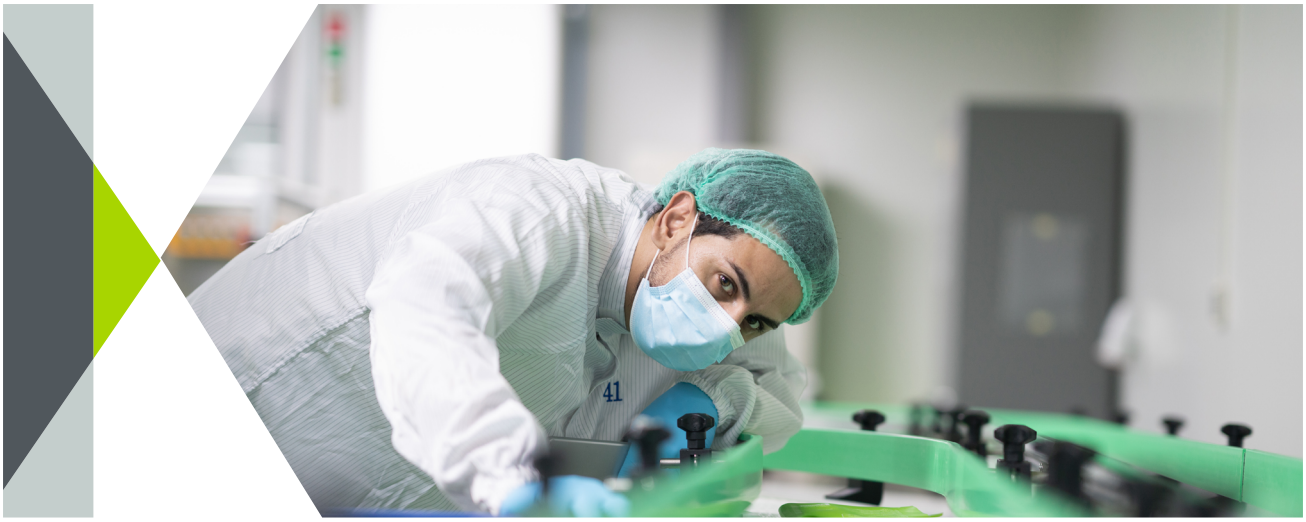


EXECUTIVE INSIGHTS

Radiotherapeutics on the Rise: Addressing Supply Chain Complexity

Key takeaways

1. Manufacturing of radiotherapeutics requires complex supply chain management, with unique challenges across isotope production, radiolabelling, dose production and distribution.
2. As radiotherapeutics gain momentum, supply chain is increasingly front of mind for biopharma to ensure security of supply, whether through in-house supply or CDMOs.
3. CDMOs and other providers considering entry in radiotherapeutics need to understand and assess which part of the supply chain is most attractive and how they can differentiate.
4. While the supply chain is fragmented today, this is likely to consolidate as players start to expand across the value chain.

No one-size-fits-all approach

Radiopharmaceuticals are a rapidly advancing class of radioactive compounds with diagnostic and therapeutic applications. We discussed the drivers for market growth in our previous *Executive Insights*, "From Niche to Widespread Use: The Turning Point for Radiotherapeutics." In this instalment, we focus on the supply chain and how players, current and emergent, should prepare for these complexities.

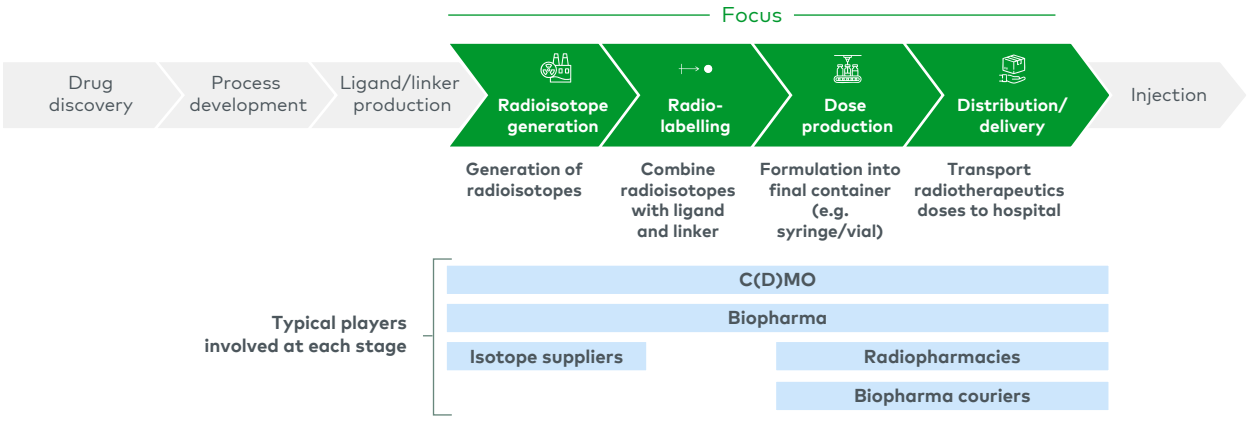
The supply chain for radiodiagnostics is relatively well established and may rely on cyclotron production of radioisotopes close to the site of administration. By contrast, radiotherapeutics manufacturing is likely to be more centralised relative to diagnostics, but it is less established and therefore likely to remain a consistent topic of discussion and focus of investment diligence. This *Executive Insights* focuses on radiotherapeutics.

Indeed, the optimal choice of radioisotope is not only dependent on clinical considerations; challenges related to supply chain, which vary depending on the radioisotope, bring with them optionality for biopharma considering in-house or outsourced manufacturing, as well as opportunities for contract development and manufacturing organisations (CDMOs) and other providers to participate and differentiate.

The radiotherapeutics value chain can be broken down into multiple steps. Here, we focus on four key manufacturing stages: radioisotope generation, radiolabelling of the radioisotope to the ligand, dose production into ready-to-administer doses and distribution/delivery. Each step involves specialised expertise and infrastructure, with different stakeholders playing critical roles (see Figure 1).

Figure 1

Radiotherapeutics value chain



Note: C(D)MO=contract (development and) manufacturing organisation
Source: L.E.K. research and analysis of company investor materials, press releases and industry reports

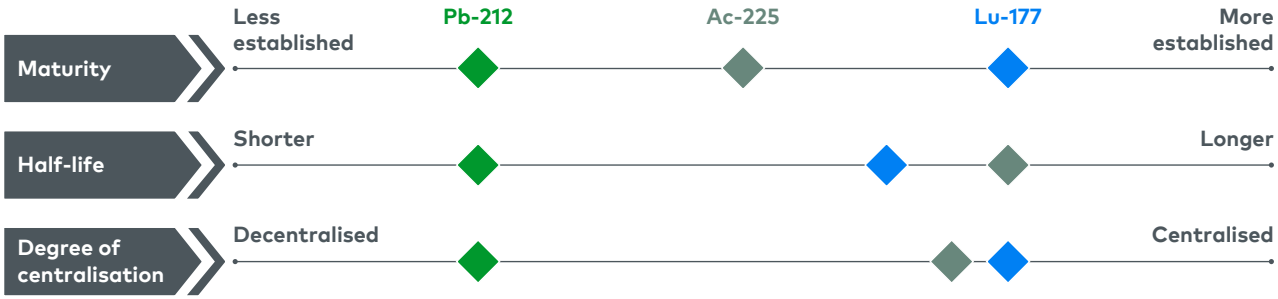
To illustrate how isotope-specific nuances impact supply chain considerations, we highlight how each step may vary for three isotopes enjoying industry interest and with varying degrees of maturity, half-life and manufacturing centralisation (see Figure 2):

- Lu-177 (half-life approximately 6.7 days), a beta-emitting isotope which has been the driver behind the radiotherapeutics resurgence through recent commercial launch successes of Novartis' Pluvicto (mCRPC, 2022) and Lutathera (GEP-NET, 2017).
- Ac-225 (half-life approximately 10 days), an alpha-emitting isotope towards which the research community had initially gravitated as the 'next wave' behind Lu-177 beta-therapies.

- Pb-212 (half-life approximately 10.6 hours), an alternative alpha-emitting isotope which has more recently been gaining development traction alongside Ac-225.

Figure 2

Comparison of key radiotherapeutic isotopes



Source: L.E.K. research and analysis of company investor materials, press releases and industry reports

External supplier participation in radioisotope generation to de-bottleneck supply

Arguably, the step historically limiting growth of the radiotherapeutics sector is radioisotope generation. Isotopes are typically provided by isotope suppliers, even to biopharma manufacturing radiotherapeutics in-house, though integrated CDMOs can produce isotopes where production does not rely on nuclear reactor processes.

Lu-177 is typically generated through nuclear reactors, led by key commercial isotope suppliers including Shine, Nusano, ITM and NRG. The industry is transitioning to non-carrier methods, which come with fewer drawbacks. These methods use Yb-176 as starting material, historically sourced from Russia. There is a push towards alternatives that are not located in Russia, including those produced by isotope suppliers such as Shine and Nusano in the US.

To ensure consistent supply, pharma needs to coordinate with these third-party suppliers for Lu-177 generation. As Lu-177 isotope suppliers do not typically handle subsequent radiolabelling and final dose formulation, this creates an opportunity for CDMOs to offer such services by partnering with isotope producers.

Ac-225's complex raw material sourcing relates to limitations of its potential production methods. Ac-225 production through separation from Th-229 comes with scalability limitations due to supply scarcity. Cyclotron production using Ra-226 requires stringent handling procedures due to safety concerns around exposure to both Ac-225 and Ra-226. Methods like Th-232 spallation require high-energy accelerators and create side reactions.

Production complexity creates opportunities for both Ac-225 isotope suppliers and CDMOs to compete and increase integration along the value chain. Some isotope suppliers (e.g. NorthStar, SpectronRx, Eckert & Ziegler) are exploring alternative scalable options such as electron accelerator photonuclear transmutation of Ra-226. These players also provide subsequent radiolabelling services, acting as CDMOs.

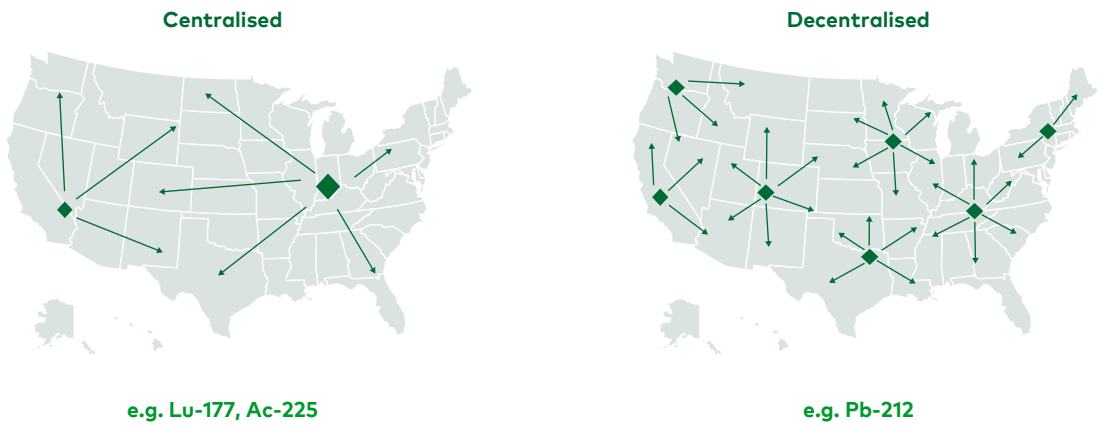
Pb-212 faces fewer supply constraints on its raw materials Th-228 and Ra-224, but it comes with a shorter half-life (approximately 10.6 hours), requiring production in decentralised generators close to the patient. To solve for this, some biotechs have chosen to become more involved in radioisotope generation.

Indeed, select companies developing Pb-212-based assets — such as ArtBio, AdvanCell, Perspective Therapeutics and Orano Med — have developed their own Pb-212 generator production capabilities. Orano Med, together with RadioMedix, have recently signed an agreement with Sanofi as part of a licensing agreement to assume manufacturing responsibility, suggesting that biopharma companies with Pb-212 generator production expertise can also act as contract manufacturers in this area.

Depending on the commercial success of Pb-212, opportunity may exist for CDMOs to position themselves as regional Pb-212 bases in a hub-and-spoke setup with large generators to be installed on-site at the CDMO, reducing the need for complex shipping logistics (see Figure 3).

Figure 3

Centralised vs decentralised manufacturing



Source: L.E.K. research and analysis of company investor materials, press releases and industry reports

Radiolabelling at the core of CDMO offerings

Subsequent radiolabelling connects the radioisotope to the targeting ligand via chelation. For Lu-117 and Ac-225, radiolabelling can be performed in centralised facilities owing to their relatively long half-lives. The specific conditions vary based on chelator and isotope, but labelling may require high temperature and pressure requirements alongside radioactive compound handling precautions.

Whilst biopharma may want to consider in-house labelling for supply security and quality control, CDMOs can play a key role to avoid costly investment as well as complexity in infrastructure (e.g. shielded laboratories, handling systems such as hot cells, glove boxes) and procedures for biopharma. CDMOs can also bring substantial expertise in chelation and ultimate linking of targeting compound and radioisotope that are difficult to establish for new entrants (see Figure 4). Example CDMOs currently in the field include SpectronRx and NorthStar.

Pb-212's shorter half-life necessitates local radiolabelling and therefore a more widespread geographical footprint. CDMOs can play a key role in accommodating local needs for radiolabelling due to the isotope's shorter half-life.

More broadly, radioactive decay drives the need for radiopharma CDMOs to more frequently produce (smaller) batches throughout the year in contrast to the potential for larger, more infrequent batch sizes for other therapeutic modalities. The more continuous nature of production drives higher utilisation rates, which could lead to different operations and levels of profitability when compared to other therapeutic-modality CDMOs.

Extending CDMO capabilities into dose formulation and logistics

Following radiolabelling, the compound is formulated into ready-to-administer syringes or vials. This stage is specialised, as the therapeutic dose needs to be accurately measured to maximise efficacy while minimising toxicity. Dosing is complicated by the radioactive decay of isotopes, which must be accounted for in the production process to ensure that patients receive the intended radiation dose.

CDMOs can oversee this process for companies without in-house capabilities. Radiopharmacies are another player that can perform this step, though some facilities operate as both a CDMO and a radiopharmacy.

Distribution and delivery represent the final step prior to patient administration. Due to radioisotope decay, this process must be carefully managed. Shipping requires compliance with strict (inter)national regulations, and specialised packaging is essential to ensure safety during transport. Depending on the isotope and capabilities of the players in the value chain, there could be anywhere between one and three players exchanging

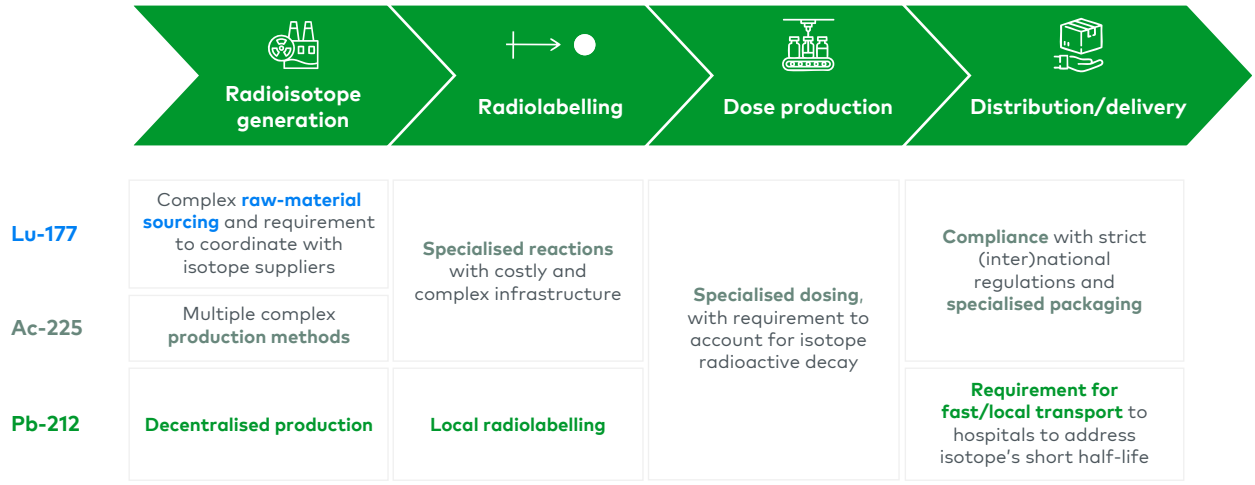
radioactive intermediates or final dose product prior to final delivery for patient administration.

The short half-life of the radioisotope is a key parameter to consider for logistics and reinforces the importance of integrated providers, as evidenced by Orano Med's specialised logistics for Pb-212. In North America, for example, Orano Med's ATLab, leveraged for large-scale production, is strategically located in Indiana next to major national and international distribution hubs and delivery companies (e.g. FedEx) to ensure fast transport to hospitals and address the 10.6-hour half-life of the isotope.

Challenges in this step may result in potential for more biopharma courier services to expand their offering into radiotherapeutics and leverage the optimisation and speed of their logistics. Companies such as Life Couriers provide logistics services for radiopharmaceuticals and may also cover other sensitive biopharma products, such as live cells, as adjacent services. Once the radioisotope is received, hospitals and treatment centres play a critical role in final correct handling, storage and patient administration.

Figure 4

Summary of value-chain complexities



Source: L.E.K. research and analysis

Implications for radiopharmaceutical supply chain participants

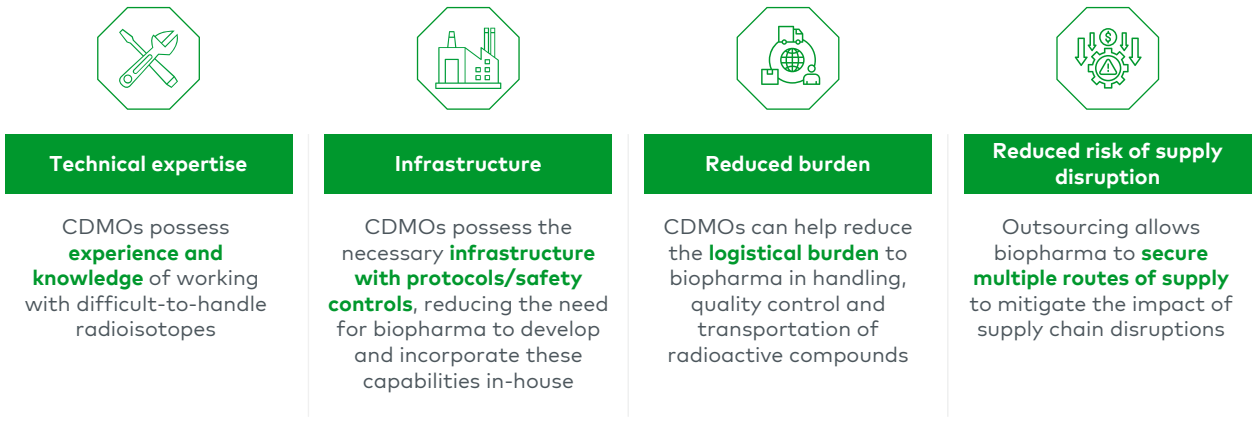
As radiotherapeutics move from niche to widespread use, an increasing number and range of players can participate in the supply chain. Some early-stage radiopharma biotechs have built manufacturing capabilities, pioneering new processes.

As the field of radiotherapeutics matures, CDMOs and other providers can play an increasingly important role; they can offer biopharma their expertise, infrastructure, logistical control and supply-risk mitigation (see Figure 5). This could be through offering

radiolabelling capabilities, or infrastructure and expertise to accommodate high-temperature/pressure chelation processes, whilst adhering to stringent requirements for radiation safety, regulatory compliance and isotope handling.

Figure 5

Value proposition of CDMOs in radiotherapeutics manufacturing



Note: CDMO=contract development and manufacturing organisation
Source: L.E.K. research and analysis of company investor materials, press releases and industry reports

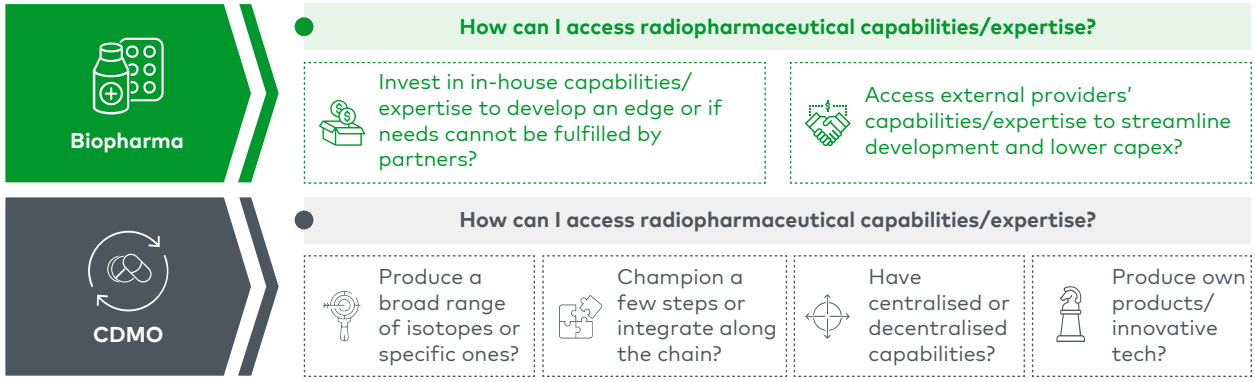
In the growing radiotherapeutics market, the supply chain is a significant complexity that companies should aim to carefully address. Biopharma exploring radiotherapeutics need to decide between investing in developing in-house capabilities and expertise or partnering with external providers to leverage their infrastructure and expertise to lower capital expenditure and focus on their own core competencies of drug discovery and development.

External providers — including CDMOs, isotope suppliers and biopharma couriers — can simplify this complex value chain, but they will need to carefully think through how they can differentiate and evolve to ensure they maintain a unique position in this fluid ecosystem where processes and technologies are not yet fully set (see Figure 6).

Over time, we anticipate that some providers will extend their offering along the value chain as consolidation takes place and as investment allows them to target adjacent areas.

Figure 6

Key radiotherapeutics chain considerations for biopharma and CDMOs



Note: CDMO=contract development and manufacturing organisation
Source: L.E.K. research and analysis

How L.E.K. can help

As radiotherapeutics grow, securing a reliable supply chain is key. Whether you're a biopharma company or a CDMO, L.E.K. can help you identify opportunities, mitigate risks and build a strategy for success.

Get in touch today to find out how to stay ahead in this evolving market.

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