CELL & GENE THERAPY INSIGHTS

INNOVATOR INSIGHT

Next-generation risk mitigation in the temperature-controlled supply chain for advanced therapies with ISO 21973 compliance

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The rapid growth of the cell and gene therapy market, projected to reach nearly US$37 billion by 2028, has highlighted the critical need for scalable, reliable logistics solutions to address the complex challenges of transporting temperature-sensitive biologics. This article evaluates the implementation of risk mitigation strategies within the cell and gene therapy supply chain, focusing on compliance with ISO 21973, a standard that provides comprehensive guidelines for the safe transportation of therapeutic cells. Cryoport Systems' innovations, including the Veri-Clean® validated cleaning protocol and the Chain of Compliance® traceability framework, are examined for their role in safeguarding therapy integrity. Advanced tools like the Smartpak II® monitoring system and the Cryoportal® logistics management system are also discussed for their contributions to near real-time tracking, risk mitigation, and regulatory adherence. Together, these strategies demonstrate how next-generation technologies ensure the quality, safety, and efficacy of cell and gene therapies throughout their supply chain journey, ultimately supporting the commercialization and scaling of advanced therapies.

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The cell and gene therapy (CGT) market is experiencing unprecedented growth with projections indicating a compound annual growth rate (CAGR) of 46%, reaching nearly US$37 billion by 2028 [1]. This rapid expansion underscores the critical need for scalable, reliable logistics solutions to meet the increasing demand for these therapies. As

the market grows, so does the complexity of the supply chain with products requiring specialized handling and transportation to maintain their efficacy [2]. ISO 21973: general requirements for transportation of cells for therapeutic use was developed to address these challenges and provides a framework for developing a risk-mitigating supply chain for the life sciences.

BACKGROUND

In the evolving landscape of advanced therapies, maintaining the integrity of temperature-sensitive biologics throughout the supply chain is paramount. Advanced therapies, such as CGTs, as seen in Figure 1, represent the forefront of medical innovation. These offer potential cures for previously untreatable conditions [3], as further illustrated in Figure 2 [4].

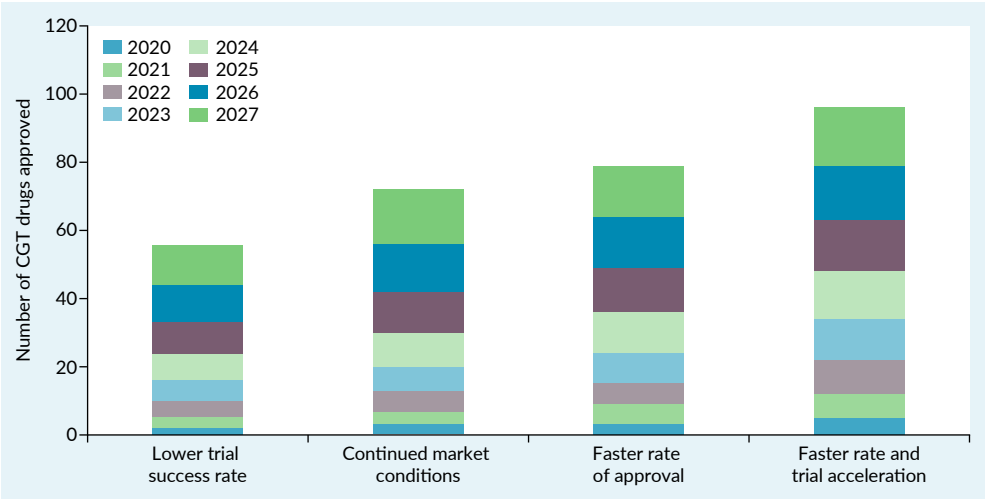
This article aims to evaluate the industry's ongoing efforts to meet and exceed regulatory requirements, particularly concerning the transportation of advanced therapies. The temperature-controlled supply chain must ensure that products remain within specified temperature ranges to preserve their viability and efficacy. Any deviation can result in the degradation of the therapeutic product, rendering it ineffective or unsafe for patient use [2]. This is where ISO 21973 plays an especially crucial role, providing a framework of minimum requirements to ensure the safe transport of these sensitive products.

This evaluation highlights best-in-class risk mitigation strategies that can be implemented to ensure the safe and effective delivery of sensitive materials, such as CGTs, within the temperature-controlled supply chain. In this context, the ISO 21973 standard, introduced in June 2020, is critical in providing a comprehensive framework for transporting cells for therapeutic use [3]. The introduction of ISO 21973 was driven by the need for standardized practices across the industry to mitigate risks associated with temperature fluctuations, contamination, and logistical disruptions during transport.

Coordinated by the Standards Coordinating Body (SCB), this standard represents the culmination of efforts from over 20 experts across government institutions, membership organizations, and

FIGURE 1

CGT drugs approved by scenario.



Comparison of the number of new therapies approved by the FDA by scenario with a breakdown by year of approval. There is a notable acceleration of therapeutic approval by year as well as an accelerating trend in terms of how quickly trials are turning into approvals. Data from Bain analysis.

industry bodies and establishes minimum requirements for IT infrastructure, Chain of Custody systems, centralized logistics management, transportation protocols, shipment tracking, and monitoring [3]. These guidelines are essential for mitigating risks and ensuring the quality and safety of advanced therapies during transit. By adhering to these guidelines, stakeholders can ensure product integrity and patient safety, which are vital in the rapidly growing and evolving field of advanced therapies.

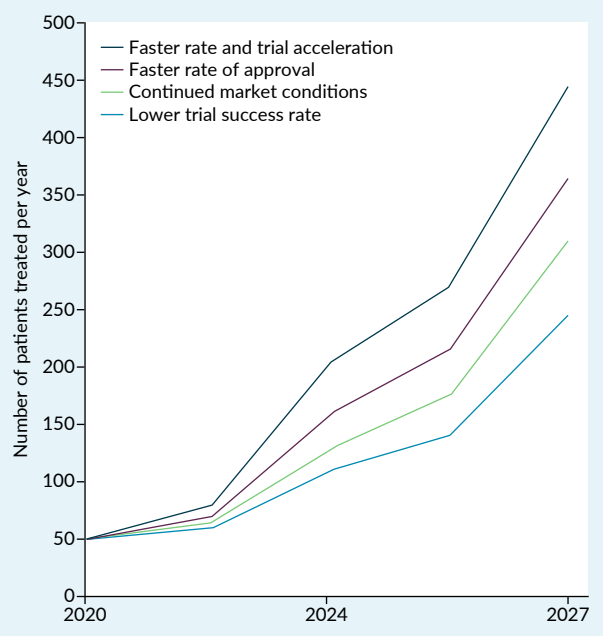
REGULATORY COMPLIANCE

ISO 21973 provides a comprehensive framework for the transportation and storage of cells for therapeutic use, including temperature-controlled and cryopreserved materials. This standard emphasizes the importance of robust IT infrastructure, comprehensive Chain of Custody systems, and centralized logistics management, as illustrated in Figure 3. The CGT industry requires end-to-end precision and traceability, everything from Chain of Custody to Chain of Condition and Chain of Identity. Adhering to these guidelines that incorporate complete traceability of the equipment, processes, and logistics used in managing the environmental control of the CGT while it is in transit ensures that operations meet the highest standards of quality and safety.

By centering operations around ISO 21973 guidelines, stakeholders can be confident in the safety and efficacy of transported therapies. This assurance is critical for product developers, healthcare providers, and patients alike. Moreover, compliance with these standards helps streamline operations, reduce risks, and enhance efficiency, ultimately supporting the successful commercialization of advanced therapies.

FIGURE 2

Patients treated per year via CGT clinical trials and/or commercially approved CGT therapies by scenario.



Growing access to advanced therapeutic treatments in coming years. Some therapies, such as those focused on treating hepatitis A and B, will drive higher patient populations. To avoid predicting the success of individual therapies, we have assumed a standard number of treatable patients per therapy based on average incident rates across indications currently in trials. This rate assumes that the total patient population treatable by each therapy does not wholly 'replenish each year' given the rare nature of many diseases that CGT targets. These therapies are highly sensitive to environmental conditions, particularly temperature, necessitating stringent control measures to mitigate risks associated with temperature excursions, contamination, and logistical disruptions [4]. Data from Bain analysis.

FIGURE 3

Multi-pronged, integrated approach to quality and compliance.

Integrated approach to regulatory compliance. An integrated approach to quality and regulatory compliance brings together critical standards and processes to ensure proactive risk mitigation from a collection of starting materials through to patient delivery.

VALIDATED CLEANING PROTOCOL

CGTs are often single-dose, one-time curative therapeutics, making the stakes of successful transportation incredibly high. Any risk of contamination could result in the loss of a potentially life-saving therapy. Given the unique nature of these treatments, which are often created for individual patients, there is no margin for error. Unfortunately, the majority of the industry does not employ validated or standardized cleaning processes for the systems used to transport these sensitive materials. Many providers make no claims or guarantees related to decontamination, leaving a critical gap in the safeguarding of advanced therapies. ISO 21973 emphasizes meticulous documentation and control of all stages of the transportation process, including equipment performance, cleaning, and equipment-use history.

Eliminating the risk of cross-contamination via a comprehensive decontamination process designed to be effective against bacteria, fungi, and viruses reduces external contaminants to virtually zero. This proactive approach further mitigates additional, avoidable risks to sensitive shipments of advanced therapies.

Veri-Clean® is Cryoport Systems' validated cleaning and disinfection process, establishing a new benchmark in the life sciences logistics industry. As the first and only validated process of its kind, Veri-Clean is designed to eliminate the risk of cross-contamination by decontaminating all shipping systems and stainless-steel accessories after every use. This innovative protocol is crucial in ensuring the safety and integrity of advanced therapies during transport, where it has achieved a >6 log (99.9999%) reduction of tested biological indicators as depicted in Table 1.

The Veri-Clean protocol is fully validated by an independent, accredited laboratory to ensure its efficacy and reliability. Through the Veri-Clean methodology, any contaminants on returned shippers are effectively eradicated to provide a robust safeguard against potential risks. Additionally, residual cleaning agents are virtually eliminated as part of this process, with <10 ppm detected once the Veri-Clean process has been completed. Additionally, it is supported by specially developed requalification protocols that certify each shipper in the active lines can support the necessary physical sustainability, LN2 capacity, and a minimum required hold time threshold. If any of the equipment does not meet the requalification specifications, it is immediately removed from the fleet after a final quality assurance (QA) evaluation. The protocols are universally applied across all Cryoport Systems facilities, ensuring consistent and high-quality cleanliness standards globally. Veri-Clean ensures that every shipping system and stainless-steel accessory undergoes rigorous decontamination and documentation procedures and maintains detailed records of each cleaning and disinfection cycle in full compliance with ISO 21973.

TABLE 1

Reduction in colony-forming units of contaminants following the cleaning and disinfection process via Veri-Clean.

Contaminant name	Reduction in CFUs following Veri-Clean
Escherichia coli	$>10^6$
Klebsiella pneumoniae	$>10^6$
Staphylococcus aureus	$>10^6$
Pseudomonas geruginosa	$>10^6$

Veri-Clean virtually eliminates the risk of cross-contamination by decontaminating all shipping systems and stainless-steel accessories. Through a comprehensive validation process that evaluates the initial bioburden when a shipping system is returned as well as manual cleaning validation and low-level disinfection validation, every shipping system achieves a >6 log (99.9999%) reduction of tested biological indicators at every use. CFU: colony-forming unit. Data from Cryoport Systems.

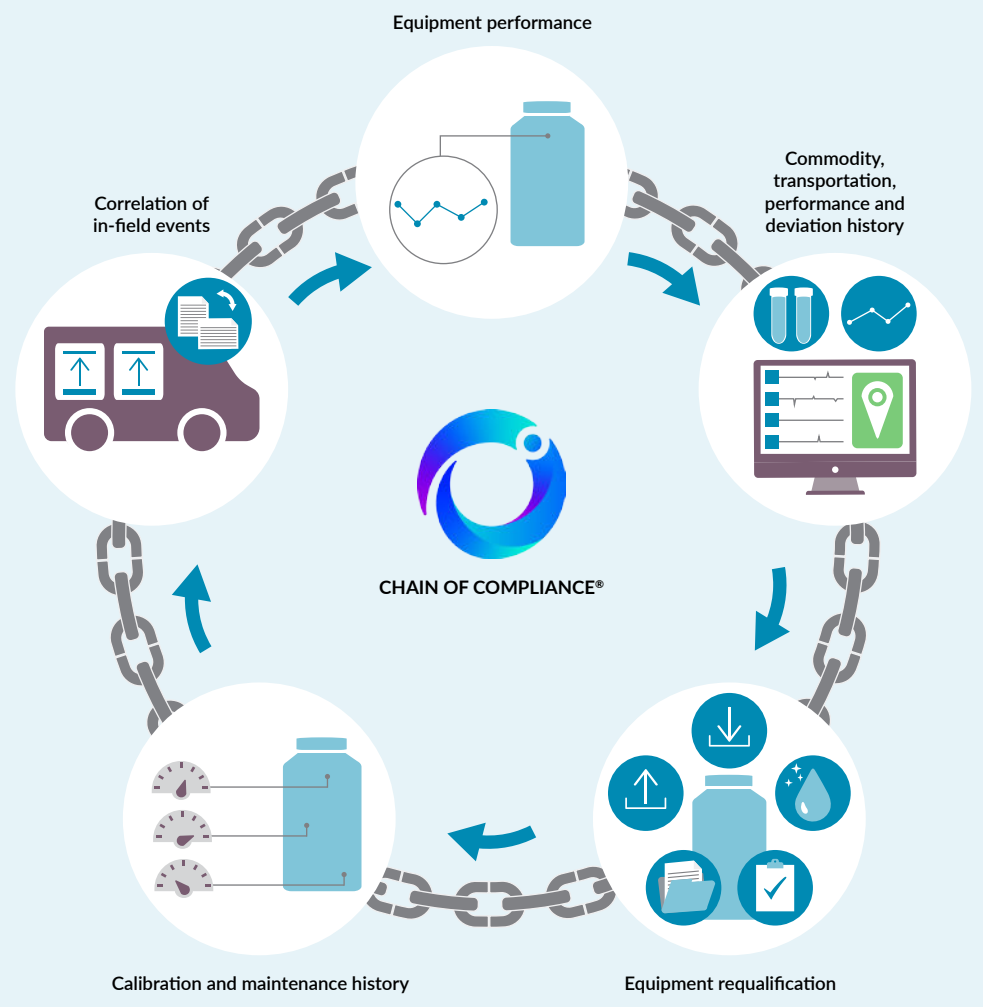
Integral to the Veri-Clean process is the manual confirmation that each shipping system is free from environmental flora to further enhance the decontamination efficacy. By meticulously validating the cleaning process, Cryoport Systems guarantees that all residues are thoroughly removed to achieve the highest level of cleanliness for each shipment. This level of cleanliness sets a new standard in the industry, providing peace of mind that advanced therapies are transported in the safest and cleanest environment possible.

CHAIN OF COMPLIANCE®

Complying with regulations from agencies, such as the US FDA, and adhering to the stringent requirements of the ISO 21973 standard involves complete tracking and traceability across three essential elements: Chain of Custody, Chain of Condition, and Chain of Identity. The Chain of Custody provides a detailed record of who has handled the therapy across every stage. This is achieved through the serialization of the shipper and its components as well as the documentation

FIGURE 4

Support of regulatory compliance with Cryoport Systems' Chain of Compliance.



The Chain of Compliance provides full traceability of the equipment and processes used in managing the environmental control of biomaterials. This assists in mitigating risk throughout the entire supply chain to ensure the safe delivery of invaluable materials.

of comprehensive data on the performance history of the shipper and courier. The Chain of Condition monitors the environmental conditions under which the therapy is stored and transported, utilizing advanced data analytics and near real-time monitoring to maintain optimal conditions. This element also includes the calibration data and history for the data logger used to track environmental conditions. Finally, the Chain of Identity safeguards the identity of each therapy, ensuring it reaches its intended destination without compromise.

To ensure the integrity of advanced therapies during transport, a robust system is required to track the complete history of each shipment, including its Chain of Custody, Chain of Condition, and Chain of Identity. This system must not only be safe and secure but also offer redundancy and reliable backup to prevent data loss or breaches. Given the critical nature of the materials being transported—many of which are potentially life-saving treatments—it is imperative that the system provides robust tracking and monitoring of critical data points like location, temperature, shipper orientation, humidity, and shock, among others, as well as comprehensive data logging. This level of traceability guarantees that any deviations in temperature, handling, or other environmental conditions can be identified and addressed immediately, ensuring the product's safety from start to finish.

Cryoport Systems' Chain of Compliance is an advanced, integrated framework designed to ensure the highest standards of quality, traceability, and accountability for temperature-controlled supply chains. The Chain of Compliance, as seen in Figure 4, integrates validated requalification procedures. This solution goes beyond basic logistics to provide end-to-end traceability and robust data-driven risk mitigation using advanced tools like the Cryoportal® logistics management system. This system maintains detailed records of every shipment, including commodity history, deviation history, transportation history, and maintenance/refurbishment history of the shipper. Additionally, to further safeguard against equipment failure, every shipper undergoes requalification after each use, ensuring it meets stringent performance standards before being deployed again. Given the irreplaceable nature of these therapies, where even a small error could lead to the loss of a life-saving treatment, this rigorous, data-driven approach is essential to maintaining product integrity throughout the supply chain. This extensive data collection and management capability allows for the anticipation and prevention of potential issues. By leveraging advanced data analytics and near real-time monitoring through the use of Smartpak II® (Smartpak), an advanced condition monitoring system integrated with the Cryoportal logistics management system, in-field events were correlated to equipment performance, thereby continuously improving the processes and mitigating risks. This seamless integration allows for immediate interventions if any anomalies are detected, ensuring that environmental conditions remain within the required thresholds throughout the entire journey.

The ISO 21973 standard was created to address the critical challenges associated with transporting sensitive, temperature-controlled therapies that are derived from human cells. These therapies, many of which are irreplaceable, one-time curative treatments, cannot afford any compromise in their quality during transit. The standard establishes clear guidelines for managing the Chain of Custody, Chain of Condition, and Chain of Identity, all of which are vital to ensuring that therapies remain safe, viable, and effective upon delivery. Cryoport Systems' Chain of Compliance supports regulatory compliance requests from agencies such as the US FDA and adheres to the stringent requirements of the ISO 21973 standard. Ultimately, ISO 21973 ensures that every possible measure is taken to safeguard the integrity of these therapies, from the moment they leave the manufacturing facility to their final delivery to patients in need.

SEGREGATED FLEET OF ADVANCED THERAPY SHIPPERS

Regulatory requirements are evolving to meet the highest standards of safety, integrity, and compliance for the transportation of engineered human CGTs and human-derived cellular and biological materials. A fully segregated fleet for human-derived advanced therapies adds an additional layer of risk mitigation by virtually eliminating the potential for contamination from non-human-based materials. Cryoport Systems developed a proprietary Advanced Therapy Shipper® (ATS) fleet that is segregated from the General Purpose (GP) fleet. Each ATS shipping system is exclusively dedicated to human CGTs. This specificity ensures that these critical materials are transported under the most stringent conditions.

The ATS fleet's design and operational protocols are purpose-built to align with the latest regulatory requirements, including ISO 21973. By adhering to these rigorous standards, Cryoport Systems guarantees that all shipments maintain the highest levels of quality and safety throughout the supply chain. The Certificate of Conformance adds an extra layer of assurance, certifying that each shipping system has only handled human CGT products. This certification is verified, signed, and kept on record for at least 10 years.

In response to growing market demand and evolving regulatory landscapes, the ATS fleet is engineered to ensure the safe and reliable transport of critical patient therapies. By anticipating and addressing future regulatory requirements within the temperature-controlled supply chain, Cryoport Systems ensures that the shipping systems and services remain at the forefront of innovation and compliance. The ATS fleet's rigorous validation protocols and exclusive use for human-derived materials provide certainty in the safety and efficacy of transported therapies, maintaining both good manufacturing practice (GMP) and good distribution practice (GDP) standards.

ADVANCED DATA MONITORING AND LOGISTICS MANAGEMENT

In response to evolving industry developments and the increasing market need for robust temperature-controlled logistics, it is increasingly critical to harness innovative informatics technology to ensure unparalleled safety and efficiency. The advanced monitoring solution offered by Cryoport Systems, comprised of the Smartpak condition monitoring system and the Cryoportal logistics management system, provides comprehensive near real-time tracking and data analytics. This combination facilitates near real-time monitoring and risk management, promoting the integrity and traceability of every shipment through the Chain of Compliance processes. This allows the customer service team, who monitor all shipments 24/7, to immediately respond to any early warning signs of potential issues. By continuously tracking shipment conditions, such as temperature or location, the team can intervene before problems escalate, ensuring that these sensitive therapies remain within safe parameters throughout their journey.

The Smartpak condition monitoring system plays a crucial role in maintaining near real-time oversight of critical shipment parameters, including location, temperature, pressure, anti-tamper status, orientation, humidity, and shock. Parameters like tilt can directly affect the effectiveness of the liquid nitrogen coolant used in cryogenic shipments. Even a slight tilt can affect liquid nitrogen evaporation rates, thereby drastically reducing hold times, potentially jeopardizing the safe transport of therapies, and potentially putting entire CAR T-cell immunotherapy clinical programs at risk [6]. This system not only safeguards the integrity of shipped materials but also delivers meticulous analytics to aid in planning, en-route mitigation, and reporting. When the system alerts the team to a potentially catastrophic issue, like a liquid nitrogen shipper placed on its side in transit, the customer support team can intervene to expedite the delivery, ensuring safe arrival

without temperature excursions that could compromise the integrity of the irreplaceable materials housed within [7]. By capturing and relaying comprehensive environmental data, the Smartpak enables interventions to secure the transport of invaluable biological materials.

The Cryoportal is an integral part of logistics management. It is an innovative, web-based platform that integrates ordering, tracking, paperwork, and communications into a single streamlined portal. Additionally, the Cryoportal platform supports enhanced security and compliance with regulatory standards, such as 21 CFR Part 11, featuring robust audit logging and the latest web security measures. It is also validated to demonstrate compliance with the International Society for Pharmaceutical Engineering, Good Automated Manufacturing Processes (ISPE GAMP). This system ensures thorough logging, capturing a comprehensive record of all activities, and securely storing this data for a minimum of 10 years. It maintains full knowledge and traceability of every piece of equipment, from its performance history to any maintenance or refurbishments. This detailed level of record keeping enables tracking of the entire lifecycle of each shipper, providing confidence that every shipment is managed with the highest standards of care, traceability, and security. Additionally, the Cryoportal ensures complete transparency through the provision of Chain of Condition, Chain of Custody, and Chain of Compliance data, facilitating comprehensive traceability and accountability. This advanced logistics management framework exemplifies Cryoport Systems' commitment to innovation, reliability, and the highest standards of service in the temperature-controlled supply chain industry.

CONCLUSION

As the demand for advanced therapies continues to surge, the temperature-controlled supply chain for CGT faces unprecedented challenges. Cryoport Systems has addressed these challenges through the implementation of next-generation risk mitigation strategies, adherence to ISO 21973 standards, and the development of innovative solutions such as the Veri-Clean validated cleaning process and Chain of Compliance traceability framework. The ATS and state-of-the-art data monitoring systems further enhance the safety and integrity of these sensitive therapies. These approaches are not merely reactive but anticipatory. By staying ahead of regulatory requirements and market needs, Cryoport Systems is committed to providing clients with novel solutions that ensure the safe and efficient transport of products. This proactive stance ensures readiness to support the scaling of advanced therapies from clinical trials to commercial distribution. By providing a comprehensive and integrated approach, Cryoport Systems ensures that the unique requirements of the CGT supply chain are met with the highest level of precision and reliability.

REFERENCES

1. Horlacher ML, Eitelwein O, Jochem L, Hohn-Honari A. Unleashing success: closing the commercial viability gap in cell and gene therapy. *Oliver Wyman* May 2024. https://www.oliverwyman.com/content/dam/oliver-wyman/v2/publications/2024/may/unleashing-success-closing-the-commercial-viability-gap-in-cell-and-gene-therapy.pdf.

2. Cell and gene therapies: how to manage supply chains. *PwC Belgium* Nov 21, 2023. https://www.pwc.be/en/news-publications/2023/how-to-manage-supply-chain.html.

3. Standards Coordinating Body. Cell transportation standard published. https://www.standardscoordinatingbody.org/release-cell-transportation-standard.

4. Meacle F, Salkin J, Brice M, Harris I. Key considerations of cell and gene therapy cold chain logistics. *Cell & Gene Therapy Insights* 2016; 2(2), 223–236.

5. International Organization for Standardization. ISO 21973:2020 Biotechnology—general requirements for transportation of cells for therapeutic use. Edition 1, 2020. https://www.iso.org/standard/72326.html.

6. Cryoport. *Cryoport's Integrated Packaging, Monitoring And Software Technologies Create A Viable Supply Chain For A Top 10 Global Pharma Immunotherapy.* Nov 2023. https://www.cryoport.com/wp-content/uploads/2023/11/Cryoport_Immunotherapy_Case_Study.pdf.

7. Cryoport. *Smartpak II Alert And Prompt Intervention Saves The Day.* Nov 2023. https://www.cryoport.com/wp-content/uploads/2023/11/Cryoport_IVF_Case_Study.pdf.

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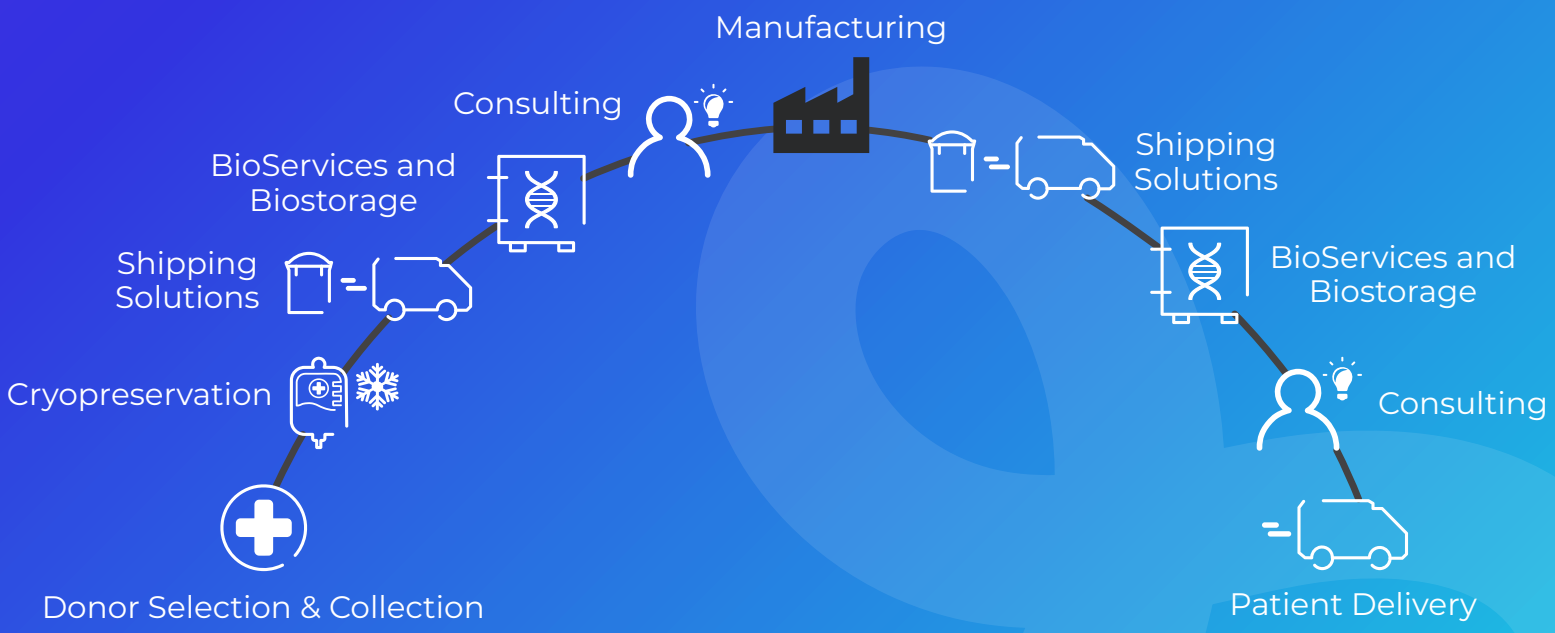

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