cencora
World Courier

Cold hard facts about cryogenic cell and gene therapy logistics:

Study confirms developers seeking logistical certainty and cold-chain integrity from providers with advanced cryogenic capabilities

Introduction

Study confirms developers seeking logistical certainty and cold-chain integrity from providers with advanced cryogenic capabilities.

Cell and gene therapies (CGTs) represent the leading edge of biomedical research. Autologous and allogeneic cell, gene, and tissue therapies are transforming healthcare and are demonstrating dramatic results. Approvals of autologous CAR-T therapies such as Kymriah, Tecartus, and Yescarta and allogeneic treatments including Rethymic and Alofisel reinforce the exceptional advancements in this space.[1]

CGT sponsors must carefully consider every aspect of their development and manufacturing journey as early as possible to ensure their discovery can be approved and commercialized with minimal delay. The logistics — of development, clinical trials, and the therapy's commercial stage — are a key part of this planning.

However, CGT therapies come with unique logistic requirements that add complexity and risk to their supply chains. Understanding the end-to-end supply chain of CGT as early as possible is critical to ensuring risks can be mitigated before they cause delays in getting a treatment to patients.

World Courier commissioned Coleman Parkes Research to survey executives and managers serving in supply chain operational roles in companies with CGTs in clinical trials or available to patients commercially.

Part 1: Market, cell and gene therapy landscape

Cell and gene therapies are set to grow rapidly at an increasing pace.

Although the field is in its relative infancy, with 22 gene therapies, and 59 non-genetically modified cell therapies approved globally as of Q3 2022, the development pipeline is growing fast. There were 3,649+ gene therapies (including genetically modified cell therapies, such as CAR-T cell therapies) in development from preclinical through pre-registration at the end of 2022.[2]

Falling under the umbrella of advanced therapy medicinal products (ATMPs), CGT modalities exhibit the potential to cure disease by addressing the root cause of the condition rather than treating it symptomatically. Based on modified human genes, tissue, or cells, ATMPs include gene therapy medicinal products, somatic cell therapy medicinal products, and tissue-engineered medicinal products.

The science behind these therapies, as well as the means to deliver them commercially, are keeping pace with the pipeline as expected. According to Research and Markets, the market for CGTs is expected to grow from $4.4 billion in 2020 to $15.5 billion in 2025 at a rate of 28.7 percent. The market is then expected to grow at a compound annual growth rate (CAGR) of 17.3 percent from 2025 and will reach $34.3 billion by 2030.[3]

This growth is being driven by both demand-side factors and actions taken by governments and key market players[4]

Patient demographics
Increased prevalence of chronic diseases

New product approvals/launches
Helping key players to expand their presence and sustain/enhance market position

Strategic acquisitions/investments
Including multinational players targeting emerging market players with strong product pipelines

Favorable regulatory developments
Including streamlining of approvals processes

Growing demand for CAR-T cell products
The fastest growing technology in cancer treatment

Complete understanding of the human genome, advances in genetic science and data analytics have allowed for the creation of targeted, personalized, and fully curative treatments for patients. Much of what's in the clinical pipeline and prescribed to treat patients today involves replacing, manipulating, or engineering cells and/or genetic material to fight disease.

Part 1: Market, cell and gene therapy landscape

Cell therapies require harvesting and inserting manipulated/modified human cells into the patient to treat the condition.

Cell therapies are treatments that introduce genetically modified or unmodified cells into the patient to modify or correct the defects that cause the disease.

There are two types:

01 Autologous therapies: by which a patient receives modified cells from their own cellular population.

02 Allogeneic therapies: where several patients are treated with donor(s) modified cells.

The ability of individuals and health systems to finance these treatments is also key. The US., Europe, and Japan are major centers of excellence, while Singapore, Israel, and South Korea are active in the sector and making positive advancements. Ethical and religious reservations and the related regulatory framework influence will also play significant roles in the acceptance of advanced therapies, especially those based on stem cells or embryonic cells.

Part 2: Providers' unique challenges and pain points

CGTs have development and manufacturing paradigms completely dependent on patients and logistics.

These therapies are at the forefront of innovation and bring much hope for the future of medicine; they have the potential to transform how healthcare treats formerly incurable diseases. The stakes are high, and potential outcomes are great but will come at a price. CGTs come with a whole new set of considerations for therapy owners as they are brought to market. Because the patient is at the center of the supply chain, the nature of these treatments and their use of living cells or genetic material create unique intricacies and dependencies that disrupt the traditional commercialization process.

A report from Scrip Pharma Intelligence summarizes the takeaways from a 2022 roundtable with a panel of experts representing early stage biotech, pharmaceutical, supply chain management and logistics companies:

- Orchestrating cell and gene therapies requires bespoke solutions in terms of storage, transportation, timelines, temperature control, and servicer flexibility.
- In these incredibly complex supply chains, forming and orchestrating partnership is a necessity.
- For logistics vendors to form partnerships with cell and gene therapy manufacturers, it is important to understand each company's unique requirements.
- Scalability of logistics solutions is also an important consideration.

Despite the positive conditions in the CGT sector, there are a number of challenges with the potential to constrain growth. Players in the sector are more likely to engage logistics suppliers with the ability to address these challenges.

Key CGT delivery challenges:

Scrutiny of biological and human cell materials
Stringent requirements for shipments in some countries, country-specific requirements in many others

Chain of identity (COI) and chain of custody (COC) management
Complexity of different requirements across countries

Label requirements
Requirement to label finished therapies in local language with full information

High operational costs
Expected to constrain the potential for growth in the market

- A typical demand with patient pool hard to predict
- Complex administration and management
- Unappealing cost structure (longer timescale to recover costs versus traditional approach)
- Requirement for precise material sourcing, tracking and delivery

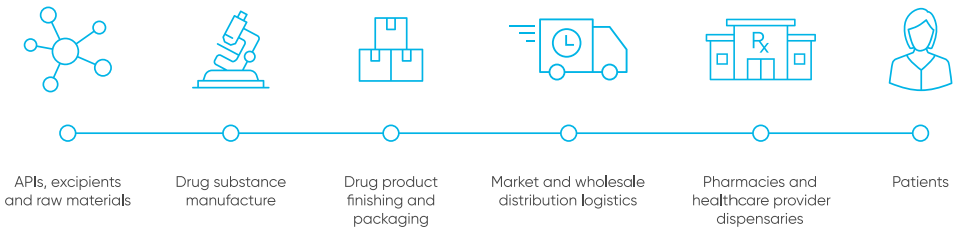
Part 2: Providers' unique challenges and pain points

CGTs introduce whole new manufacturing and distribution paradigms to support patient populations of one.

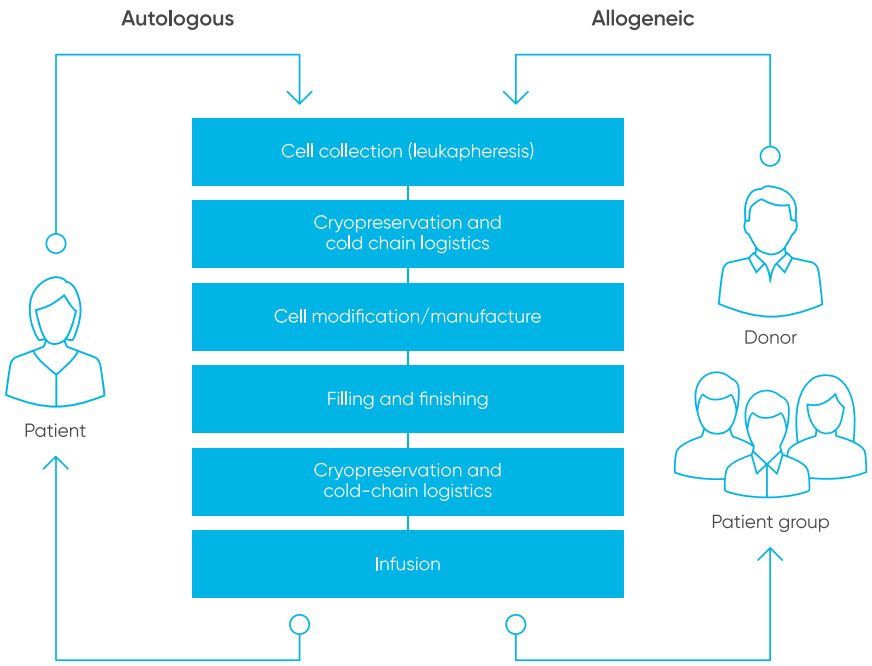
Prevailing supply chains for small-molecule and large-molecule drugs traditionally extend linearly from manufacturing; distributed to markets and patients and dispensed through healthcare providers (HCPs). While the number of links in a traditional pharma supply chain supporting the development, commercialization, and dispensing of today's pharmaceuticals do make it complex, the dependencies between the patient and producer in current pharma development and manufacturing remain marginal.

ATMP versus traditional biologics supply chains

Supply chains for mass-produced biologics traditionally extend linearly from manufacturing to packaging, from distribution to dispensing, and then to patients.



ATMP treatment supply chains are circular, require cryopreservation, and serve patient groups as small as one.



Part 2: Providers' unique challenges and pain points

Storage and/or shipping conditions of current cell therapy products

A patient's autologous treatment involves entirely different dependencies and an entirely different sequence of events. As a result, a manufacturer's decisions in clinical trials have more immediate implications for the commercial supply chain to an extent not present in traditional mass-produced pharmaceuticals. The interconnected and personalized aspects associated with ATMP therapies require the highest levels of operational integration between logistics, the processes, patients, and prescribing physicians.

To meet patient and provider expectations, the therapy owner must ensure that collection, manufacturing, and administration are coordinated in a compliant and validatable manner. Furthermore, therapy-appropriate handling techniques, environmental controls, worker protection, and unbroken data traceability must also be guaranteed for quality and compliance reasons at all times.

The focus on the human material supply chain is vital. Still, the scheduling, access, and logistics dependencies are equally essential and require CGT developers to cope with several interdependent layers of processing and treatment complexity.

CGT development and commercialization success involves:

- Patient recruitment and retention
- Manufacturing facility location, capacity availability
- Patient-centered processes
- Regulatory compliance
- Sterility and containment
- Visibility and data management
- Contingency planning
- Optimal temperature control
- Cold-chain integrity, cryopreservation capabilities
- Good manufacturing practice (GMP) process/product quality control
- Digital supply chain transparency

Part 2: Providers' unique challenges and pain points

Cryogenic preservation's essential role in CGT logistics.

The cold chain for a cell-based product must be capable of maintaining the living organism in a viable state during storage and distribution and dispensing to patients. Compared to small-molecule pharmaceuticals and biologics, human cells are highly labile, remaining viable only within narrow ranges of time and temperature. Cells also require oxygen and nutrients when metabolically active. Therefore, post-manufacture, many allogeneic and autologous cell therapy products require either just-in-time fresh transfer delivery to patients or cryogenic storage temperatures to preserve the cells in a metabolically inactive state during distribution.

While cell and gene therapy products share the same goal for their cold chains as "standard" biological products, to ensure the product is maintained within appropriate temperature specifications, there are specific features of cell therapy products that make their cold chains uniquely challenging.

Gene therapy products based on nucleic acids are typically packaged in viral vectors, inorganic complexes, or naked deoxyribonucleic acid (DNA)/ribonucleic acid (RNA). Because these ATMPs are inherently more stable than cell-based therapeutics, cold chains are required to control room temperature (15–25°C) or maintain stable refrigeration (2–8°C) or cold-chain at -80°C, while products are in custody. Although sustaining cold-chain integrity for these products may present fewer challenges for developers relative to other CGT therapeutics, they still require a considerably well-controlled and validatable cold-chain custody.

Cryopreservation is a key enabling technology in regenerative medicine because it provides stable and secure extended cell storage for primary tissue isolates, constructs and prepared cell preparations. Significant difficulties arise, noted a study on cryopreservation, when the required point of use is separated by distance and, often symbiotically, by time from the facilities where the cells were isolated and then prepared.[4]

For example, an apheresis is picked up at a treatment center, shipped at 2–8°C to a freezing center and then at cryogenic conditions to the manufacturing site.

A long-term, practical solution to these challenges lies in successful cryopreservation that offers secure, stable storage at temperatures below −130°C where metabolic change will not occur.

Part 2: Providers' unique challenges and pain points

To freeze or not to freeze

Whether the cells are transported fresh or frozen will depend on their unique needs.

Some but not all ATMP treatment supply chains are circular and serve patient groups as small as one. But all require speed, environmental control and robust chain of custody to ensure they are in the best possible condition on arrival.

Autologous cell therapy

Logistics platforms for autologous and allogeneic supply chains

Autologous cell therapies need;

- Integration with cellular orchestration platforms to receive shipment orders
- Cryo- and temperature-controlled shippers with GPS loggers
- Specialized team

Allogeneic cell therapies must have;

All of the above, plus:

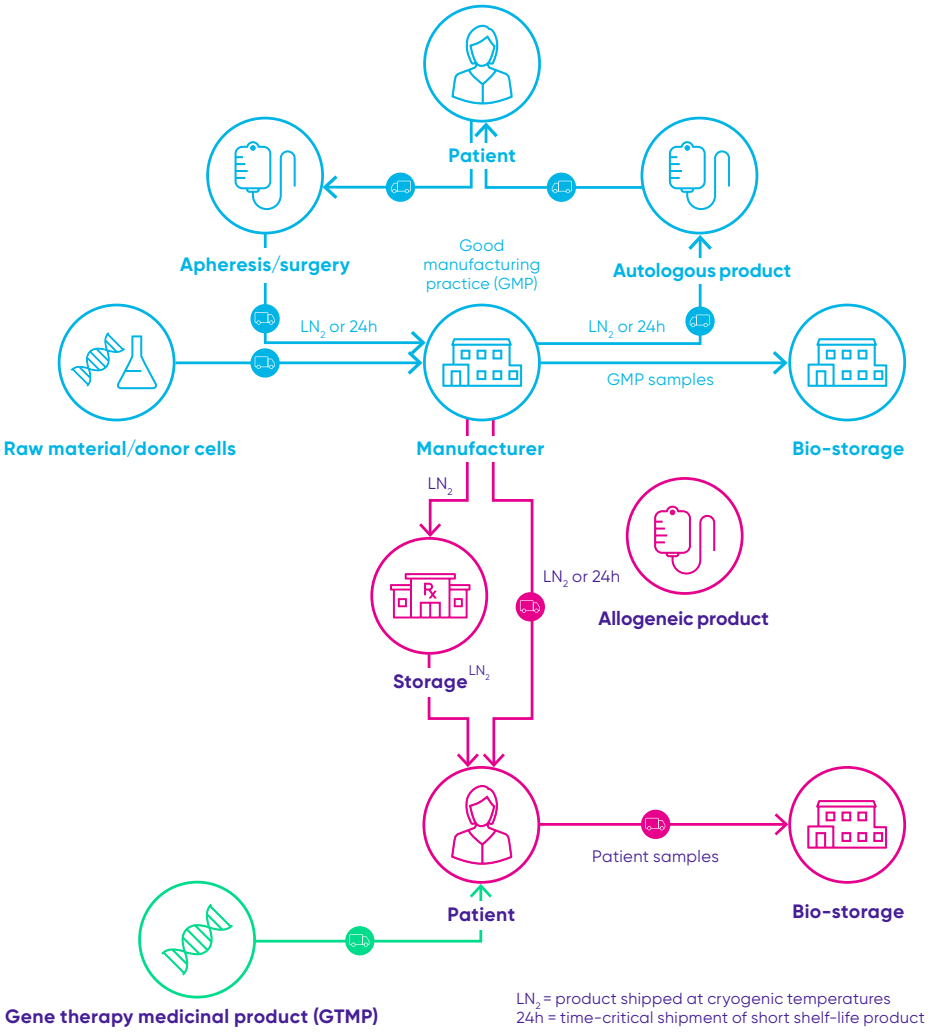
- Cryogenic storage in key locations
- Capability to handle large volumes at central depots in US and APAC

Gene therapies require;

- -70°C to -80°C/dry ice storage and shipments
- GMO/UN3245 expertise

Allogeneic cell therapy

Gene therapy



LN_2 = product shipped at cryogenic temperatures
24h = time-critical shipment of short shelf-life product

Part 2: Providers' unique challenges and pain points

The benefits of fresh transfer

Fresh transfer has particular advantages for autologous therapies, where quality and quantity of cells from patients are critical.

- No quality, viability or time loss due to freezing and thawing
- No requirement for added freeze protection agents
- Maximum number of cells can be used for manufacturing

However, cells - both patient samples and finished CGTs have a fresh shelf life of 12 to 96 hours. This makes fresh transfer unsuitable for reaching treatment centers a great distance away or across international borders from the manufacturing site.

The benefits of cryopreservation

Cryopreservation is accomplished by freezing cells – of finished therapies or patient samples – below -140°C, e.g., in liquid nitrogen (LN_2 150°C to 196°C). Cryopreservation reduces logistical risk and extends critical timelines required for commercial delivery of both allogeneic and autologous therapies.

- Extended shelf life for cells, allowing long-term storage of finished therapy and sample
- Time for quality control and import/export processes, allowing global distribution

In cases where samples or therapies need to travel great distances or cross international borders, cryogenic logistics is the ideal solution to ensure cell viability and product stability.

Part 3: Logistics strategies and third-party logistics (3PL) suppliers

Managing the cost and complexity of cold-chain CGT logistics

Advanced therapies require huge investment to launch effectively, and the same can be said of the logistics to support them. Demand for CGTs will soon be global, and as a result, the scaled-out supply chain will cross international boundaries, time zones, and climatic regions. Manufacturing, logistics, and storage capabilities all have to scale up and scale out to serve an increasing number of patients while additional stakeholders join the supply chain.

Drug strategists understand that to successfully commercialize CGT modalities cost-effectively, the process and operations have to scale both up and out to create capacity. Planning for future success must be emphasized from the very beginning with any initial processes/providers able to scale and grow into fully fledged commercial, prescribed operations.

Regardless of the reason, a breakdown in the CGT supply chain, whether the manufacturing cycle, logistics coordination, or shipping process, can have an extremely high impact on quality and patient access to treatments. CGT companies are inextricably involved in both upstream and downstream activities related to making and delivering these therapeutics to patients. Fortunately, CGT sponsors and developers don't have to build out logistics capabilities by themselves, and many don't, relying on logistics suppliers to ensure patient access to treatments. Cryogenic capabilities are a key enabling technology and a must-have. Much of the necessary operations and enabling technologies behind cryogenic logistics are already established by prominent global service providers with the infrastructure to support commercial CGT drug strategies.

Part 3: Logistics strategies and third-party logistics (3PL) suppliers

According to a Deloitte study, growth in the CGT market will drive growth in demand for outsourced cryogenic transport and storage services.

Deloitte: Key considerations for selecting a logistics partner

1. External partners' capacity and capabilities in **material sourcing, tracking, and delivery** will be vital, reflecting more flexible process controls versus other types of products
2. **Procedures for sample collection and shipment** can be standardized and complex. Logistics partners could help to improve and standardize these, and there may be greater willingness to work with companies that can make the training and on-boarding experience as easy as possible
3. **Physical delivery 'and' delivery-related customer service** are potential areas of innovation for logistics vendors

"The number of service providers and the service footprint would have to increase drastically once CGTs are produced at scale"

"Delivering scientific innovation requires operating model innovation"[5]

Deloitte Insights

Part 4: Study and findings

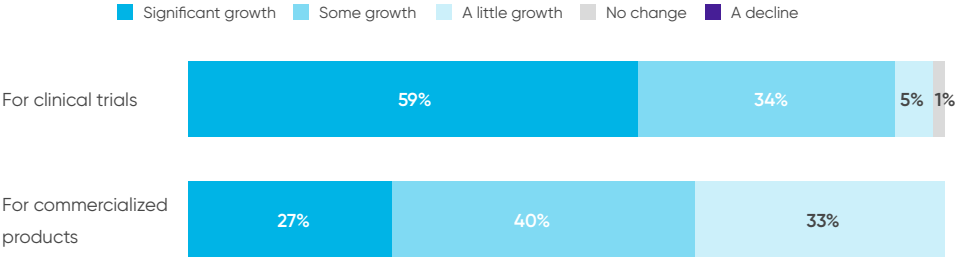
Almost all survey respondents expect the need for cryogenic transportation and storage services to grow in the short to medium term, with a higher rate of growth predicted for clinical trials.

Study reveals CGT sponsors' stress points on the path to patients

In 2021, World Courier and ICS commissioned Coleman Parkes Research to survey executives and managers serving in supply chain operational roles in companies with CGTs in clinical trials or available to patients commercially. The study's 100 qualified respondents all had a strong level of involvement in decision-making around sourcing transportation and storage related to the cell and gene therapies developed by their companies.

In general, how do you see the need for cryogenic transportation and storage services changing across the industry in the next three years?

Expected change in the need for cryogenic transportation and storage services in the next three years



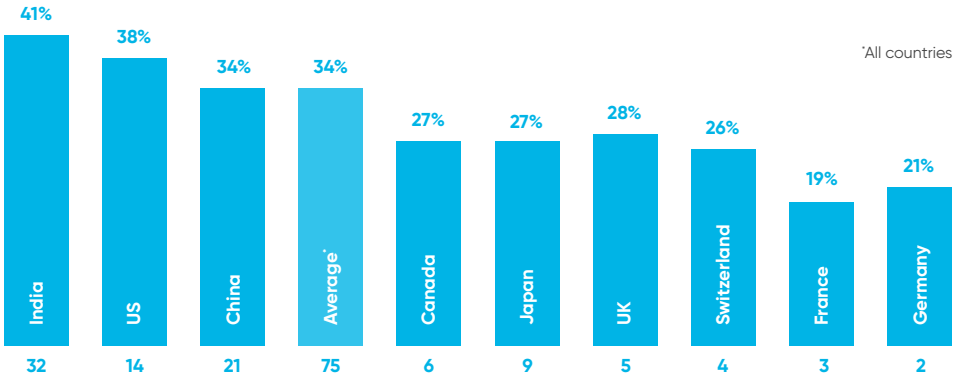
Base: All respondents – clinical trials (75) commercialized products (68)

Part 4: Study and findings

According to our Coleman Parkes research, India and the US are predicted to see the greatest rate of growth in cryogenic transportation and storage needs relative to clinical trials. For commercialized products, predicted growth rates are slightly lower, and there is less differentiation between countries.

What rate of growth do you expect to see in cryogenic transportation and storage needs related to clinical trials in [country] over the next three years?

Average expected growth rate across respondents

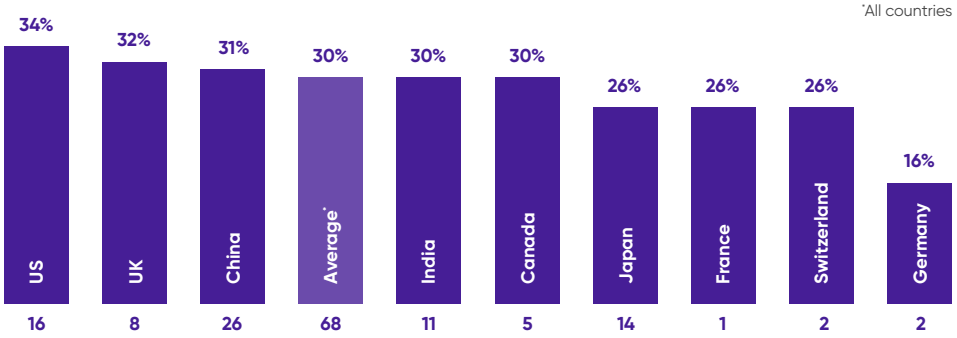


Base: Respondents involved in clinical trials identifying relevant country as single greatest area of opportunity - overall (96), APAC (62), North America (20), Europe (14). See chart for individual country bases.

In general, predicted growth in demand for cryogenic transportation and storage needs related to clinical trials is attributed to the "knock-on" effect of the increasing investment and the expected growth in the number of trials.

What rate of growth do you expect to see in cryogenic transportation and storage needs related to commercialized products in [country] over the next three years?

Average expected growth rate across respondents



Base: Respondents involved in commercialized products identifying relevant country as single greatest area of opportunity – overall (85), APAC (51), North America (21), Europe (13). See chart for individual country bases.

Part 4: Study and findings

Key drivers of growth for commercialized products, particularly in Asia Pacific, are more specifically related to capacity and capability in transport and storage.

According to our research, in relation to commercialized products, particularly in Asia Pacific, the key drivers of growth are more specifically related to capacity and capability in transportation and storage.

Key drivers of growth in cryogenic transportation and storage needs related to clinical trials

Asia Pacific

- Support from government and other agencies
- Increase in cost-effectiveness of clinical trials
- Expansion of activity by multinational firms
- Improved safety standards
- New network/ collaborations
- Increase in chronic diseases
- Increased investment activity

North America

- Government/hospital/ public support
- Increased funding/ investment
- Increased popularity of personalized therapies
- Increased collaborations

Europe

- Appetite for a more customer-oriented approach
- Availability of funding
- Demand for CGT solutions to combat diseases
- Growing demand for specialized transportation and storage

Key drivers of growth in cryogenic transportation and storage needs related to commercialized products

Asia Pacific

- Advancements in technology for transportation and storage
- Stricter monitoring/ compliance/safety protocols
- Expansion in strategic investment in cryogenic transportation and storage
- Role of transportation and storage in last-mile delivery
- Need to support global access/access for a wide range of users

North America

- Promotion of the industry
- Cross-border approval of products
- Regulatory relationship and enhanced flexibility
- Increased profit margins

Europe

- Need for relevant containers, operational processes and safety measures
- Increased investment interest
- Opportunities for partnership working

Part 4: Study and findings

Cryogenic logistics partner selection appears to be a particular concern in relation to commercializing CGT products.

Regulation/compliance issues present challenges in relation to both clinical trials and commercial development. Where respondents are engaged in both activities, there are certain challenges that are more likely associated with clinical trials (e.g., storage costs, packaging availability), while other concerns are more likely to be associated with commercialized products (e.g., security compliance, having an integrated partner).

Key findings include:

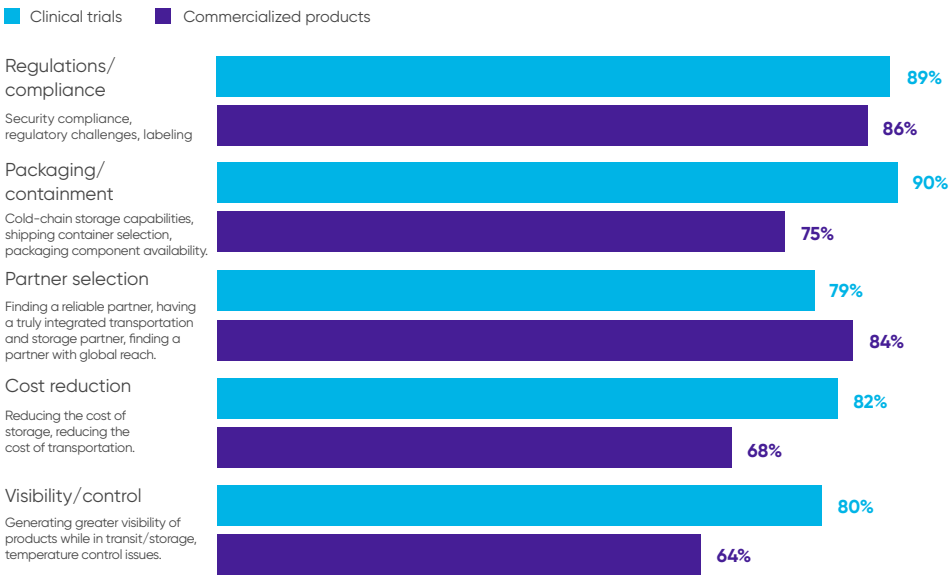
- Those involved in clinical trials are most likely to identify reducing the cost of storage as a challenge if they also face challenges around finding a reliable partner or having a truly integrated partner, suggesting an interest in relevant partners that can offer cost-effective storage.
- Those involved in commercialized products are most likely to identify security compliance as a challenge if they also face challenges around visibility, reducing transport costs or partner selection. This suggests an interest in relevant partners able to offer a cost-effective transport solution while guaranteeing security and visibility.

For those involved in clinical trials, key challenges include reducing costs, component availability, global reach, and visibility. For commercialized products, challenges relate to security, finding a reliable and integrated partner, temperature control, and regulation.

Regulation/compliance issues present challenges in relation to both clinical trials and commercialized product activities. Partner selection appears to be a particular concern in relation to commercialized products.

In terms of cryogenic transportation and storage, what are the key challenges that you currently face?

Key challenges of cryogenic transportation and storage – challenge themes



Base: All respondents – clinical trials (96) commercialized products (85) - the number of respondents serving in supply chain operational roles in companies with CGTs in clinical trials or available to patients commercially.

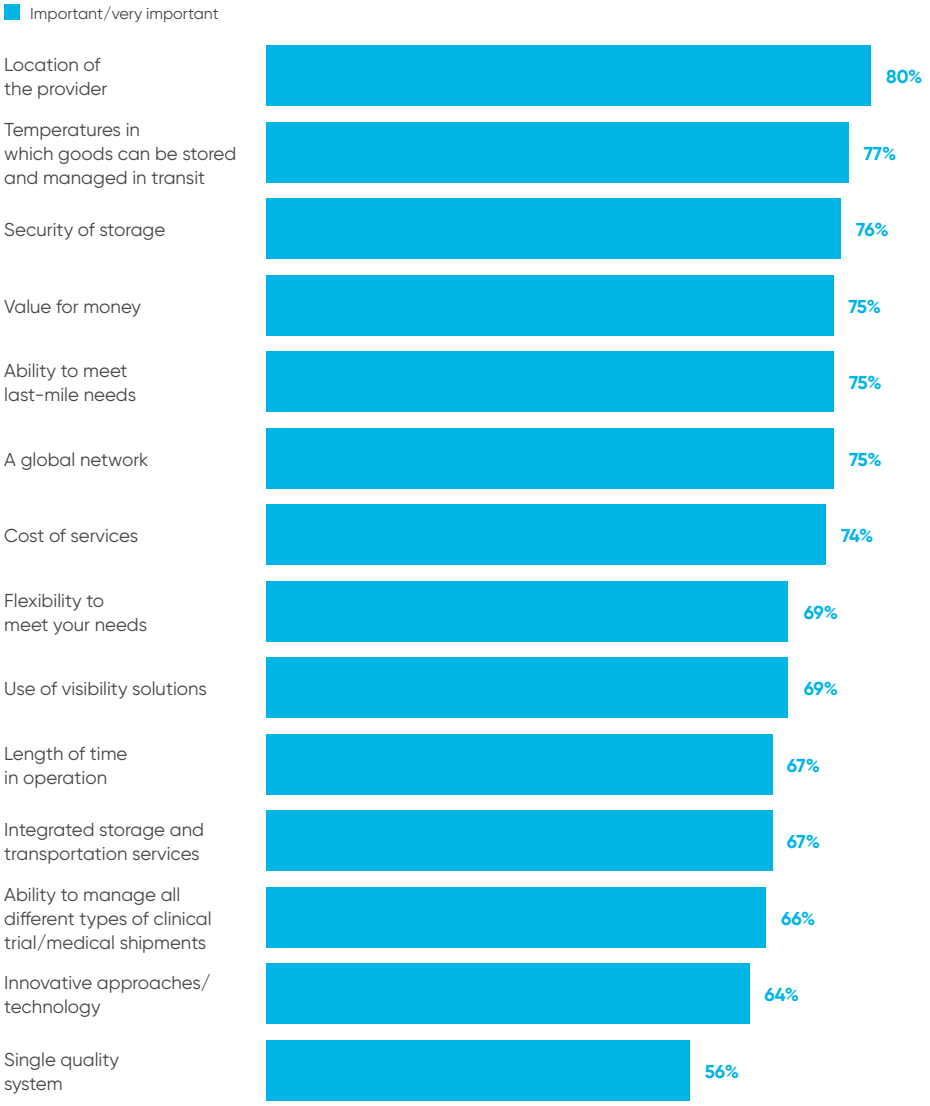
Part 4: Study and findings

Location, temperature and security are of key importance to manufacturers.

Survey participants were asked to rank 14 key vendor selection criteria on a scale, from "very important" to "not at all important." Among the most important selection criteria for users were — location (80 percent), temperature capabilities (77 percent), and storage security (76 percent).

In the chart below, the selection criteria ranking the highest in importance overall received a higher percentage of the top two positive choices "very important" and "important."

Important factors when selecting a provider of cryogenic transportation and storage services



Base: All respondents (100).

About World Courier

World Courier delivers the global network, integrated digital solutions, and operational excellence required to support successful CGTs.

World Courier and ICS, both Cencora companies, integrate closely to deliver an end-to-end cryostorage and transportation solution to CGT developers.
In recent years, we have enhanced our global CGT network and cryogenics capabilities to support development and growth in the sector. Cryogenic storage technologies from ICS, combined with World Courier's packaging solutions and a global network of depots, provide a fully integrated solution designed to support CGT innovators — regardless of size or stage of development.

For sponsors and innovators navigating the complexities of commercial ATMP delivery, World Courier and ICS align supply chain strategy to the therapy's business goals to deliver a tailored healthcare logistics solution that increases efficiency and enhances patient care. To meet the needs of ATMP developers worldwide, World Courier and ICS offer:

- Ultra-frozen and cryogenic storage capabilities
- A comprehensive global logistics infrastructure
- Proven methodologies and validated technologies
- Order-to-cash financial management
- Tailored product distribution models

World Courier has dedicated teams in over 50 countries, and through our network of more than 120 offices, operations are integrated and managed through a single quality system. The system enables highly controlled and monitored shipments of live cells in real time across international and domestic boundaries. This transparency ensures cell viability and transport security, even when X-ray scans are prohibitive. We can manage everything from tissue donors (e.g., tumor, apheresis, and bone marrow) to handling these critical blood samples into and from the processing lab and on to the delivery of therapies to patients.

About World Courier

World Courier's network capability enables access to a full range of cryogenic shippers with shorter lead times and reduced positioning costs.

World Courier's network is built on existing infrastructure, leveraging the current office and depot network, capabilities, and quality systems. This means that advanced therapy companies can immediately access an established and qualified operation with proven cryogenic shipping solutions close to processing facilities, patients, and HCPs.

One of the challenges facing CGT developers is the delivery of critical shipments, including tissue donations and final patient-ready therapies. The short shelf life of cell or tissue shipments and the complexity of the resulting logistics are encouraging therapy developers to qualify cryopreserved transport to be compliant and ensure quality control. To enable cryogenic transportation, dry shippers must charge container cooling systems with liquid nitrogen (LN2) within a qualified, controlled environment.

This is a specialized process in which dry shippers are:

- Inspected and cleaned prior to use
- Fully charged, with supporting documentation
- Positioned so they can be loaded with the critical shipment

Only after those stringent steps have been followed can the critical shipment take place. These preparations take time, especially when the charging station may be located in another country from the clinic or manufacturing site.

World Courier's fleet of cryogenic dry shippers provides the international capability to charge and ship customers' units as they travel the global network from point to point. Charging centers have been identified throughout the global network based on their capacity and geographical requirements.

Strategically, World Courier is expanding the role and operations of its network of charging stations and growing them into centers of global cryogenic service excellence. World Courier has been managing cryogenic shipments for more than 20 years, and its existing global quality systems in place, supported by established standard operating procedures (SOPs), ensure operational excellence and proactive quality assurance.

About World Courier

Our full-service logistics and storage solutions help you seamlessly deliver innovation.

We manage the logistics for your most precious innovations. And we don't take that responsibility lightly. Across our global network of dedicated team members, we monitor the safety and integrity of your product proactively, ensuring it reaches patients without delay. We plan for contingencies, so you don't have to, leveraging our global capabilities and local, on-the-ground knowledge to navigate logistics complexities.

We go the extra mile to ensure increased supply chain efficiency, maximum return on investment, and enhanced patient care.

World Courier designs tailored logistics solutions to fit your supply chain requirements. Learn more about our full range of solutions or contact an expert now.

References

1. https://www.prnewswire.com/news-releases/global-21-2-bn-advanced-therapy-medicinal-products-market-to-2028-breakthrough-approvals-of-tecartus-and-abecma-post-approval-of-zolgensma-kymriah-and-yescarta-have-bolstered-rapid-advancements-301383901.html
2. https://asgct.org/global/documents/asgct-citeline-q3-2022-report.aspx
3. https://www.businesswire.com/news/home/20210712005409/en/Global-Cell-and-Gene-Therapy-Market-Report-2021-Opportunities-Strategies-COVID-19-Impacts-Growth-and-Changes-to-2030---ResearchAndMarkets.com
4. https://www.genengnews.com/insights/bright-outlook-for-the-global-cell-and-gene-therapy-market/
5. https://www2.deloitte.com/uk/en/insights/industry/life-sciences/operating-models-for-gene-cell-therapy-manufacturing-process.html

cencora
World Courier