Worldwide Clinical Trials

Radiopharmaceuticals — Operational Implications in Strategic Program Design

Matthew Confeld, PharmD, PhD, Associate Director, Clinical Research Methodology
Michael Perfetti, PhD, Clinical Trial Liaison, Global Oncology, Scientific Solutions
Sue Batchelor, Executive Director, Project Management

Worldwide | August 2025

Abstract

Many operational challenges and necessary strategies exist for successfully integrating radioligand therapy (RLT) into clinical trials. As a result, protocols must address unique regulatory requirements, such as obtaining and amending radioactive material licenses and the specialized logistics involved in producing, transporting, and handling these therapies. In addition, trial designs must emphasize site readiness, vendor management, and risk mitigation to ensure patient safety and trial efficiency. With proper strategic decisions, RLTs can significantly shift treatment opportunities despite their complex operational demands. This white paper explores approaches for successful RLT implementation in clinical trials, focusing on radiation regulations, isotope production, and operations.

Introduction

The unmet need that remains for many diseases has led to several innovations in therapeutic interventions. One promising realm is RLT, a targeted therapy methodology that uses radioactive isotopes attached to disease-specific ligands to elicit a therapeutic response (Figure 1).

These therapeutics hold life-changing potential and offer hope to those diagnosed with various diseases; despite their promise, these therapies require a complex orchestration for successful implementation at the clinical trial level. RLTs require special manufacturing and transportation methods to develop and ship radioactive interventions. Due to radioactive decay, the therapy has a limited time frame of use, emphasizing the need for each dose to reach the patient within days post-production, adding to the overall complexity, and underscoring the importance of working with experienced personnel with operational expertise and a clear understanding of the therapeutic landscape.

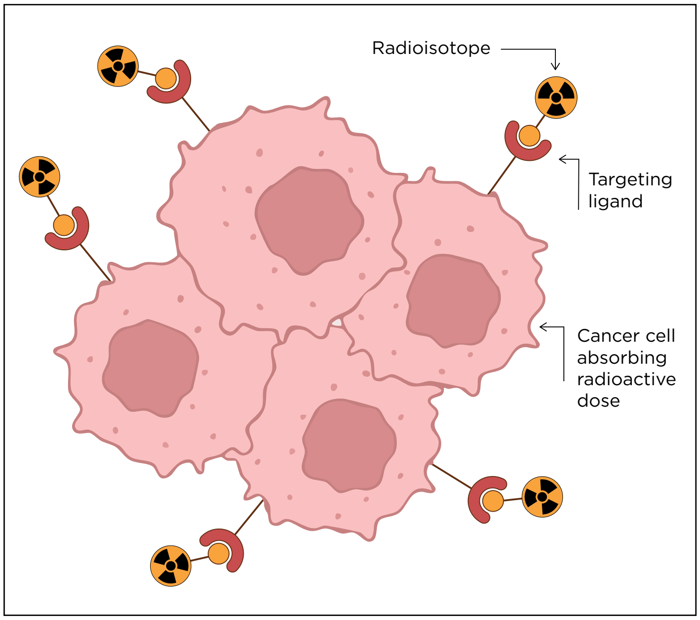

Figure 1: *Radioisotopes are radioactive particles that emit ionizing radiation that damages cells and DNA. Targeting ligands selectively bind to proteins or often overexpressed receptors to ensure the radiation is delivered precisely to the cells or tissues of interest.*

Regulatory Expectations: FDA and EMA

Studies involving radioactive chemicals require specialized operations distinct from traditional clinical trials and begin with regulatory compliance. Regulatory bodies have specific requirements for handling and administering radioactive substances, acquiring nuclear licenses, and demonstrating safety protocols while minimizing radiation exposure to staff and surrounding patients. The FDA and EMA have overlapping requirements that broadly emphasize radiation shielding, dosimetry monitoring systems, and rigorous pharmacokinetic (PK) data while enforcing current Good Manufacturing Practices (cGMP).[1-4] Depending upon the intended plans for distribution, it is best practice to ensure the protocols and intended studies harmonize across regulatory bodies, facilitating broader access post-approval (Figure 2).

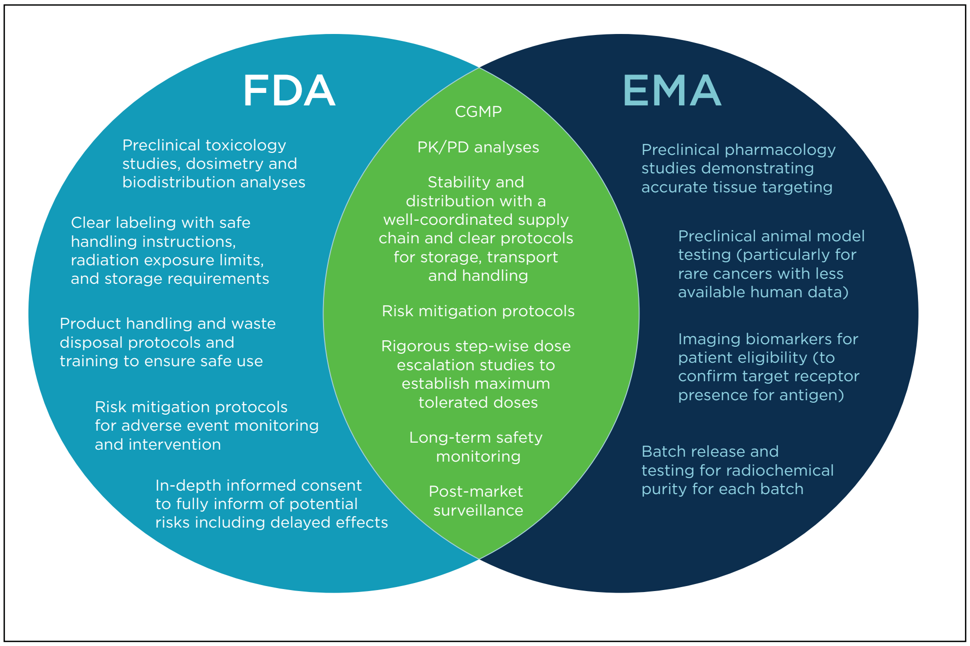

Figure 2: *FDA and EMA clinical RLT requirements. While there are subtle differences between EMA and FDA expectations, they share significant overlap, focusing on production, risk mitigation, and patient safety.*

In the U.S., RLT use requires a license issued by the Nuclear Regulatory Commission (NRC). The NRC approves the facility, accredits staff, and regulates all workflow for manipulating radiopharmaceuticals.[5] A new license application is required if a clinical site has not previously used radioactive materials. Alternatively, if a site already uses radioactive materials, its license may need to be amended to use additional radioisotopes or to increase the quantity of isotopes currently in use. All license applications must define authorized use, a dedicated space for handling, and a radiation safety and waste management program. Notably, while federal regulations define who an authorized user (AU) can be, state-level regulations determine how they can operate. For example, states often differ in the degree of proximity of the AU (i.e., physician) and the treated patient, and the AU may be required to be in the same room during therapy.

On an institutional level, sites require an institutional review board and a radiation safety committee (RSC) or radioactive drug research committee (RDRC). They focus on protecting patients, staff, and the environment, and must clear all clinical research that delivers radiation above the standard of care, whether or not the study is under an IND. RDRCs are a similar committee; however, they can approve certain human studies of radioactive drugs without an IND for studies of “basic science” that use minimal amounts of radiation with no intended pharmacologic effect (e.g., tracers) and deliver doses below specified limits. While most countries have a similar requirement for RSC-like oversight, the U.S. is the only country with the RDRC pathway, allowing for more straightforward conduct of tracer studies that would otherwise require additional regulatory approval elsewhere.

An extra layer of consideration and diligent site selection is required, particularly for E.U.-based radiotherapy trials. Countries like the Netherlands offer relatively fast radioactive licensing of approximately one to four months, whereas Spain’s review and approval process can take one to two years for formal site approval. Additionally, regulatory agency-level guidance has not kept pace with the development of this class of agents, further extenuating the importance of a regulatory strategy. For agents undergoing enabling preclinical research, the FDA’s initial targeted engagement for regulatory advice on CBER/CDER products or INTERACT meetings is a unique opportunity to discuss a development program not yet at the pre-IND stage. The agency can provide targeted feedback related to IND-enabling studies, dose optimization considerations, and novel endpoints that may be specific to a theranostic agent. Later phase development necessitating a more global footprint should include EMA scientific advice and FDA meetings to ensure agreement on the registrational study design across jurisdictions.

> RSCs are required by the NRC whenever a medical facility administers radioactive material.

Production Factors

Production costs and shipping speed accentuate the need for an optimized and efficient clinical trial timeline, as minor delays can have costly effects on both the product and patients. Beyond this, many of these isotopes are rare and thus have a limited supply with limited manufacturing locations. Radioisotopes used in RLTs are manufactured using a cyclotron or irradiating source materials with neutrons in a nuclear reactor. Both production methods work to enrich the source material into the desired isotope. The enriched isotopes are placed into capsules during irradiation to keep them secure. The isotopes are packaged inside a small lead container, roughly the size of a credit card; lead being a strong insulator that prevents radiation from escaping. The drugs get stored inside an additional container called a Type-A container, which is made of polystyrene and helps to maintain the target temperature.

Shelf life varies by therapy; for example, Pluvicto® expires five days after it is packaged, while Lutathera® has a 72-hour shelf life. The capsules get transferred to an isotope-precursor production facility, where they are further purified and concentrated into a radioactive liquid salt solution. At the end of this stage, which takes around 48 hours, there is enough radioactivity in one vial to treat between 30 and 50 patients.

> The strength of the radiation starts to decay as soon as the capsules are removed from the reactors, creating a race against a ticking clock.

Due to careful packaging, the risk of radiation exposure is minimal, so radioligand therapy is often transported via commercial airlines and cargo planes. When transporting doses on the ground, a private courier van service may be a solution to ensure the isotopes reach their destination as quickly as possible.

Operations and Logistics

Roughly one-quarter of interventional clinical trial sites are radiotherapy “ready,” making site relationships and strategic study feasibility assessments a cornerstone of a successful RLT trial. In addition, sites often need license amendments to include specific isotopes, activity limits, or clinical trials added to their radioactive-material license. A one-to-six-month process must occur before the formal IRB and RSC meetings and reviews. Given the complexity of the evaluation, reviewers often require the “package” of relevant information three to four weeks prior to the meeting. With some RSCs meeting only quarterly, it is prudent to understand each site’s processes and submission package requirements to prevent significant delays in study start-up.

> While radioactive decay greatly impacts the RTL site delivery logistics, it is not the only radioactive hurdle to consider.

RTL PK analysis occurs in nearly all phases of development, but managing these PK samples presents another challenge. First, collecting these samples requires specialized personal protective equipment and often utilizes a designated radiotherapy collection area. In addition to the trefoil (radiation warning symbol) label, these samples must be stored in a secure location that complies with radiation safety regulations, often using lead-lined refrigerators or freezers.

Analytical labs may not be qualified to receive “hot” samples, and sponsors may need to ask sites whether they have the infrastructure to store samples until the radioactivity reaches a safe level. Fortunately, given the growing use of RTLs, various vendors and central labs may be contracted to fill that logistics gap. It is critical to have a logistics coordinator who takes the lead in mapping out the site-specific processes, tracks the locations of PK samples (both stored on-site and those at the central lab), and then meets with the PK analysis lab to agree on which samples have had a sufficient storage time of radioactive decay for safe analysis.

Critical Vendor Contributions

A larger-than-average vendor repertoire is necessary as RLT trials combine the usual drug development activities with the additional rules that govern radioactive material management. In addition to having a full-service CRO partner, Table 1 highlights some additional vendors required to ensure smooth trial conduct.

An experienced CRO partner will be able to provide vendor recommendations based upon a thorough qualification process that ensures that the vendor complies with all applicable regulatory requirements and has a proven track record for delivering their respective services. Additionally, a risk-based quality management review is essential to identify any possible areas of error and have contingency plans and mitigation strategies to address and resolve these operational hurdles quickly. A full-service CRO will provide a comprehensive plan for managing these additional vendors and will be able to compile relevant metrics for monitoring and identifying any potential bottlenecks that may impact trial logistics or operations.

Table 1: Additional Vendor Considerations for a Successful Trial.

Vendor Type	Services Provided
Radiopharmaceutical CDMO	• GMP isotope procurement • Radiolabeling • CoA generation
Central Nuclear Pharmacy & Site Dispensing Network	• Same-day or next-day delivery • Dose calibration • Decay-in-storage
Shipment & Cold-Chain	• Class 7 air and ground transport • IATA paperwork • 24-hour tracking
Dosimetry & Radiobiology Services	• Organ-level MIRD • Biokinetic modeling • Absorbed-dose reports

Conclusion

Implementing RLT hinges on a multifaceted approach that addresses regulatory compliance, specialized manufacturing and transportation, and robust operational logistics. The unique challenges posed by the radioactive nature of these therapies, such as the need for rapid delivery due to radioactive decay and the requirement for specialized handling and storage, demand a strategic partnership with experienced vendors and a comprehensive risk management plan.

To avoid delays, it is critical to ensure that clinical trial sites are radiotherapy-ready and that all necessary regulatory approvals and amendments are in place. Additionally, coordinating PK sample collection and analysis and managing a well-coordinated supply chain are essential to a successful trial. By integrating these key considerations, trial protocols can navigate the intricacies of radiopharmaceutical trials and bring these innovative therapies to patients safely and efficiently.

The authors would like to acknowledge the contribution of Zach Rosinger, PhD, in the preparation of this manuscript.

References

1. EMA. Non-Clinical Requirements For Radiopharmaceuticals – Scientific Guideline. Current Guidance. 2019. Available from: https://www.ema.europa.eu/en/non-clinical-requirements-radiopharmaceuticals-scientific-guideline.

2. EMA. Clinical Evaluation of Therapeutic Radiopharmaceuticals in Oncology - Scientific Guideline. Current Guidance. 2025. Available from: https://www.ema.europa.eu/en/clinical-evaluation-therapeutic-radiopharmaceuticals-oncology-scientific-guideline.

3. EMA. Radiopharmaceuticals - Scientific guideline. Current Guidance. 2007. Available from: https://www.ema.europa.eu/en/radiopharmaceuticals-scientific-guideline.

4. FDA. Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations Guidance for Industry. Current Guidance. 2019. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oncology-therapeutic-radiopharmaceuticals-nonclinical-studies-and-labeling-recommendations-guidance.

5. Baldwin JA, Bag AK, White SL, Palot-Manzil FF, O'Malley JP. All You Need to Know as an Authorized User. AJR Am J Roentgenol. 2015 Aug;205(2):251-8. PMID: 26204272. doi: 10.2214/AJR.14.13283.

About Worldwide Clinical Trials

Worldwide Clinical Trials (Worldwide) is a leading full-service global contract research organization (CRO) that works in partnership with biotechnology and pharmaceutical companies to create customized solutions that advance new medications – from discovery to reality.

Anchored in our company's scientific heritage, we are therapeutically focused on cardiovascular, metabolic, neuroscience, oncology, and rare diseases. Our deep therapeutic knowledge enables us to develop flexible plans and quickly solve problems for our customers.

For more information on Worldwide, visit www.worldwide.com or connect with us on LinkedIn.