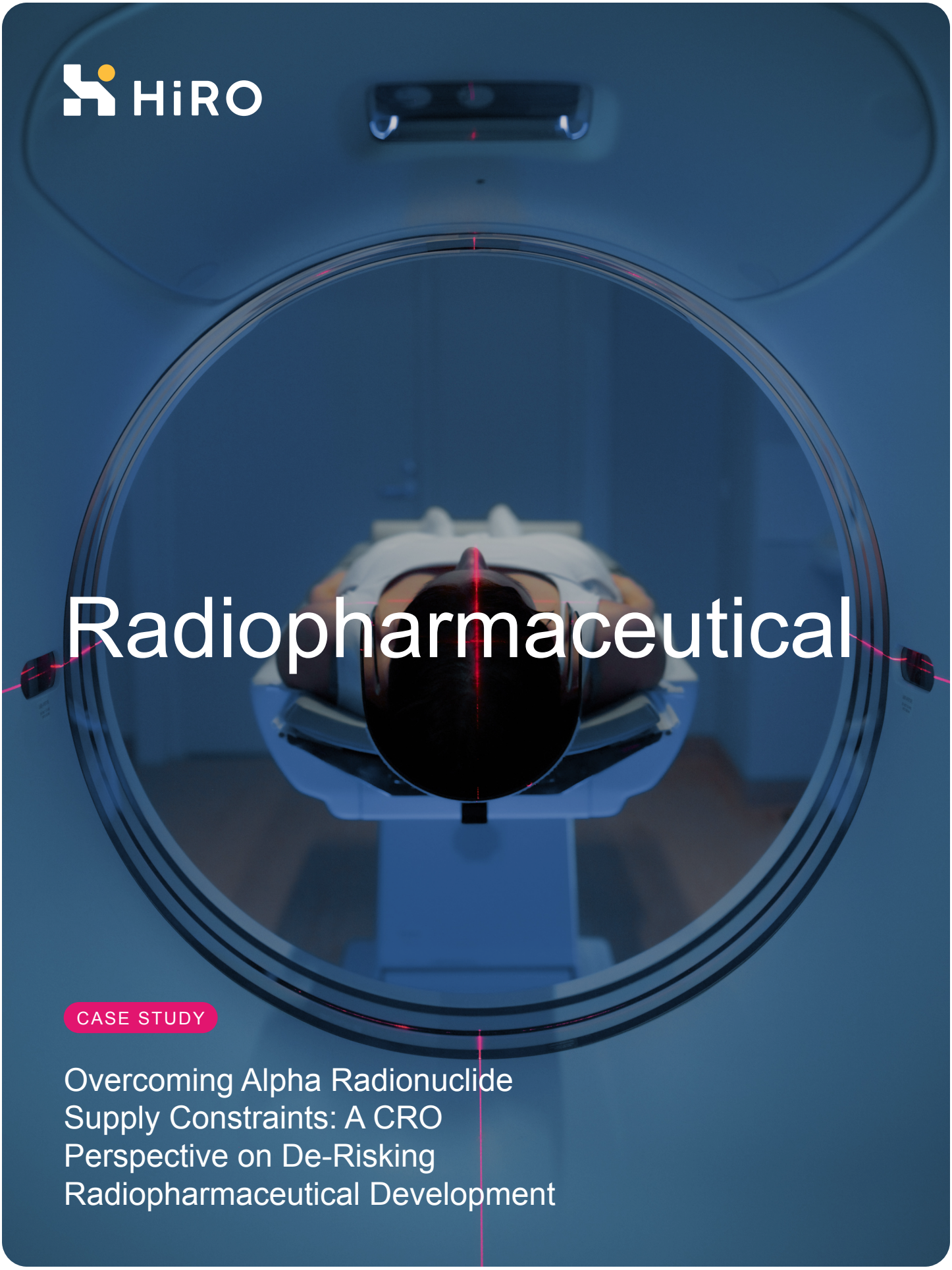
HiRO



Radiopharmaceutical

CASE STUDY

Overcoming Alpha Radionuclide Supply Constraints: A CRO Perspective on De-Risking Radiopharmaceutical Development

The Modern
Global CRO

INTRODUCTION

Targeted alpha therapies (TATs) are rapidly transforming oncology, offering highly potent and selective tumour cell kill through high linear energy transfer. Radionuclides such as actinium-225 (^{225}Ac) and lead-212 (^{212}Pb) are central to this innovation wave. However, while scientific progress has been rapid, the operational reality of delivering radiopharmaceutical trials remains complex.

As a full service CRO specialising in radiopharmaceutical development for us at

HiRO the key challenges are no longer purely clinical or scientific. Instead, they sit at the intersection of isotope supply, logistics, and regulatory alignment. These constraints can materially affect timelines, feasibility, and ultimately the success of a development programme.

At the same time, they present a clear opportunity: with the right strategy, partnerships, and operational model, these risks can be anticipated, mitigated, and in many cases transformed into competitive advantage.

DEMAND OUTPACING SUPPLY — AND HOW EARLY STRATEGY CHANGES OUTCOMES

The rapid expansion of interest in alpha therapies has created a structural imbalance between demand and supply. Production of ^{225}Ac and ^{212}Pb remains limited, with global capacity supporting only a relatively small number of patients annually. Supply chains are concentrated and vulnerable, often relying on a small number of production sites.

In our experience, this imbalance becomes a critical determinant of programme success far earlier than many Sponsors anticipate. Trials that approach isotope sourcing as a downstream operational task frequently encounter delays at the point of site activation or first-patient-in. By contrast, programmes that integrate isotope strategy at the earliest stages—alongside clinical and regulatory planning—are significantly more resilient.

We work with our Sponsors to map isotope demand across the full development lifecycle, aligning supply agreements, manufacturing capacity, and trial design before protocols are finalised. This forward planning is often the difference between predictable execution and prolonged delays.

BOOK A MEETING

The Modern Global CRO

MANAGING HALF-LIFE CONSTRAINTS THROUGH OPERATIONAL DESIGN

The physical properties of alpha-emitting radionuclides introduce an additional layer of complexity. Even relatively longer-lived isotopes such as ^{225}Ac require tightly coordinated logistics, while shorter-lived isotopes impose strict geographic limitations on where trials can be conducted.

Rather than treating half-life as a constraint to work around, we approach it as a core design parameter. Clinical protocols, site selection, and supply chain models must all be aligned to the decay profile of the isotope in use. This includes:

- Selecting trial sites within viable distribution radius
- Aligning manufacturing and dosing schedules with predictable decay windows
- Building redundancy into logistics pathways to minimise the risk of missed doses

In a Phase I solid tumour study for a small biopharma client, we supported protocol development by evaluating the optimal radionuclide for labelling based not only on biological targeting considerations but also on real-world supply chain and half-life constraints. This involved comparative assessment of candidate isotopes, modelling their production availability, distribution feasibility, and alignment with proposed dosing schedules. By integrating these factors early, we were able to guide isotope selection toward an option that balanced clinical intent with operational feasibility. This approach reduced the risk of downstream protocol amendments and ensured that the selected isotope could be reliably manufactured, distributed, and administered within the required therapeutic window throughout the study.

With the right operational framework, it is possible to maintain consistency in dosing schedules and reduce product loss, even in complex multi-centre studies.

BOOK A MEETING

The Modern Global CRO

PROTECTING TIMELINES IN A CONSTRAINED SUPPLY ENVIRONMENT

Supply limitations have a direct and quantifiable impact on development timelines. Industry experience indicates that isotope constraints can delay trial initiation by 6–18 months and reduce recruitment rates by up to 50% where supply is inconsistent. Studies may take two to three times longer to complete if dosing cannot be sustained at planned intervals. However, these outcomes are not inevitable. Through proactive planning and adaptive trial design, we support Sponsors in maintaining momentum even under constrained conditions. This includes:

- Forecasting isotope availability alongside enrolment projections
- Structuring dose-escalation cohorts to align with realistic supply cadence
- Implementing flexible scheduling models that preserve protocol integrity

Our experience shows that aligning clinical design with supply reality early in development can significantly reduce downstream disruption.

ENSURING TRIAL CONTINUITY AND PATIENT ACCESS

One of the most immediate consequences of isotope scarcity is the disconnect between patient identification and treatment availability. Sites may screen patients successfully but be unable to dose them within required timeframes, leading to inefficiencies and potential loss of patient trust.

We address this by tightly integrating site operations with supply chain visibility. Real-time coordination between manufacturing, distribution, and clinical sites allows for more accurate scheduling and reduces the likelihood of missed treatment windows.

In a recent rare disease gene therapy programme incorporating a radiopharmaceutical component, we supported a multi-region clinical strategy spanning the United States and Western Europe.

To mitigate supply risk, we designed and implemented a dual-continent production and distribution model. A central production site in the United States supplied all US clinical sites, ensuring consistency and minimising cross-border transport complexity. In parallel, we worked with the Danish Medicines Agency (DKMA) to secure approval for local site-level production to support the Danish clinical site. This regulatory engagement enabled a decentralised manufacturing approach that reduced reliance on long-distance transport for time-sensitive doses. For the remaining Western European sites, we established a regional production hub in Poland. From this site, we coordinated cross-border logistics into multiple EU countries and into the United Kingdom, managing regulatory, customs, and radiological transport requirements.

This integrated supply model enabled continuity of dosing across regions, reduced the risk of missed administrations, and maintained alignment with protocol-defined treatment schedules despite the inherent constraints of radionuclide half-life and supply.

BOOK A MEETING

The Modern Global CRO

SUPPORTING SMARTER PORTFOLIO DECISIONS

For Sponsors, isotope availability is increasingly influencing portfolio strategy. Assets reliant on constrained isotopes may face delays or reprioritisation, while alternative programmes progress more rapidly. This creates a risk of stranded investment, where promising early-stage data cannot be translated into later-phase success due to supply limitations.

Our role extends beyond individual trials to supporting portfolio-level decision-making. By providing early insight into isotope availability, supply risk, and operational feasibility, we help Sponsors prioritise programmes with a clear understanding of execution risk.

In practice, we position ourselves not only as a delivery partner but as a development partner and trusted advisor. In several programmes, we have worked alongside Sponsor leadership teams to evaluate trade-offs between competing assets, balancing scientific promise against operational feasibility driven by isotope availability. Our flattened management structure enables direct communication between project teams and executive stakeholders, ensuring that critical decisions around portfolio prioritisation, trial timing, and resource allocation are made quickly and with full visibility of supply chain realities. We complement this with tailored governance models that adapt to the needs of each programme and portfolio.

This includes structured decision forums, transparent escalation pathways, and integrated planning across clinical, regulatory, and supply functions.

In addition, we have implemented flexible contracting approaches aligned to commercial and development milestones. This allows sponsors to manage financial exposure while maintaining momentum across their portfolio, particularly in scenarios where supply constraints may impact sequencing or timing of programmes. This combination of strategic input, operational transparency, and flexible engagement enables more informed decision-making and supports sustained portfolio progression, even in a constrained supply environment.

BOOK A MEETING

The Modern Global CRO

REGIONAL DISPARITIES AND HOW TO NAVIGATE THEM

Radiopharmaceutical development varies significantly by region, reflecting differences in infrastructure, regulation, and access to isotope production.

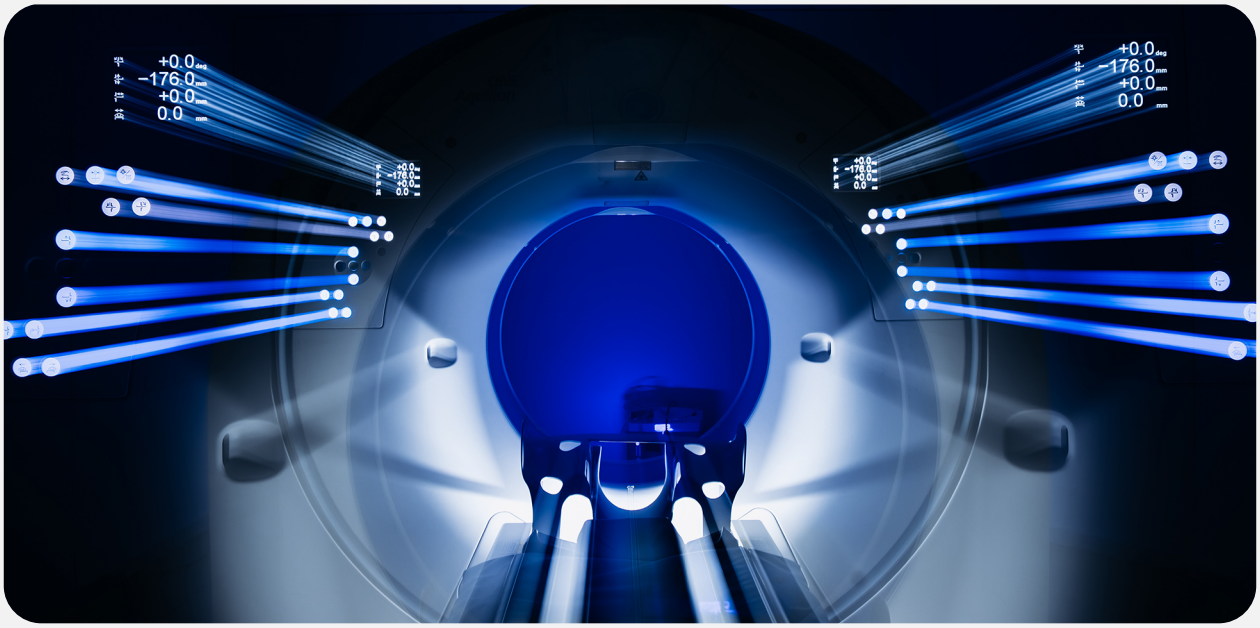
REGION	CHARACTERISTICS	CONSTRAINTS	HOW WE SUPPORT
North America	Established production ecosystem and clinical infrastructure	Demand exceeding supply for alpha isotopes	Established partnerships and early access strategies
Europe	Fragmented supply landscape; reliance on ageing infrastructure	Cross-border logistics and regulatory complexity	Integrated regulatory and logistics planning across jurisdictions
Asia-Pacific	Growing investment and emerging capabilities	Limited large-scale production; evolving regulatory frameworks	Regional feasibility assessment and site network development
Rest of the World	Limited infrastructure and access to isotopes	Barriers to trial participation	Selective site strategy and centralised supply models

These differences are shaped by both geopolitical factors, such as access to nuclear materials and production facilities, and regulatory considerations, including transport rules and GMP requirements. Our global footprint enables regionally optimised trial strategies that balance patient access with supply feasibility.

In a separate programme, we conducted a comprehensive feasibility assessment across more than 50 sites in the United States to support data-driven site selection and tiering. This assessment extended beyond standard feasibility metrics such as patient population and site experience. We overlaid detailed analysis of radiopharmaceutical production facility locations and modelled realistic distribution radii based on isotope half-life and logistics constraints. This enabled us to identify which sites could reliably receive, prepare, and administer product within an acceptable usability window.

Importantly, this approach also allowed us to avoid overreliance on any single production facility by strategically distributing selected sites across multiple supply nodes. The result was a more resilient site network capable of maintaining dosing continuity even in the event of localised supply disruption. This integrated feasibility methodology ensured that selected sites were not only clinically appropriate but also operationally viable within the constraints of radiopharmaceutical supply and distribution.

The Modern
Global CRO



REGULATORY ALIGNMENT AS A RISK MITIGATION TOOL

Regulators including the U.S. Food and Drug Administration, European Medicines Agency, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency, and Therapeutic Goods Administration are increasingly focused on the challenges associated with radiopharmaceutical supply.

There is growing emphasis on early engagement, particularly around manufacturing strategy, supply chain robustness, and risk mitigation. At the same time, regulators are demonstrating increased flexibility in areas such as decentralised manufacturing and adaptive trial design. HiRO supports Sponsors in navigating these evolving expectations, ensuring that supply considerations are clearly articulated within regulatory submissions and that potential risks are proactively addressed.

BUILDING RESILIENCE THROUGH INNOVATION AND PARTNERSHIPS

Addressing isotope scarcity requires coordinated action across the industry. Advances in production technology, particularly accelerator-based approaches, are beginning to expand supply potential. At the same time, partnerships between pharmaceutical companies, isotope producers, and radiopharmacies are becoming increasingly important.

We actively support sponsors in establishing and managing these partnerships, ensuring alignment across the supply chain and reducing dependency on single sources.

In parallel, we work with Sponsors to evaluate alternative isotopes and development strategies that may offer greater supply stability without compromising clinical objectives.

BOOK A MEETING

The Modern
Global CRO

THE HIRO APPROACH: TURNING CONSTRAINTS INTO COMPETITIVE ADVANTAGE

While the challenges associated with alpha radionuclide supply are significant, they are not insurmountable. In our experience, the difference lies in how early and how systematically these challenges are addressed.

Our approach combines:

- Early integration of isotope strategy into clinical development planning
- Deep partnerships across the radiopharmaceutical supply ecosystem
- Flexible, adaptive trial designs aligned with real-world constraints
- Global operational expertise with regional execution capabilities

Our experience shows that aligning clinical design with supply reality early in development can significantly reduce downstream disruption.

The success of targeted alpha therapies will depend not only on scientific innovation but on the ability to deliver complex clinical programmes in a constrained and evolving environment. Supply limitations, logistical complexity, and regional variability are now central considerations in radiopharmaceutical development.

For Sponsors, the opportunity lies in partnering with organizations that understand these challenges in depth and can translate that understanding into practical, executable strategies. With the right expertise and planning, the risks associated with isotope supply can be mitigated, enabling programmes to progress with confidence and ultimately deliver on the promise of targeted alpha therapy.

BOOK A MEETING

The Modern
Global CRO

NOTES / THOUGHTS

BOOK A MEETING