White Paper

Cell and Gene Therapy Logistics Management:

A holistic approach.

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Summary

Logistics management is a key element of operationalizing cell and gene therapy (CAGT) trials. There are unique logistics requirements for autologous cell therapy modalities and allogeneic cell therapies, as well as for in vivo and ex vivo gene therapies and gene editing. Authored by an IQVIA expert, this paper explores key logistics requirements, proposing a holistic and comprehensive approach to logistics management to address the spectrum of complexity across all types of CAGT assets.

Introduction

Defining characteristics of cell and gene therapy (CAGT) clinical trial operations include complex protocols, the need to manage expensive and often irreplaceable assets, and accelerated timelines. These features demand that clinical operations teams ensure meticulous planning, oversight, and training around supply chain logistics. The interdependency of the manufacturing process, shipping, site handling of the asset, and the patient journey require a holistic logistics management strategy that takes into account all these factors from the beginning and addresses needs beyond simply tracking assets. A holistic approach to logistics management is also key to supporting sites, because it allows for better risk management and compliance.

Key CAGT logistics requirements

Gene therapies

Logistics management for in vivo gene therapies must address a unique type of complexity. Gene therapies and gene editing technologies (such as CRISPR/ Cas9 base editors) can feature a similar divergence of logistical complexity from the chain of identity/chain of custody asset tracking of ex vivo gene therapies, to a broader set of challenges tied to the preparation and administration of in vivo gene therapies.

The supply chain demands of in vivo gene therapies are more streamlined given the "off-the-shelf" nature of the manufacturing process; however, these assets often require complex methods of administration, delivering the asset directly to a specific organ or system. Diverse, multi-disciplinary care teams at sites are frequently involved in receiving, preparing, and administering gene therapy assets.

Gene therapies in CNS and ophthalmology indications are often surgically delivered to a target area within the brain, eye, or sensory organs. In the cardiovascular setting, gene therapy administration needs to be coordinated between the cardiac catheterization lab, interventional cardiologists, and interventional radiology teams. Additional complexity comes in the form of blinding and masking approaches to placebo or sham controls.

The logistical challenges in these therapies are predominantly centered around the coordination of multiple resources and the need for careful planning and timing, even after the asset is received at the site.

Autologous cell therapy

Historically, the CAGT market was largely comprised of ex vivo autologous cell therapy, where cells are derived from an individual patient before being isolated, genetically modified, and then ultimately re-administered back into that same patient. Chimeric antigen receptor (CAR-T) therapies, such as tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®), emerged as one of the first breakthrough cell therapy platforms, based on an autologous development model. CAR-T ushered in a new era of truly personalized medicine, but also introduced a level of logistical complexity rarely seen previously and difficult to scale commercially.

Some of the key logistics management requirements for this approach include: understanding the protocol, the patient's disease stage, existing comorbidities, the timing of apheresis, tracking of cells, coordination of shipping, handling, and administration to the patient and reconciliation of the "unused product".

Solutions required to optimize the logistics management of ex vivo autologous therapies include a dedicated Logistics Manager responsible for coordinating and overseeing slot management and supply chain vendor integration, along with highly specific, role-based training of sites.

Allogeneic cell therapy

The logistical complexity in autologous therapies has increased the demand for allogeneic cell therapies, which are products derived from healthy, screened donors that are expanded and available to be used "off the shelf." An allogeneic platform significantly streamlines the asset journey because manufacturing is not dependent upon procuring and isolating individual patient cells or tissue to yield the finished product. In turn, this reduces shipping time, potential for damage, and cost.

Aside from those considerations, there are still complexities to be considered in ex vivo allogeneic cell therapy, including manufacturing and depot location, chain of custody tracking, tailored site training on asset storage, preparation, and administration.

Table 1 shows components of logistics management in CAGT therapies, sorted by asset platform.

Table 1: Logistics requirements of various types of CAGT assets

CELL THERAPIES (AUTOLOGOUS)		
• Apheresis /cell procurement	• Chain of identity tracking	• Chain of custody tracking
• Manufacturing location & timeline	• Shipping, storage, & temperature	• Cell thaw, prep, & administration
CELL THERAPIES (ALLOGENEIC)		
• Apheresis (only if donor-derived)	• Chain of custody tracking	• Manufacturing location
• Shipping, storage, temperature & prep/administration		
GENE THERAPIES (EX VIVO)		
• Manufacturing location	• Chain of identity tracking	• Chain of custody tracking
• Shipping, storage, temperature & prep/administration		
GENE THERAPIES (IN VIVO)		
• Shipping, storage, and temperature	• Blinding and placebo/sham controls	• Potentially complex (invasive/ surgical) administration

The heterogenous nature of cell therapy modalities means that logistics management and supply chain support capabilities need to be customizable and right sized to the specific considerations unique to each platform. A holistic approach to CAGT logistics management provides a durable, nimble, and multi-disciplinary set of capabilities that can be configured to optimize clinical delivery within any CAGT platform.

Defining a holistic approach to CAGT logistics management

A holistic approach to CAGT logistics management for clinical trials should offer the following interconnected, synergistic capabilities:

- **Site training,** with bespoke, role-based, training focused on the investigational asset and the specific procedures associated with the therapy. This training should include the shipping, storage, preparation, and administration of the asset. Training should also highlight the patient journey and coordination of patient treatment (including cohort management, manufacturing slots, and surgical/interventional radiology involvement).
- **Vendor oversight, integration, and partnerships:** Supply chain vendors in CAGT often include couriers, depot networks, tracking platforms, and even patient concierges. Integrating the oversight of these vendors into the scope of work for a logistics lead is necessary to support seamless coordination of the patient and asset journeys, which are each uniquely linked in CAGT. IQVIA leverages strategic preferred partnerships with specialty couriers and services to help support sites and sponsors.
- **Blinding/unblinding support:** The deployment of a dedicated CAGT Logistics Manager, who also serves as an unblinded resource to support study and site adherence to clinical trial blinding schema, is an essential step.
- **Supply chain vigilance/asset tracking:** A CAGT Logistics Manager, often supported by technology platforms, is also needed to ensure on-time delivery of the investigational asset. In addition, this resource should be able to support additional investigational medical product (IMP) capabilities such as temperature excursion management, packaging/labelling expertise, interactive response technology (IRT) setup and integration.

Evolving trends in CAGT logistics management

In addition to the progressive shift from autologous, patient-derived cell therapy to allogeneic cell therapies and immense growth in in vivo CAGT in indications outside of oncology, other themes are creating an environment where a more holistic approach to logistics management is paramount. These include:

1. **Globalization of CAGT and expansion into emerging markets:** Adoption of cell and gene therapies/ regenerative medicines in regions outside of North America, Western Europe, and Australia has been steadily increasing within the last several years. New regions bring both opportunities and challenges, as sites in those regions often need extensive training around shipping, storing, handling, and administering these assets. Other factors to take into account include shipping requirements, vendor identification, the need for depots and storage facilities that have infrastructure to support CAGT.
2. **Growth and expansion of gene therapy assets in diverse therapeutic areas:** The opportunity to address unmet medical needs, particularly in rare diseases, has provided a catalyst for expanding CAGT into new therapeutic areas and indications. These often involve more complex and invasive administration of the asset. Surgical delivery of assets is not uncommon in the gene therapy space, which leads to additional scheduling, timing, and

coordination challenges for sites and study teams. Logistical oversight that goes well beyond simply tracking of an asset from Point A to Point B is critical.

3. **Point-of-care manufacturing of CAGT assets:** Asset manufacturing is a key determinant of the complexity of the clinical development process, especially for cell therapy trials. Moreover, those involving multiple sites have historically been some of the most logistically complex. Some stakeholders have been championing a decentralized model of manufacturing where patients are treated with cells manufactured within the treating institution. This approach can theoretically reduce the shipping and supply chain length and complexity. Several proprietary mobile units or devices, such as the Cocoon Platform (Lonza) and the CliniMACS Prodigy (Miltenyi Biotec) have been designed and deployed to support point-of-care manufacturing. The potential for decentralization of manufacturing will require more of an emphasis on site setup, site training, and supporting hybrid models (centralized and decentralized) for manufacturing within a single study or program.

Conclusion

The adoption of cell and gene therapies has been a true therapeutic paradigm shift, not only in the ability to tackle unmet medical needs, but also in the complexity of the clinical delivery of the assets themselves. As CAGT platforms mature and expand, so must the approach to defining and managing logistics that are inherent to the assets. The ability to holistically address the logistics and supply chain implications of CAGT enables better prepared sites, fewer investigational product (IP) errors, faster trials, and ultimately lower cost.

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