRS) for treatment of brain tumors. Beta radiation is commonly used to treat certain types of cancer, eye conditions and to alleviate pain in bone metastases. Proton beam therapy is a radiation treatment that precisely delivers a beam of protons to disrupt and destroy tumor cells while ultraviolet radiation can be used to treat skin conditions like psoriasis.

Auger electrons are another type of particle that is used in therapy. The advantage of Auger electron therapy is high linear energy transfer. They deliver intense radiation damage within an extremely short range, potentially minimizing damage to surrounding healthy tissues when properly targeted to cancer cells.

Therapy most frequently employs beta or alpha emitters which offer tissue-damaging properties while imaging typically requires gamma or positron emitters which show up on scans. Some radioisotopes emit multiple types of radiation, allowing for the combination of therapy and diagnostic imaging. These are known as theranostic applications.

In the context of Actinium Pharmaceuticals, Ac-225 is the relevant radioisotope. It emits high energy alpha particles used in targeted alpha therapy. Several other radionuclides similarly emit alpha radiation including radium-223, lead-212,³ thorium-227 and astatine-211 among others. Alpha-emitters give off small, high-energy particles composed of two protons and two neutrons tightly bound together.⁴ Their range extends the length of a few cells⁵ and the particles are able to cause fatally damaging double-strand DNA breaks (DSBs). The short range helps reduce damage to healthy tissue. The nucleus emits the particles during its radioactive decay. Alpha emitters contrast with beta radiation which delivers lower linear energy transfer over a longer path length. While alpha therapy works best for small-volume, targeted disease, beta radiation is more appropriate for larger tumor masses.⁶

A Condensed History of Radiopharmaceuticals

Radiation has been associated with medicine for over a century with X-rays producing some of its earliest benefits. X-rays were used to image and treat cancer in the late 19th century in Germany.⁷ In 1928, head and neck cancers were cured with fractionated X-rays and a decade later the first patient was treated with neutron beams.⁸ As the science advanced, the first radiopharmaceuticals were developed that could serve as either diagnostic tracers or therapeutic agents.

³ Lead-212 does not directly emit α radiation; instead, it acts as an in vivo beta-minus (β^-) emitter that decays into bismuth-212, which subsequently emits alpha particles.

⁴ Australian Radiation Protection and Nuclear Safety Agency. [Alpha Particles](#). Accessed July 2026.

⁵ α particles typically travel from 50 – 100 μm . Human cells generally range from 10 – 30 μm .

⁶ Karimi, H., *et al.* [Alpha and Beta Emitters in Translational Nuclear Medicine: Clinical Advances, Challenges, and Future Direction](#). International Journal of Molecular Sciences. February 2026.

⁷ On November 8, 1895, physicist Wilhelm Conrad Röntgen (1845-1923) became the first person to observe X-rays, a significant scientific advancement that would ultimately benefit a variety of fields, most of all medicine. In 1896 Röntgen presented a lecture on the X-ray. Within months, systems were being devised to use x-rays for diagnosis, and within three years radiation was used to treat cancer. American Cancer Society, [History of Cancer Treatments, Radiation Therapy](#).

⁸ Connell, P.P., Hellman, S. [Advances in Radiotherapy and Implications for the Next Century: A Historical Perspective](#). Cancer Research. January 2009.

Other mentions of radiopharmaceuticals in the early twentieth century relate to radiotracers and their use to conduct diagnostic procedures. The first use of a radiotracer is often credited to George de Hevesy in the 1920s. He used radioactive lead to study lead metabolism in plants, which is considered one of the pioneering experiments in nuclear medicine and radiotracer technology.⁹ In 1925, at the Beth Israel Hospital in Boston, Hermann Blumgart measured circulation using radium C to generate vapor trails in a modified Wilson cloud chamber.¹⁰ In the 1930s, Emilio Segre and Carlo Perrier isolated technetium, which was the first synthetic element and now widely used in medical imaging as technetium-99m.¹¹ After World War II, the Atomic Energy Commission began to regulate how radioactive materials were used. One of the early radioactive substances purchased from the US government's national laboratories was Iodine-131, which was employed as a radiotracer to diagnose thyroid cancer. Abbott Laboratories established a radiopharmaceutical laboratory in the mid-1950s which provided early products to researchers. Soon after, competitor E.R. Squibb emerged on the scene providing more flexible timing for radiopharmaceutical product availability which allowed scheduling of patient imaging any day of the week.

The FDA first began to regulate radiopharmaceuticals in the 1970s. This regulatory change foreshadowed their wider use in oncology imaging and therapy in the 1980s. During the 1970s, the FDA withdrew the exemptions granted to radioactive products used in medicine and began regulating them as drugs in a process completed in 1975.¹² With the realization that technetium-based products were effective for imaging, their use later expanded substantially. The 1980s saw the development of several new oncology agents such as I-meta-iodobenzylguanidine which could be used for imaging and treatment. The 1990s produced the first monoclonal antibody bound to a radionuclide for tumor imaging called In-satunomab pentetide. PET imaging was also evolving during the 1990s and 2000s as 3-D PET scanning was introduced and improved detector designs allowed for better resolution. The use of this modality also became more widespread for cancer staging and monitoring along with growing applications in neurology. PET/CT hybrid systems also were deployed beginning a multimodal imaging approach that improved accuracy and combined anatomical and functional information.

Radiotherapy

While many radiopharmaceuticals are used for diagnostics, some are used for treatment. Most of the therapies are directed towards hematological malignancies, solid organ cancers or blood dyscrasias. The autoimmune disorder Graves' disease is responsive to radioactive Iodine (I-131) therapy, which gradually shrinks the thyroid. Oncology related uses include I-131 for treating thyroid cancer and hyperthyroidism, lutetium-177 for treating neuroendocrine tumors and prostate cancer and yttrium-90 microspheres for liver cancer to name a few.

Radioligand Therapy

An emerging subcategory of radiopharmaceuticals is radioligand therapy (RLT). It is a form of targeted cancer treatment that combines molecular targeting with the killing ability of radiation. RLT employs a ligand that targets cancer cells expressing a specific biomarker which is bound to a therapeutic radionuclide to deliver cytotoxic radiation. The compound may provide both diagnostic features and therapy. Examples of RLTs include Lutathera and Pluvicto which were approved in 2018 and 2022 respectively.

Some of the more common ligands used are somatostatin receptor ligands (SSTR2 for example), CXCR4 ligands and those used to bind to the prostate-specific membrane antigen (PSMA). The ligands are usually conjugated with chelators that can bind radioactive isotopes such as lutetium-177, actinium-225 or yttrium-90 for therapeutic purposes. The specific isotope chosen depends on the specific cancer type, target expression and treatment goals. Actinium's portfolio uses Ac-225 for its acute myeloid leukemia (AML) and solid tumor applications. The main emissions from Ac-225 are alpha particles. A feature of Ac-225 is that its decay chain daughter isotopes also emit alpha particles, reinforcing its utility in medical applications.

An important feature of radioligands is the chemical structure of the attachment between the ligand and the radioisotope. For metal elements, a chelator is used to bind the two parts of the RLT. The chelator securely holds the radioisotope to prevent its early release into the body and to maintain the stability of the radioligand complex while it is in the patient's circulation. The choice of a chelator can affect the pharmacokinetics and biodistribution of the radioligand. Other types of connections can be used including covalent bonding, encapsulation or nanoparticles.

⁹ Hevesy, G. [The Absorption and Translocation of Lead by Plants: A Contribution to the Application of the Method of Radioactive Indicators in the Investigation of the Change of Substance in Plants](#). The Biochemical Journal, 1923.

¹⁰ Patton, D.D. [The Birth of Nuclear Medicine Instrumentation: Blumgart and Yens](#), 1925. The Journal of Nuclear Medicine. 2003.

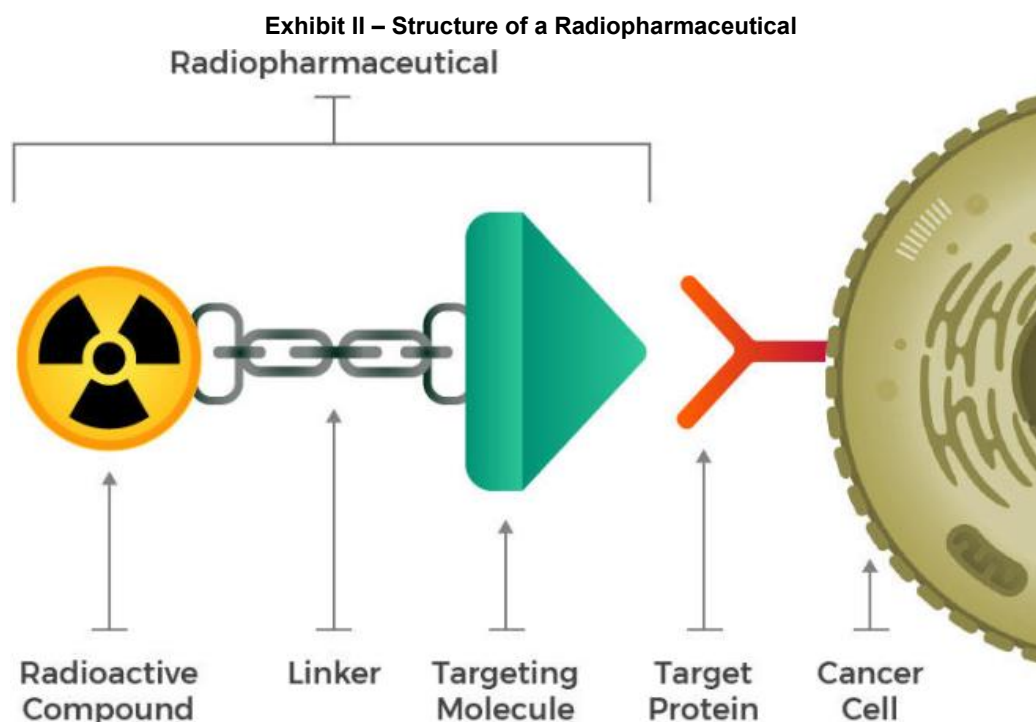
¹¹ Spagnolo, B. [1937, Palermo: the discovery of technetium](#). Il Nostro Mondo. February 2019.

¹² Siegel, B.A. [Radiopharmaceuticals and FDA: A Clinician's Perspective](#). Journal of Nuclear Medicine Technology. February 1983.

Yet another domain of RLT uses monoclonal antibodies (mAbs) for molecular targeting in a discipline called radio-immunotherapy. The related medicines are called radioimmunoconjugates (RICJs) and can be used for both imaging and therapy. This technology labels mAbs with a radionuclide directed against tumor-associated antigens that is specific to a certain biomarker. This approach increases the dose delivered to tumor cells and minimizes off-target binding to normal tissues.¹³ Some of the common radioisotopes used with RICJs include Iodine-131, Yttrium-90 and Indium-111.¹⁴ One example of an approved RICJ is [Zevalin](#), which is indicated for non-Hodgkin's lymphoma and uses a mAb that targets the CD20 receptor. Antibody-bound complexes such as Zevalin are also called radioconjugates and are discussed further in the next paragraph.

Radiopharmaceutical Structure

Diagnostic and therapeutic radiopharmaceuticals are frequently designed with a targeting molecule-linker-radioisotope construct to bind selectively to specific receptors on or within target cells and deliver cytotoxic radioisotopes. This is illustrated in the following exhibit.



Traditional radiation therapy can damage healthy tissue near tumors that are receiving treatment. Radiopharmaceuticals can minimize this risk by direct delivery of the radionuclide to the diseased cell. The structure of many radiopharmaceuticals includes a radioactive compound that is bound to a targeting molecule with a linker, quite similar to the structure of an antibody drug conjugate (ADC). In some cases, a diagnostic can be combined with a therapeutic to measure and treat simultaneously. This class of product falls into the radiotheranostic domain.

Radiopharmaceuticals for Conditioning

Conditioning is a preparatory treatment given to a patient before a bone marrow transplant, gene therapy or chimeric antigen receptor (CAR) T cell therapy. It seeks to destroy cancer cells or other mutant cells, suppress the immune system and create space in the bone marrow for new stem cells to engraft and grow. Traditional conditioning involves administration of chemotherapy, radiation therapy and immunosuppressive drugs in an approach that varies depending on the underlying disease, type of transplant and the patient's health. Major categories include full-intensity myeloablative conditioning, reduced intensity conditioning (RIC) and non-myeloablative conditioning. Myeloablative conditioning seeks to eradicate the patient's existing bone marrow and hematopoietic cells. In cases of blood cancers such as leukemia, lymphoma or myeloma, this means destroying malignant cells in the bone marrow and bloodstream. Eliminating the patient's immune cells is critical to prevent them from rejecting the incoming donor stem cells (in allogeneic transplants). This immunosuppression prevents host-versus-graft disease. Myeloablative conditioning creates space in the bone marrow niche for the new donor cells or collected stem cells to

¹³ Yeong, C.H., et al. [Therapeutic radionuclides in nuclear medicine: current and future prospects](#). Journal of Zhejiang University. 2014

¹⁴ Parakh, S. et al. [Radiolabeled Antibodies for Cancer Imaging and Therapy](#). Cancers. March 2022.

engraft and establish themselves. The bone marrow microenvironment has limited capacity, so clearing out existing cells allows the transplanted cells to home to the marrow and begin producing new blood cells.

RIC is used for patients who cannot tolerate the toxicity of myeloablative regimens. Older patients or those with co-morbidities such as organ dysfunction may require a lower intensity approach. RIC may be considered when the therapy aims to induce the graft vs tumor effect. This may be used for chronic lymphocytic leukemia, follicular lymphoma or some myelodysplastic syndromes. RIC improves mortality for the conditioning component of treatment; however, it is associated with a higher risk of relapse following hematopoietic stem cell transplant (HSCT).

Nonmyeloablative conditioning is used for immunosuppression in order to allow donor engraftment. It has the benefit of supporting faster immunologic recovery after allogeneic stem cell transplant and can result in a mixed chimeric state in the host, which may protect against graft vs. host disease (GVHD) by promoting immune tolerance.¹⁵ Nonmyeloablative conditioning and lymphodepleting chemotherapy have differing objectives. Nonmyeloablative conditioning seeks partial cytoreduction of malignancy and sufficient immunosuppression to allow donor graft or adoptive T cells to engraft and exert graft-versus-tumor effects and removal of regulatory and competing lymphocyte populations. Nonmyeloablative conditioning is used specifically as a less severe, low-toxicity method to achieve lymphodepletion, which suppresses the patient's existing immune system to create space and an optimal biological environment for newly infused cells to thrive, multiply and target cancer.

Appropriate Populations for Myeloablation

Myeloablative conditioning is most appropriate for younger patients in otherwise good overall health with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), high-grade lymphomas and myelodysplastic syndromes. RIC falls between myeloablative and nonmyeloablative conditioning and uses moderate doses of chemotherapy and radiation. RIC seeks to significantly damage the bone marrow but not completely ablate it. Older patients with co-morbidities, heavily pretreated patients and patients with prior transplants are candidates. The option of RIC has opened up transplantation for populations that were previously too sick or weak to undergo full-intensity myeloablative conditioning. Nonmyeloablative conditioning is an alternative for elderly patients or those with comorbidities. This less intense approach contributes to improved non-relapse mortality. Many *ex vivo* gene therapies require nonmyeloablative conditioning which must be sufficiently intense to allow modified cells to engraft and produce a therapeutic level of corrected blood cells. Dosing is tailored to achieve adequate engraftment while minimizing toxicity.

Toxicities

Specific toxicities for myeloablative conditioning include irreversible cytopenia which requires a stem cell graft to recover. Less toxic approaches such as RIC decrease these risks but more intensive regimens are associated with a lower relapse rate, a higher transplant related mortality and similar overall survival. The lesser intensity approach may produce worse outcomes in patients with active disease at transplantation and may be less effective for acute leukemia.¹⁶

Summary of Conditioning Risks and Toxicities¹⁷

- Hematologic toxicity and infections
- Organ damage
- Liver injury (hepatic veno-occlusive disease)
- Pulmonary fibrosis and interstitial pneumonitis
- Cardiomyopathy
- Hemorrhagic cystitis (bladder bleeding)
- Reduced kidney function
- Mucositis (painful inflammation/ulcers of mouth and gut lining)
- Nausea, vomiting & diarrhea
- Seizures
- Infertility & endocrine effects (gonadal failure)
- Secondary malignancies

¹⁵ Munchel, A.T., *et al.* [Treatment of hematological malignancies with nonmyeloablative, HLA-haploidentical bone marrow transplantation and high dose, post-transplantation cyclophosphamide](#). Best Practice & Research Clinical Haematology. September 2011.

¹⁶ Shimoni, A., *et al.* [The EBMT Handbook: Hematopoietic Cell Transplantation and Cellular Therapies, Chapter 13, Conditioning](#). April 2024.

¹⁷ Uchida, N., *et al.* [Fertility-preserving myeloablative conditioning using single-dose CD117 antibody-drug conjugate in a rhesus gene therapy model](#). Nature Communications. October 2023.

Conditioning can directly or indirectly cause life-threatening complications, including severe infections, organ failure or toxic metabolic syndromes. High-dose cyclophosphamide can cause a syndrome of cardiac toxicity or inappropriate antidiuretic hormone secretion and tumor lysis can occur if there is residual tumor kill. GVHD is another common reaction caused by tissue damage, cytokine release and profound immune dysregulation brought on by conditioning. The regimen essentially brings patients to the brink of fatal organ failure that is addressed by the transplant. Reports of treatment-related mortality rates vary, but for myeloablative allogeneic transplants it can be in the range of 10-20%. Gene therapy trials for sickle cell disease using busulfan have also resulted in deaths attributed to conditioning toxicity.^{18,19,20,21,22}

Unmet Needs in Conditioning

As discussed above, pre-transplant conditioning is harsh on the body. Patients need a regimen that can specifically and selectively ablate bone marrow and hematopoietic stem cells while sparing off-target tissues and organs. Approved genotoxic conditioning regimens are limited by significant morbidity and mortality, as they must simultaneously eradicate the patient's own hematopoietic stem cells, eliminate residual malignant cells and establish potent immunosuppression. Beyond off-target tissue injury, acute toxicities pose a serious clinical challenge. Chemotherapy-induced nausea and vomiting, mucositis, transplant-associated thrombotic microangiopathy and sinusoidal obstruction syndrome can present significant implications for patients. The side effects can coincide with the start of conditioning and persist into the post-transplant period. Prolonged cytopenia further heightens susceptibility to life-threatening infections, adding to the burden of treatment-related morbidity. Reducing toxicity often comes at the cost of disease control. Additional long-term risks include infertility, especially for pediatric patients, secondary malignancies and heightened sensitivity to DNA-damaging agents.^{23,24}

A new approach to conditioning employs radiopharmaceuticals that enhance targeting through the use of antibodies. Radioactive agents are delivered with precision essentially creating a targeted total body irradiation (TBI) centered on hematopoietic cells. Radiopharmaceutical conditioning links a radioisotope to a monoclonal antibody that is raised to bind to a specific receptor. When injected, the radio-labeled antibody circulates and binds to its target cells (for example, leukemia cells or HSCs in the marrow), and the radioactive decay of the isotope delivers lethal radiation to the target cells and, when β -emissions are present, to neighboring cells as well. This can achieve myeloablation and kill tumors with precision.

Actinium-225 Production

Actinium-225 is a rare radioisotope which naturally occurs only in trace amounts. It is manufactured using technically difficult production methods that are capacity limited and tightly controlled. Most Ac-225 is sourced from milking Thorium-229, itself a rare by-product of Uranium-233. Th-229 decays through radium to Ac-225; these Th-229 inventories are small and decay slowly, so the yield is low.²⁵ High-energy proton or other particle beams are needed to generate Ac-225 from targets such as thorium or radium, but only a few facilities have suitable accelerators and radiochemistry infrastructure, and these machines primarily serve other research missions. As a result, global annual production had been likened to less than a grain of sand in total mass.²⁶

There are multiple methods that can be used to produce Actinium-225 including Radium-226 irradiation, use of Thorium-229 generators, and high-energy proton spallation. Each has favorable features with Radium-226 irradiation driving material production and generating non-carrier added (n.c.a.) product that is free of Ac-227 impurities. Cyclotron production is another method which directs a cyclotron to irradiate an Ra-226 target. The process must be precise otherwise the co-production of the Ac-226 impurity will be too high. Thorium-229 generators produce higher purity with the Th-229 extracted from Uranium-233. U-233 naturally decays into Th-229 which is placed in a

¹⁸ Sawyer, J., *et al.* [Prevention and management of acute toxicities from conditioning regimens during hematopoietic stem cell transplantation](#). Clinical Hematology International. April 2024.

¹⁹ Zain, J.M., Safdar, A. [Complications Arising from Preparatory Conditioning Regimens for Stem Cell Transplantation](#). Springer Nature. June 2019.

²⁰ Maffini, E., *et al.* [Neurologic Complications after Allogeneic Hematopoietic Stem Cell Transplantation](#). Biology of Blood and Marrow Transplantation. March 2017.

²¹ Styczynski, J., *et al.* [Death after hematopoietic stem cell transplantation: changes over calendar year time, infections and associated factors](#). Bone Marrow Transplantation. August 2019.

²² Penack, O., *et al.* How much has allogeneic stem cell transplant-related mortality improved since the 1980s? A retrospective analysis from the EBMT. Blood Advances. December 2020.

²³ Uchida, N., *et al.* [Fertility-preserving myeloablative conditioning using single-dose CD117 antibody-drug conjugate in a rhesus gene therapy model](#). Nature Communications. October 2023.

²⁴ Agarwal, R. *et al.* [Irradiation- and busulfan-free stem cell transplantation in Fanconi anemia using an anti-CD117 antibody: a phase 1b trial](#). Nature Medicine. July 2025.

²⁵ [This Potential Cancer Treatment Requires Modern Alchemy](#). Scientific American. February 2024.

²⁶ [Actinium-225: A breakthrough in cancer treatment](#). Canadian Nuclear Laboratories. Accessed March 2026.

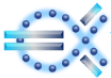
generator which can be milked to produce Ac-225. Yet another approach employs the accelerator to emit high-energy protons to bombard a Th-232 target. The protons' impact spallates or fragments the thorium nucleus producing various isotopes including Ac-225.

The bulk material from these processes requires downstream processing such as separation and purification. Extraction chromatography is used for primary separation and is followed by secondary purification using lanthanide-selective resin and cation exchange. The thorium generator is preferred despite the limited supply of U-233 that is required to seed it. It generates fewer long-lived isotopic impurities, but only produces enough Ac-225 to treat fewer than 1,000 patients per year.²⁷ High-energy proton spallation co-produces Ac-227, which has a ~22-year half-life. While small relative to Ac-225 production, the concentration of Ac-227 creates waste management burdens and additional regulatory hurdles.

Historically, the radiopharmaceutical space relied almost exclusively on Thorium-229 decay stockpiles that were managed by the U.S. Department of Energy. However, in the last few years, Ac-225 production has become more diversified through the expanded use of thorium generators and accelerator-based production. TerraPower Isotopes is [building](#) an Ac-225 manufacturing facility in Philadelphia which is expected to expand production 20-fold. TerraPower uses the natural decay method for production that harvests Ac-225 from Th-229. NorthStar [manufactures](#) Ac-225 using electron-accelerator technology in Wisconsin. It recently secured \$185 million to support scale-up of Ac-225 to meet anticipated demand growth for the radionuclide. In August, BWXT Medical sold its medical business to Nordic Capital who will invest in increasing Ac-225 production. BWXT uses both high-energy proton spallation and a radiochemical generator system to produce the radioisotope. Actinium Pharmaceuticals is also developing its own Ac-225 manufacturing initiative using cyclotron-based production technology and proton irradiation of Ra-226.

Actinium asserts that its manufacturing process for Ac-225 produces higher quality output at lower cost than more common methods of production. The process generates Ac-225 that matches Ac-225 output from a thorium generator and is free from long-lived contaminants.

Exhibit III – Actinium's Ac-225 Production Profile



Actinium
Pharmaceuticals, Inc.

C13/2008-B

Specification of Ac-225 Radiochemical

General Information		
Active Ingredient:	Ac-225	
Chemical Composition:	Solid Ac nitrate, carrier free	
Batch number:	C13/2008-B	
Activity of Ac-225 in batch:	17	MBq @ EOP by high res. γ-spec.
Packing	Quartz glass vial with screw cap in lead container	
Quality Data		
Chemical Impurity:	Determination by weight:	not detected
Radioisotopic Purity:	99.8%	
	Ra-226*	not detected
Dose Rate		
Outside lead container	max. 1	mSv/h
On the vial	8	mSv/h
Remarks		
No precipitates noticed in the vial.		

Ra-226* = Ra-226 and daughters

Source: [Actinium Pharmaceuticals Website](#)

Actinium Pharmaceuticals' uses a proprietary, patented cyclotron-based approach for the commercial-scale production of Ac-225. The process is designed to provide high-purity material at a significantly lower cost than existing

²⁷ Robertson, A.K.H., *et al.* [Development of ²²⁵Ac Radiopharmaceuticals: TRIUMF Perspectives and Experiences](#). Current Radiopharmaceuticals. December 2018.

methods, addressing the global shortage of medical-grade alpha emitters. The traditional method relies on extracting Ac-225 from the natural decay of Th-229 which is in limited supply. Actinium's methodology involves the direct proton irradiation of Ra-226 targets. Its cyclotron method generates high yields and is commercially scalable.

Actinium's proprietary Ac-225 generation employs a medium-energy cyclotron of approximately 20 MeV. The method irradiates Ra-226 targets for approximately 120 to 150 hours. It produces up to 100 mCi of Ac-225 per production cycle, in contrast to the low yield of approaches using Thorium 229.^{28,29} The company holds intellectual property covering target design and proprietary methods for the purification and recycling of Ra-226 from various sources, which ensures a sustainable feedstock for continuous production. While Ra-226 requires special handling and has a 1,600-year half-life, it is able to produce Ac-225 with 99.8% radioisotope purity and over 99% radiochemical purity. Ac-227 contaminants are less than 0.001%.

In March 2024, Actinium Pharmaceuticals [launched](#) a strategic initiative to scale this technology for commercial purposes. The company estimates that this method can provide material at a cost of 5% to 10% of standard approaches. According to Actinium, [estimated costs range](#) from \$650 to \$1,000 per mCi.

Actinium is completing construction of a radiopharmaceutical manufacturing facility that will synthesize Ac-225-based final drug products for clinical supply. In its most recent [Form 10-Q](#) filing, Actinium identified key capabilities of its New York Ac-225 manufacturing facility:

- Therapeutic Drug Product Manufacturing: production suites for radioconjugate synthesis, formulation, fill-finish, and quality control testing, designed to support multiple simultaneous programs;
- Quality Control and Analytics: Comprehensive analytical capabilities including radiochemical purity testing, stability assessment, sterility testing, and release testing in accordance with regulatory requirements;
- Radiation Safety Infrastructure: Shielded manufacturing suites and a comprehensive radiation safety program to protect personnel and environment.

Radiopharmaceutical Considerations

Radiopharmaceuticals require additional considerations compared to biologic or chemical molecules with respect to inventory, shelf life, product safety, storage, handling, licensing and disposal among other factors. These requirements create barriers to entry that limit competition. These products are classified as specialty medicines containing radionuclides whose half-lives range from a few minutes to several days. This short product life requires efficient transportation timelines and protocols as well as local manufacturing.

Handling

Substances containing radioactive isotopes used for medical imaging or therapy require strict handling procedures to protect both healthcare personnel and patients from radiation exposure. Lead shielding is used to protect individuals transporting and manufacturing the nuclear medicines and products are clearly labeled. The International Atomic Energy Agency (IAEA) sets regulations for radioactive materials. Shipments must be meticulously documented, identifying the radioactive material and its properties. Transport security and emergency response plans must be in place.

Transportation

Time is of the essence when transporting radiopharmaceuticals. Over medium to long distances, air transport is frequently the most effective method to deliver these ephemeral products to their final destination. Radionuclides with short half-lives must be produced locally to allow for rapid delivery. For products with medium-term half-lives, transportation between distant cities is possible, but radioactive decay must be considered. Timely delivery requires expedited shipping and tightly coordinated logistics to avoid product loss. Type A packaging, which is durable against water and impact damage, is required during transport.

Regulation

In the United States, the primary regulators of radiopharmaceuticals are the US Nuclear Regulatory Commission (NRC) and the FDA. In Europe, the European Medicines Agency (EMA) oversees regulation of the class. The radioactive products must be manufactured in nuclear research reactors or cyclotrons which are approved by the NRC or its designated state agency. In the United States, F-18 radiolabeled products are manufactured using a cyclotron at a site which must be approved by the FDA. For a license from the NRC, a sponsor must apply for a license to

²⁸ Diamond, W.T., Ross, C.K. [Actinium-225 Production with an Electron Accelerator](#). January 2021.

²⁹ National Isotope Development Center. [Multiple Production Methods Underway to Provide Actinium-225](#). Webpage.

manufacture and distribute the products. The Application for Materials License requires information about the radioactive materials to be used, their purpose, individuals responsible for the radiation safety program, training, facilities, radiation safety procedures and waste management practices. Following inspections and a review, a license may be granted for a specific type and quantity of radioactive material to be allowed and any limitations or conditions imposed are listed. The license must be renewed every ten years.

Waste Disposal

Radioactive material waste disposal is another consideration. Waste can either be short or long lived with each category requiring different treatment. Waste with a short half-life can be stored on site until it has reached radiological clearance. Generally, waste with a half-life of less than 120 days falls into this category. After radiation levels reach background levels, it can be disposed of as regular medical refuse. Longer lived waste may be sent to specialized long-term storage facilities. It is stored in specially shielded containers and can be transferred to a licensed disposal facility. Liquid waste from either the fluids used in the laboratory or urine or feces from a treated patient are many times placed into a separate septic system where it is held in tanks until it decays to background levels and is then placed into the regular sewer system.³⁰

Finished Product

In contrast to other medical products, radiopharmaceuticals are decaying radioisotopes with half-lives ranging from a few hours to several days. Therefore, they are almost exclusively produced on demand with minimal lead time which requires an efficient production and distribution mechanism. Finished goods, especially diagnostics, cannot sit in inventory because of their rapid decay. These products are produced using just-in-time manufacturing, processing and distribution. Supply chains define the limitations that determine which products can be used and where.

³⁰ Tas, A., Ozer, A.Y. [Waste Disposal and Management in Radiopharmaceuticals](#). Journal of Pharmaceutical Science. 2020.



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