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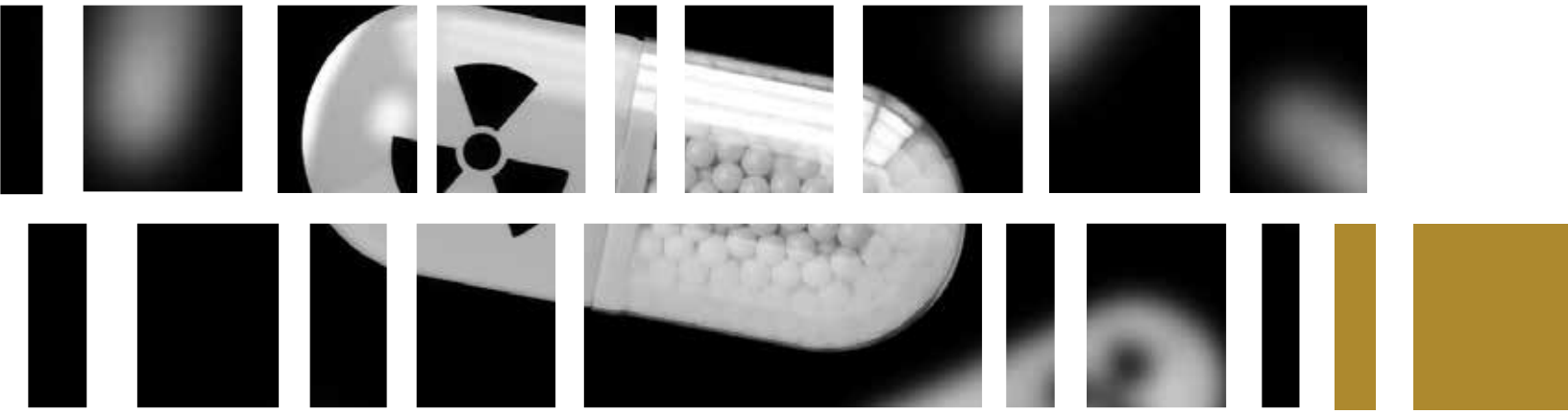

A WHITEPAPER FROM INSTITUTE@PRECISION

Advancing Radiopharmaceuticals From Regulatory Approval to Global Access

Perspectives from FDA Oncology Experts

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Executive Summary

Radiopharmaceuticals have evolved from niche nuclear medicine therapies into a meaningful therapeutic class in oncology, with expanding applicability across disease areas.[1] Advances in targeting ligands, theranostic strategies, and radionuclide engineering enable late-stage clinical programs that are now evaluated against the same efficacy, safety, and quality-of-life benchmarks applied to systemic oncology therapies.

Five therapeutic radiopharmaceuticals are approved by the U.S. Food and Drug Administration (FDA) for oncology indications (e.g., Sodium iodide I-131, Xofigo®, LUTATHERA®, AZEDRA®, PLUVICTO®, and ZEVALIN®). However, regulatory approval does not always translate into global patient access.

Radiopharmaceuticals face structural constraints that distinguish them from other therapeutic modalities, including limited isotope production capacity, uneven radiopharmacy infrastructure, specialized workforce shortages, and fragmented reimbursement environments.[2] These constraints shape post-approval adoption and the feasibility and integrity of global clinical development programs.

One of the most consequential downstream effects of access limitations is the selection of comparators and control arms. When an approved radiopharmaceutical cannot be deployed across regions, the definition of "standard of care" diverges, introducing ethical, operational, statistical, and regulatory challenges. Comparator strategy, therefore, becomes a first-order development risk, influencing protocol complexity, site participation, statistical power, and the generalizability of trial results.[3]

This article examines how access constraints intersect with trial design, regulatory expectations, and evidentiary robustness in global radiopharmaceutical development. Drawing on regulatory perspectives and real-world examples, it articulates an access-aware approach to comparator planning and site strategy, one ideally integrated as early as first-in-human and Phase 1 studies, rather than deferred to late-stage trial design. Radiopharmaceuticals serve as an early warning signal for other infrastructure-dependent precision therapies, highlighting that scalable innovation requires alignment between scientific ambition and system readiness.

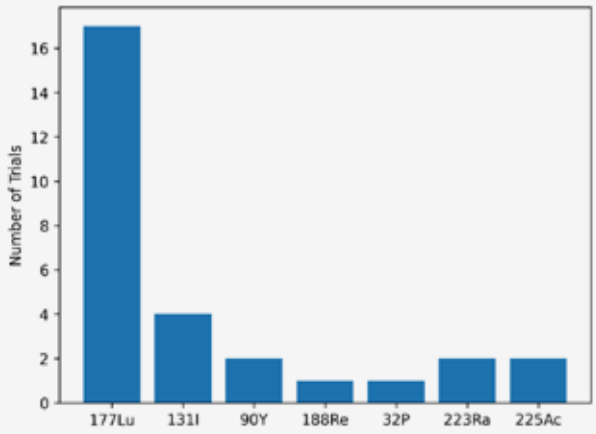
Radiopharmaceuticals Enter the Oncology Mainstream

Radiopharmaceuticals have matured over the past decade, progressing from diagnostic imaging agents used to interrogate tumor biology to radiopharmaceuticals with or without integrated theranostic platforms that deliver targeted, disease-modifying radiation therapy in oncology.

Early radiopharmaceutical applications include radiolabeled tracers like [^{18}F] fluorodeoxyglucose ([^{18}F]FDG) and other positron emission tomography (PET) agents to visualize tumor biology and guide clinical decision-making. Over the past decade, the field has been moving toward radiopharmaceuticals and radiotheranostics, in which paired diagnostic and therapeutic radiopharmaceuticals, such as gallium-68 (68Ga)-Dotatate for imaging and lutetium-177 (177Lu)–Dotatate for treatment, enable targeted delivery of cytotoxic radiation to malignant cells. This approach has demonstrated favorable benefit–to–risk profiles relative to conventional systemic chemotherapies, driven by tumor-selective radiation exposure and reduced off-target toxicity.[5]

The radiopharmaceutical pipeline now rivals that of antibody-drug conjugates (ADCs) and cell-based therapies in scale and velocity, spanning beta-emitters (e.g., lutetium-177) and alpha-emitters (e.g., actinium-225), as well as diverse targeting ligands across prostate cancer, neuroendocrine tumors, hematologic malignancies, and emerging solid-tumor indications.[4] Multiple therapies are approved in the United States and Europe, with dozens more investigational therapies in Phase 2 and Phase 3 development (see Figures 1 and 2).[6]

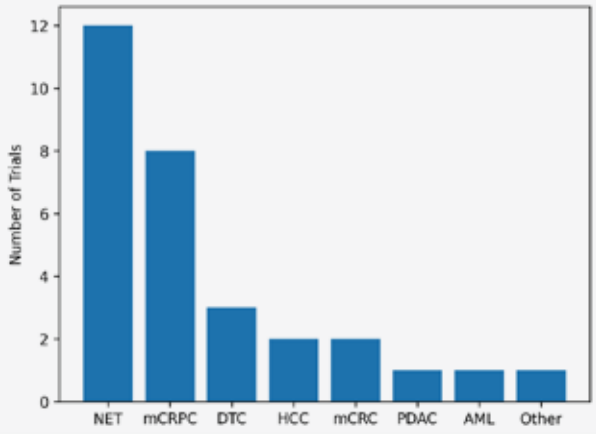
Figure 1: Number of Phase 3 Trials by Radionuclide



This figure illustrates the concentration of late-stage radiopharmaceutical development around a limited number of radionuclides, particularly lutetium-177 and emerging alpha emitters. The clustering of Phase 3 activity highlights growing clinical confidence in these isotopes while underscoring structural risks associated with constrained isotope production capacity and supply-chain fragility. As more programs advance into pivotal trials using the same radionuclides, competition for limited infrastructure becomes a determinant of trial feasibility and timelines.

Source: Adapted from Lepareur, N. (2025).

Figure 2: Number of Phase 3 Trials by Indication*



This figure demonstrates the expansion of late-stage radiopharmaceutical development across multiple oncology indications, reflecting the maturation of the modality beyond traditional niches. As clinical development activity broadens, variation in SOC, comparator availability, and healthcare infrastructure across disease areas and geographies increasingly shapes trial design, evidentiary consistency, and global registrability.

Source: Adapted from Lepareur, N. (2025). *Indication: **AML**: acute myeloid leukemia; **DTC**: differentiated thyroid cancer; **HCC**: hepatocellular carcinoma; **mCRC**: metastatic colorectal cancer; **mCRPC**: metastatic castration-resistant prostate cancer; **MFS**: metastasis free survival; **mHSPC**: Metastatic hormone-sensitive prostate cancer; **NET**: neuroendocrine tumor; **PDAC**: pancreatic ductal adenocarcinoma; **PFS**: progression-free survival.

As development activity accelerates, the industry's definition and measurement of success is evolving. Early radiopharmaceutical programs used imaging endpoints, biodistribution, and dosimetry.[7] Conversely, today's drug development programs are evaluated against the same outcomes expected of systemic oncology drugs: overall survival, radiographic progression-free survival, response rate, safety and tolerability, and patient-reported outcomes.

In pivotal randomized trials, targeted radiopharmaceuticals demonstrated improvements in survival and progression endpoints (e.g., ^{177}Lu–labeled prostate-specific membrane antigen [PSMA]-617 in metastatic castration-resistant prostate cancer[8]; ^{177}Lu–Dotatate in midgut neuroendocrine tumors[5]), with supportive quality-of-life benefits reported.[9] This evidentiary shift positions radiopharmaceuticals as treatment options across defined lines of therapy, rather than as adjunctive diagnostic procedures.[4]

Concomitantly, radiopharmaceutical therapies are competing with ADCs, chimeric antigen receptor (CAR) T-cell therapies, bispecific antibodies, and targeted small molecules within overlapping biomarker-defined indications and patient populations, driving convergence in drug development standards, including dose and posology justification, trial-design rigor, and fit-for-purpose endpoint selection.[10,11]

Radiopharmaceuticals, however, face a structural constraint absent from competing modalities: their clinical and commercial scalability is inseparable from radioisotope production capacity, radiolabeling and dose-prep capabilities, time-sensitive distribution logistics, and site readiness (i.e., specialized facilities, trained personnel, radiation safety, and dosimetry workflows). Consequently, infrastructure availability and supply-chain resilience affect clinical development timelines, site selection, and dosing strategies as much as the biology.[10,12,13,14]

Why Radiopharmaceutical Access Remains Constrained

Despite this progress, regulatory approval does not guarantee access for radiopharmaceuticals. Even after approval, the same infrastructure dependencies previously noted continue to constrain where and how these therapies can be delivered, limiting real-world availability and trial feasibility.[2,15]

For example, the rollout of ^{177}Lu–based radiopharmaceuticals (e.g., Lutathera and Pluvicto) exposed persistent dependencies on synchronized production and delivery. Lu-177 supply is concentrated among a small number of nuclear reactors and processing facilities, creating vulnerability to capacity constraints and scheduling disruptions.[16,17,18] Those challenges are compounded by Lu-177's physical half-life (~6.7 days), which imposes rigid time windows for radiolabeling, quality control, transport, and administration, limiting geographic reach and constraining site-level scalability.[19,20]

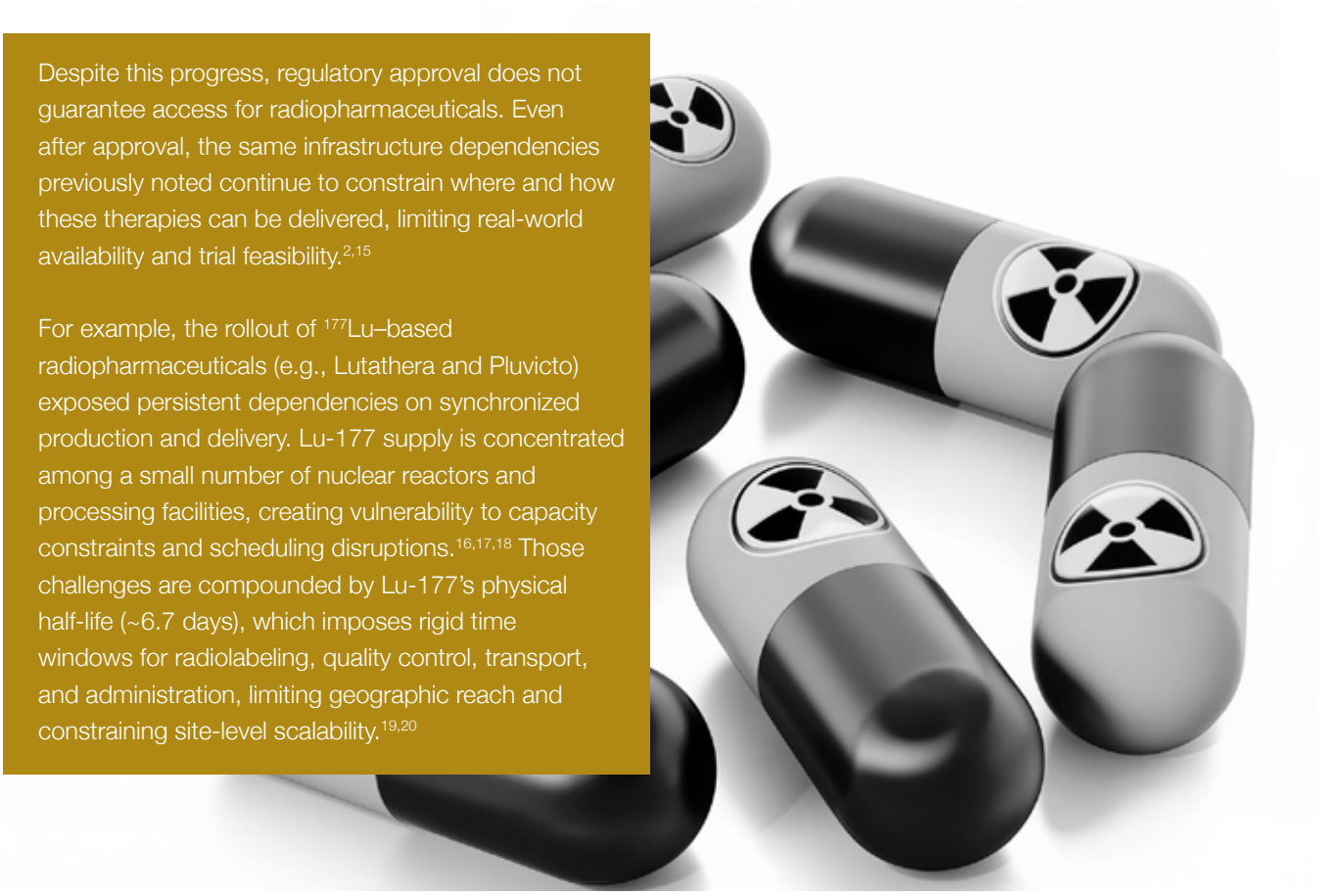


Table 1. U.S. Radiopharmaceutical Infrastructure and Clinical Trial Activity

State-level radiopharmaceutical trial activity shares are mapped to regional isotope production, radiopharmacy and logistics, and anchor clinical trial centers. The data demonstrates that trial concentration aligns with infrastructure readiness, indicating that access is driven by system capacity rather than regulatory approval alone.

Region	Share of U.S. Radiopharmaceutical Trial Activity	Primary Isotope Production	Production Modality / Key Isotopes	Radiopharmacy & Logistics Infrastructure	Anchor Clinical Trial Centers
South	**Highest (TX 10%; MD 12%)**	**Oakridge National Laboratory**	**Reactor-based; ~70% global Ac-225; Cf-252**	PET Labs (FL); Texas-based Sunbelt distribution hubs	MD Anderson Cancer Center (TX); Emory University (GA)
West	High (CA 20%)	Los Alamos National Laboratory	High-energy proton labs	California biotech corridor distribution networks (e.g., RayzeBio, Lantheus)	UCSF; UCLA; Stanford
Midwest	**Moderate (MN 6%)**	**University of Missouri Research Reactor (MURR); Argonne National Laboratory**	**Reactor-based neutron irradiation**	Cardinal Health (OH); Curium (MO) national distribution	Mayo Clinic (MN); University of Wisconsin
Northeast	**Moderate (NY 9%, MA 6%)**	**Brookhaven National Laboratory**	**Accelerator-produced isotopes**	High density of PETNET and SOFIE radiopharmacies	Memorial Sloan Kettering (MSKCC); University of Pennsylvania; Dana-Farber
Mountain	**Emerging (Included in "other states" 36%)**	**Idaho National Laboratory**	**ATR high-flux neutron irradiation**	Emerging hubs in Denver and Salt Lake City	Huntsman Cancer Institute (UT); University of New Mexico

Sources: ClinicalTrials.gov (2026) analysis for U.S. radiopharmaceutical clinical trial activity. Isotope production assets and modalities are based on publicly available documentation from the U.S. Department of Energy Office of Isotope R&D and Production, U.S. national laboratories, and International Atomic Energy Agency reports. Radiopharmacy and logistics infrastructure are derived from disclosures from Cardinal Health, Curium, PETNET Solutions, and the Society of Nuclear Medicine and Molecular Imaging (SNMMI). Anchor clinical trial centers are identified using institutional trial portfolios and SNMMI Centers of Excellence listings.

Radiopharmacy capacity also represents a critical constraint on the scalability of radiopharmaceuticals. The ability to compound, manage quality-control, and dispense these agents varies across and within geographies, reflecting disparities in facility availability, capital investment, and regulatory maturity. Stringent requirements for radiopharmacy licensure, facility shielding, radiation-safety systems, and radioactive-waste management further limit expansion, particularly in low- and middle-income countries where infrastructure development and regulatory harmonization lag clinical demand.[21,22,23]

In parallel, workforce training pipelines trail accelerating clinical demand, resulting in shortages of qualified personnel and creating downstream delays in site activation and patient throughput, even in high-income health systems where capital and approved therapies are available.[22,23] Table 2 provides an overview of the key challenges that affect access to global radiopharmaceutical development. These constraints cluster into a small number of structural barriers that shape both clinical development feasibility and post-approval access.

Table 2: Barriers to Radiopharmaceutical Development and Delivery

Domain	Key Challenges
Clinical Infrastructure and Workforce	**Limited availability of PET/CT, SPECT, cyclotrons, and radiopharmacies; shortages of trained nuclear medicine professionals; site readiness constraints affecting trial activation and patient throughput.**
Isotope Supply and Distribution	Concentrated and aging isotope production infrastructure; short radionuclide half-lives; time-sensitive manufacturing and transport; dependence on cross-border supply chains.
Economic and Reimbursement Constraints	**High capital and operating costs; misaligned reimbursement models; limited cost-effectiveness evidence; financial barriers affecting provider adoption and patient access.**
Regulatory, Policy, and System Factors	**Complex multi-agency licensing and safety requirements; inconsistent clinical guidelines; regulatory lag for novel agents; geopolitical instability affecting infrastructure, workforce, and supply continuity.**

Adapted from: Al-Ibraheem, A., Brink, A., Lee, S. et al. (2025).

Best-in-Class Expertise and Training to Support Radiopharmaceutical Clinical Development

Precision for Medicine brings end-to-end experience in radiopharmaceutical development, supporting multiple clinical programs, including first-in-human and international studies where access, infrastructure readiness, and comparator feasibility are critical. This deep experience spans a broad range of radionuclides, reflecting the operational and scientific complexity of this therapeutic class. Highly trained clinical, operational, and regulatory teams with specialized expertise in nuclear medicine workflows, radiopharmacy coordination, imaging requirements, and site readiness further underpin Precision for Medicine's capability.

When Control Arms Become a Strategic Risk

As radiopharmaceutical programs progress from proof-of-concept studies to confirmatory, multi-regional late-stage development, control-arm selection emerges as a strategic risk that determines whether generated evidence is both interpretable and globally registrable.

Regulators view control-group selection as foundational to the credibility of treatment-effect estimates and, in multi-regional clinical trials, favor active comparators or standard-of-care (SOC) controls that support consistent inference across regions.[24,25] Recent oncology-focused guidance reinforces that inappropriate or regionally misaligned comparator choices can undermine global regulatory acceptance, highlighting the need for feasible, locally relevant comparator strategies in oncology trials.[3]

In practice, however, global radiopharmaceutical development faces a structural paradox: a radiopharmaceutical therapy may be approved as standard of care in one region, yet remain inaccessible in others due to limitations (see Table 2). In these settings, mandating therapy as a control arm is challenging, raises ethical concerns, and introduces systematic variability that can undermine trial execution and the interpretability of outcomes.[3]

Sponsors, ethics committees, and investigators must reconcile global regulatory expectations with local realities. Randomizing patients to a control arm that cannot be delivered at a given site risks creating ethical and operational challenges, including implications for informed consent, patient safety, and trial feasibility. Faced with these constraints, sponsors confront a set of unattractive trade-offs: excluding entire regions from participation, or adopting alternative comparators that fragment study populations and undermine the consistency and generalizability of clinical data.

> "As standards of care evolve, comparator strategy must be addressed early as a core development decision to protect trial feasibility, evidentiary clarity, and global registrability."
>
> – Harpreet Singh, CMO, Precision for Medicine

When access to a reference therapy (i.e., an approved drug, guideline-recommended standard of care, or regionally accepted therapy) lags regulatory approval, clinical development timelines extend. Sponsors encounter delays in site activation, are forced into protocol amendments to accommodate regional disparities, and often enter protracted regulatory negotiations over comparator acceptability. These cascading operational adjustments can yield fragmented and regionally stratified data sets, outcomes that diminish evidentiary coherence and weaken the persuasiveness of submissions to regulators seeking global, generalizable evidence.[3,25]

Why Comparator Access Reshapes Methodology and Statistics

Comparator access shapes the evidence a trial can generate. When a single global SOC comparator cannot be used, sponsors often default to investigator's-choice control arms to preserve trial enrollment and regional clinical relevance (Table 3).

Table 3: Structural Drivers of Comparator Risk in Radiopharmaceutical Development

Multiple SOC Options Available	• **Several regimens qualify as SOC across or within regions.** • **Selecting one risks appearing outdated or non-representative.** • **"Investigator's choice" or regional controls increase feasibility but add statistical and interpretive complexity.**
Shift in SOC	• New therapies may be approved mid-trial, shifting SOC expectations. • Mid-study changes can affect equipoise, enrollment, and interpretability.

Expanding comparator options, however, increases statistical and regulatory risk. Heterogeneity in the control regimen can dilute or mask true treatment effects, complicate statistical modeling and sensitivity analyses, and weaken the clarity of the causal contrast the trial is designed to evaluate.[27]

Regional stratification and prespecified sensitivity analyses are used to manage comparator heterogeneity, but these approaches require larger sample sizes, more complex estimands, and expanded statistical analysis plans, increasing operational burden and regulatory scrutiny.

Adaptive trial designs, such as delayed randomization or crossover, can address concerns when access to standard therapies is uneven; however, these approaches often compromise interpretability by confounding time-to-event outcomes and introducing treatment-switching bias, particularly for survival endpoints.[28,29] As a result, external control arms derived from historical trials or high-quality real-world data are emerging as a pragmatic supplement when randomized comparators are not feasible.[30,31]

Regulators, however, have signaled cautious optimism toward these approaches, emphasizing the need for exceptional methodological rigor, high-quality and contemporaneous data, and full transparency around assumptions and bias-mitigation strategies.[30] Importantly, while external control arms may offer a supportive role, they are not considered substitutes for randomized evidence in pivotal trials except under well-justified and defined circumstances.[30,31]

> "Sponsors face a set of competing imperatives: maintaining statistical rigor, meeting ethical obligations, and adapting to real-world site constraints. Addressing these trade-offs requires an access-aware trial design approach grounded in early and sustained alignment across clinical, regulatory, statistical, and operational teams."
>
> – Kurt Preugschat, Biostatistician, Precision for Medicine

PLUVICTO: A Case Study in Comparator Feasibility for Radiopharmaceuticals

Situation

PLUVICTO (^{177}Lu-PSMA-617) represents a major advancement in the treatment of PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). Initially approved by the FDA in 2022 for patients who had progressed after both androgen receptor pathway inhibitor (ARPI) therapy and taxane-based chemotherapy, PLUVICTO demonstrated statistically significant improvements in overall survival and radiographic progression-free survival in the pivotal VISION trial when added to standard of care, supporting regulatory approval in the United States and Europe. In 2025, the FDA expanded Pluvicto's indication to allow use earlier in the treatment sequence (i.e., after progression on ARPI therapy but prior to chemotherapy), broadening patient eligibility and increasing access to radioligand therapy earlier in the disease course.[8]

Challenge

PLUVICTO'S deployment as a comparator in subsequent trials has been constrained by structural access limitations. The therapy depends on a short-half-life radioisotope (^{177}Lu), centralized isotope production, specialized radiopharmacy infrastructure, and highly trained nuclear medicine personnel. These requirements are unevenly distributed across regions, limiting supply outside major academic and high-income settings, as documented in regulatory assessments and post-approval implementation experience.[32]

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Trial Design Adaptations

Sponsors developing next-generation radioligand or combination therapies have struggled to adopt PLUVICTO as a universal randomized comparator. In regions where supply cannot be assured, its use becomes infeasible, forcing geographically segmented protocols, alternative control strategies, or regional exclusion. While these adaptations preserve feasibility, they reduce effective sample sizes, complicate statistical analysis, and weaken the generalizability of results.[31]

Why It Matters

PLUVICTO illustrates that access to comparators is a first-order design variable, not a post-approval concern. Radiopharmaceutical trials function as infrastructure tests as much as efficacy studies, with enrollment and execution constrained by isotope supply, not science alone. Left unaddressed, these constraints can limit the choice of comparators and erode evidentiary strength beyond regulatory approval.

What Radiopharmaceuticals Reveal About the Future of Precision Therapies

Radiopharmaceuticals foreshadow the constraints that will define the real-world reach of other infrastructure-dependent therapies. For example, CAR-T and gene therapies depend on controlled, multi-step manufacturing and logistics, as well as specialized clinical teams operating within accredited centers. Today, these capabilities are concentrated within a limited number of countries and institutions.[34,35]

Even in high-resource settings, requirements for intensive monitoring and complex administration, such as step-up dosing and clinic-based observation to mitigate cytokine release syndrome, and neurotoxicity associated with T-cell-engaging bispecific antibodies, underscore how the delivery of care is the binding constraint on a global scale.[36,37]

Taken together, the access gap already evident in radiopharmaceuticals serves as a leading indicator of which advanced therapies are likely to scale beyond privileged health systems. Therapies that cannot be operationalized risk remaining boutique interventions, confined to centers of excellence and high-income markets. The lessons emerging from radiopharmaceutical delivery, including coordinated supply chains, standardized certification, and sustained workforce investment, show that these therapies represent a stress test for the next generation of precision medicine, where infrastructure readiness will shape real-world impact as much as scientific innovation.

Key Takeaways

Radiopharmaceuticals have entered the oncology mainstream, yet regulatory approval alone does not ensure global patient access. For these promising therapies, clinical development, regulatory expectations, and real-world feasibility are inseparable. When access varies across regions, the comparator and control-arm strategy shifts from a technical design choice to a decisive development risk, shaping trial architecture, evidentiary credibility, and time to approval.

Transforming the promise of radiopharmaceuticals into approval, access, and adoption depends on coordinated actions across sponsors, regulators, and health systems, as highlighted in Table 4. It underscores the opportunities to shape access well before approval, through early development choices, regulatory alignment, and infrastructure readiness, rather than determining it at launch alone.

Table 4: Recommendations to Enable Scalable Radiopharmaceutical Access Globally

Stakeholder	Strategic Opportunities	Strategic Takeaways
Sponsors	**Integrate comparator strategy, access modeling, and infrastructure feasibility early in development.**	**Early, access-aware design choices accelerate regulatory alignment and expand patient reach.**
	Use early regulatory engagement to align evidence generation with real-world implementation.	Proactive dialogue enables flexible, scalable trial designs without compromising rigor.
Regulators	**Adapt comparator and evidentiary expectations as radiopharmaceutical modalities evolve.**	**Fit-for-purpose frameworks support timely access to infrastructure-dependent innovations.**
	Sustain multistakeholder engagement across the development lifecycle.	Ongoing dialogue aligns regulatory standards with clinical and operational realities.
Health Systems	**Coordinate isotope supply, radiopharmacy standards, and workforce development.**	**System-level readiness enables consistent delivery and broader geographic access.**
	Treat infrastructure investment as a strategic enabler of innovation.	Health system preparedness determines whether innovation scales beyond early-adopter markets.

"Radiopharmaceutical clinical development depends as much on infrastructure as on innovation. Strategic investment in isotope supply, radiopharmacy standards, and workforce capacity can determine whether global clinical trials can be executed and whether clinical data translates into better patient care."

– Nicolas Richardson, VP Clinical Development, Precision for Medicine

Further Insights From the Institute@Precision Radiopharmaceutical Series

This article is part of the Institute@Precision radiopharmaceutical series, which examines these therapies across the full clinical development-to-access continuum. Additional articles in the series extend the analysis, exploring:

- **Operationalization** — isotope supply resilience, radiopharmacy capacity, workforce readiness, and end-to-end logistics.
- **Regulatory strategy** — comparator feasibility, evolving evidentiary expectations, and global alignment for infrastructure-dependent therapies.
- **Commercialization** — pricing and reimbursement dynamics, provider adoption, and market readiness across global regions.
- **Investor perspectives** — commercial and reimbursement realities, globalization tailwinds, upcoming clinical, regulatory and manufacturing milestones, and capital market sentiments.

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About Precision for Medicine

Drawing on deep oncology and radiopharmaceutical expertise, Precision for Medicine partners with sponsors to design global trials, accelerate clinical development, and ensure scientific and regulatory integrity.

Authors

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Harpreet Singh, MD, is Chief Medical Officer at Precision for Medicine, where she provides medical and scientific leadership for biomarker-driven clinical development across oncology and rare diseases. Prior to joining Precision, Dr. Singh served in senior leadership roles at the U.S. Food and Drug Administration, most recently as Director of the Division of Oncology, overseeing the regulatory review of drugs and biologics for a broad range of solid and rare tumors. A medical oncologist by training, she is widely recognized for her leadership in precision medicine, innovative clinical trial design, and regulatory science, including spearheading FDA initiatives to streamline and modernize oncology trials. Dr. Singh completed her medical training at the Keck School of Medicine of the University of Southern California and was a fellow at the National Cancer Institute.

Dr. Nicholas Richardson

Nicholas Richardson, DO, MPH, is Vice President of Clinical Development at Precision for Medicine and former FDA Deputy Director of the Division of Hematologic Malignancies 2. At the FDA, Dr. Richardson led regulatory oversight for development of therapies for hematologic malignancies including lymphoma, chronic lymphocytic leukemia , and multiple myeloma (MM). Dr. Richardson also spearheaded initiatives to develop novel endpoints in blood cancer, such as minimal residual disease (MRD) in MM and chronic lymphocytic leukemia, helping accelerate drug development.

Kurt Preugschat

Kurt Preugschat is a seasoned biostatistician with over 14 years of experience in pharmaceutical and biotechnology drug development. He brings deep expertise across the full clinical trial lifecycle, from early-phase development through regulatory submission and post-marketing activities. His work spans Phase I–IV clinical trials, with a strong focus on delivering high-quality, scientifically rigorous statistical strategies that support informed decision-making and successful regulatory outcomes.

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