Clinical trial services

Article

From clinical to commercial: Streamlining cold chain logistics for advanced therapies

Cell and gene therapy (CGT) products often require ultracold temperatures for both manufacturing and distribution, posing substantial challenges, particularly during the transition from clinical to commercial stages. Maintaining product integrity while navigating complex global logistics requires efficient supply chains, seamless end-to-end services, and strict adherence to evolving regulatory standards. This article highlights the benefits of leveraging a global network and innovative cold chain solutions to address these challenges, thereby facilitating the successful commercialization and worldwide distribution of CGT products. Key topics covered include precise temperature-controlled packaging, late-stage customization, and a case study that illustrates the transition of a first-in-class allogeneic cell therapy from clinical to commercial production.

Overcoming supply chain challenges in the dynamic cell and gene therapy market

Temperature-sensitive therapies, particularly CGT, have experienced double-digit compound annual growth rates (CAGR) in recent years. This robust growth is anticipated to persist as an increasing number of products secure marketing approval. However, the rapid escalation in the number of products with ultracold chain requirements transitioning from clinical to commercial stages presents significant challenges (Figure 1).

Cell and gene clinical trials take place on a global scale

Efficient and secure logistics are vital for the safety and efficacy of critical materials in geographically complex clinical trials.

Ultracold temperatures are required for late-stage customization

Personalized therapies may necessitate late-stage packaging and labeling modifications, including patient-specific dosing or HLA typing.

Complex regulatory requirements

Regulatory compliance requires expertise to navigate complex, evolving standards globally and regionally.

Commercial infrastructure for scalability

Ensure that the supplier is commercially approved, scalable, and licensed to provide an end-to-end solution that offers cost savings and a shorter learning curve.

Figure 1. Considerations for temperature-sensitive CGT products transitioning from clinical to commercial stages.

Tackling global challenges in CGT clinical trials

Ensuring the integrity of ultracold chain CGT products requires meticulous attention to the infrastructure and logistics necessary for global distribution. As these products move towards commercialization, it is essential to establish robust infrastructure and support systems for global operations, regardless of whether a centralized or decentralized manufacturing model is chosen.

Beyond the manufacturing process, efficient and secure logistics are critical for the success of geographically dispersed clinical trials. Establishing a global supply chain network necessitates selecting a service provider capable of supporting production and patient distribution on both global and regional scales. For instance, CGT product manufacturers often need regional infrastructure that can maintain –80°C and cryogenic cold chains up to the point of care.

Addressing this challenge involves partnering with a service provider that offers comprehensive global infrastructure to support ultracold products throughout clinical trials and global distribution. This includes access to a worldwide network of cGMP-compliant facilities equipped with –80°C and cryogenic storage, regional distribution centers with similar capabilities, and a global network of qualified couriers to ensure rapid delivery while mitigating the risks associated with complex international shipping regulations.

Thermo Fisher Scientific's global network, for example, supports clinical and commercial ultracold chain products worldwide through a network of GMP-compliant facilities for storage, distribution, manufacturing, packaging, and labeling.

Navigating the challenges of late-stage customization

Late-stage customization of CGT products introduces additional complexities to cold chain management. Autologous cell therapies, allogeneic cell therapies, and AAV-based *in vivo* gene therapies each have unique supply chain models tailored to reduce both the number of required steps and associated risks. For autologous cell products, packaging, labeling, and distribution typically occur at the manufacturing site to expedite the vein-to-vein timeline. Conversely, off-the-shelf allogeneic CGT products often necessitate late-stage customization, such as patient-specific dosing, human leukocyte antigen (HLA) typing, and packaging and labeling while maintaining cryogenic conditions to preserve stability.

Accurate, temperature-controlled packaging and labeling for both clinical and commercial products, including custom and patient-specific labels, are essential for off-the-shelf CGT products. For instance, when a patient is identified and a specific dosage needs to be prepared on short notice, it is imperative to have procedures in place to manage the tight timeframe while minimizing temperature fluctuations to ensure product integrity and viability.

To address these challenges, implementing robust protocols and working with specialized service providers is crucial. These providers should be equipped with the necessary infrastructure to handle precise temperature-controlled environments and facilitate the timely delivery of customized CGT products, thereby maintaining their efficacy and safety throughout the supply chain.

Navigating the complex landscape of regulatory requirements

As a relatively young industry, the CGT sector contends with evolving and diverse regulations that vary significantly across different countries and regions, making regulatory compliance a constantly shifting target. The complexity of regulatory requirements depends on the specific market where the product is manufactured and distributed. For instance, CGT products are subject to unique regulatory mandates concerning packaging, distribution, import, export, customs clearance, duties, and taxes, all of which can differ markedly from one jurisdiction to another.

To navigate these challenges, it is essential to collaborate with a partner who possesses deep expertise in developing and implementing comprehensive standard operating procedures (SOPs) that align with both regional regulations and international best practices. This ensures the establishment of robust quality management systems (QMS) and effective management of cold and ultracold chain materials. For example, the EU market has specific requirements for ultracold chain advanced therapy medicinal products (ATMPs), including detailed documentation to support the Qualified Person (QP) declaration.

By partnering with an experienced provider, CGT companies can better manage regulatory complexities and ensure compliance across multiple regions, thereby safeguarding the integrity and viability of their products throughout the global supply chain.

Overcoming scalability challenges in commercial infrastructure

The infrastructure necessary for the commercialization and distribution of ultracold chain CGT products has not yet reached the scalability required by the rapidly expanding industry. Although numerous service providers are active in the CGT commercialization and storage sectors, traditional supply chain and distribution networks often fall short of meeting the specific demands of these products.

To address this challenge effectively, it is crucial to engage with a service provider early in the clinical stage—one that has a proven network and infrastructure for bringing ultracold chain products to market. Given the low volume and high value of CGT products, it is essential that the service provider has experience in scaling operations up or down as needed. This flexibility is vital for adapting to fluctuating market demands and ensuring efficient operations.

Another critical factor is the implementation of integrated solutions to enhance operational efficiency. Minimizing product handoffs through an end-to-end solution can significantly reduce associated risks. A one-stop shop for product receiving, importation, storage, late-stage customization, and distribution can streamline processes and mitigate risks associated with unnecessary handoffs and ensuring a more seamless operation..

Moreover, an integrated solution means that the service provider not only offers comprehensive end-to-end services but also leverages the entire supply chain. This includes managing critical raw materials, consumables, and equipment. Such an integrated network provides better visibility and planning capabilities, thereby reducing risks associated with additional handoffs and ensuring a more seamless operation.

By focusing on these strategies, the CGT industry can better navigate the complexities of ultracold chain product commercialization and distribution, ultimately supporting its continued growth and success.

Key steps in partnering with the right ultracold chain packaging and labeling services provider

To effectively navigate the complexities of transitioning to the commercial stage, it is advisable to select a global ultracold chain packaging and labeling partner as early as phase II clinical development, particularly if the product is on a fast-track regulatory pathway. This selection should occur no later than the commencement of pivotal clinical trials. Maintaining the same service provider from clinical to commercial stages helps reduce the learning curve and minimize handoffs.

Collaboration with a service provider typically begins with the project setup step, during which order requirements including packaging materials, shipping lanes, and shipping methods are gathered (Figure 2).

Following the project setup, the tech transfer stage involves developing the batch record, master batch record, specific packaging, and SOPs. This stage also includes the validation of necessary documentation for regulatory submissions, such as a US FDA Biologics License Application (BLA) or other specific regulatory agency requirements. This process usually takes between 6 and 9 months, depending on the complexity of the supply chain. Serialization is another critical element to consider; while it may not be the primary focus during preclinical or early clinical development, certain gene therapies and allogeneic cell therapies require serialization during tech transfer unless a waiver is obtained.

Once the process performance qualification (PPQ) runs have been successfully completed and the documentation and process validation are finalized, preparations for site inspection readiness begin.

After the site is deemed inspection-ready and all regulatory documentation has been submitted, the next step is to seek final approval from a regulatory body. This body may inspect either the entire supply chain or select service providers within it. Upon receiving regulatory approval, commercial execution can commence.

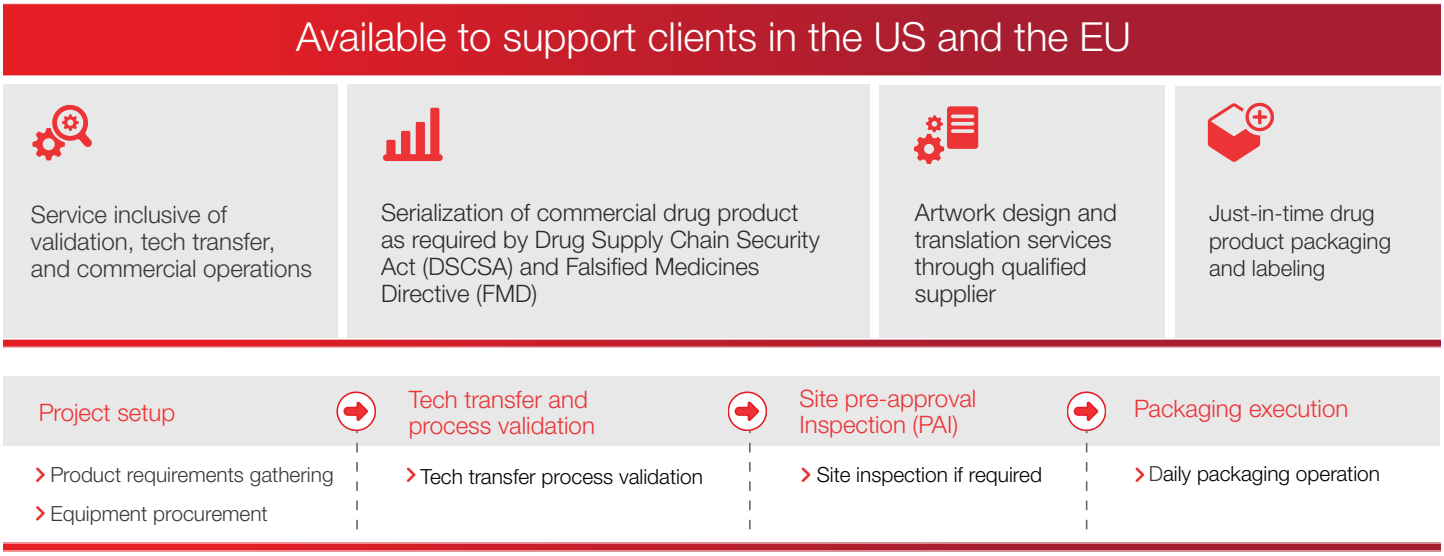


Figure 2. Timeline of commercial packaging development of ultracold chain CGT products to support clients in the US and EU.

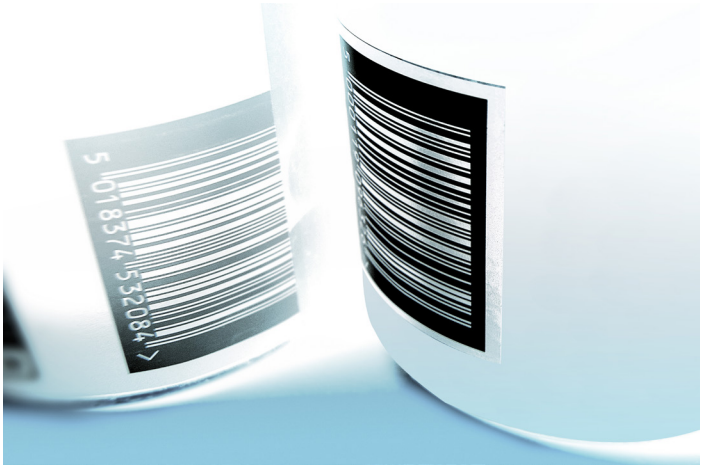
Innovations in cold chain packaging and labeling

To meet the specific manufacturing and supply chain requirements of CGT products, specialized packaging and labeling solutions are essential.

For instance, gene therapy products must minimize exposure to CO_2, especially from dry ice, during packaging, labeling, and distribution. To address this challenge, Thermo Fisher has innovated CO_2-free labeling and packaging solutions that operate at –80°C without relying on dry ice.

Additionally, the selection of packaging materials for CGT products is crucial. Labels, cartons, and foam inserts must endure ultracold chain temperatures for prolonged periods to meet commercial application standards. Thermo Fisher has developed proprietary, validated packaging materials that ensure product integrity and performance under these conditions.

Finally, one of the most demanding aspects of delivering off-the-shelf CGT products to patients is the need for late-stage customization. To apply or update labels on already frozen products without affecting temperature stability, Thermo Fisher has introduced ultracold product labeling techniques designed to prevent temperature excursions.



Case study: A first-in-class allogenic cell therapy approved in the EU

Thermo Fisher supported the transition of an allogeneic cell therapy product from clinical to commercial stages and provided clinical support for a developer's global trials. This process involved supporting the developer's Phase III open-label studies, which required just-in-time (JIT) packaging and distribution to clinical sites in both the US and the EU. More specifically, the requirements included JIT packaging with a 3-day turnaround, variable information on secondary package labels, multiple doses and shipments per patient, and packaging in cryotemperatures such as –196°C.

To meet these requirements, Thermo Fisher applied the innovations and solutions mentioned above, completing JIT late-stage packaging, labeling, and distribution to support the client's global clinical trials in the US, EU, and other regions.

Beyond clinical support, Thermo Fisher collaborated on the tech transfer process, identified critical steps, supported SOP development, designed processes, and conducted validation during PPQ runs to ensure site readiness. Ultimately, Thermo Fisher successfully supported the product's commercial launch in the EU, beginning patient shipments in early 2024.

In summary, the cold chain innovations developed by Thermo Fisher ensured on-time delivery for every shipment with products having spent zero time spent outside of the required temperature range, thus enabling the commercial success of an allogeneic cell therapy product.

Discover how Thermo Fisher can optimize cold chain logistics for your advanced cell and gene therapy project.

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