whitepaper

IntegriCell™

Standardizing Cryopreservation for a Sustainable Cell Therapy Supply Chain

Cryoport Systems

Americans · EMEA · APAC | info@cryoport.com | +1 949.232.1900 | cryoport.com

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IntegriCell™: Standardizing Cryopreservation for a Sustainable Cell Therapy Supply Chain

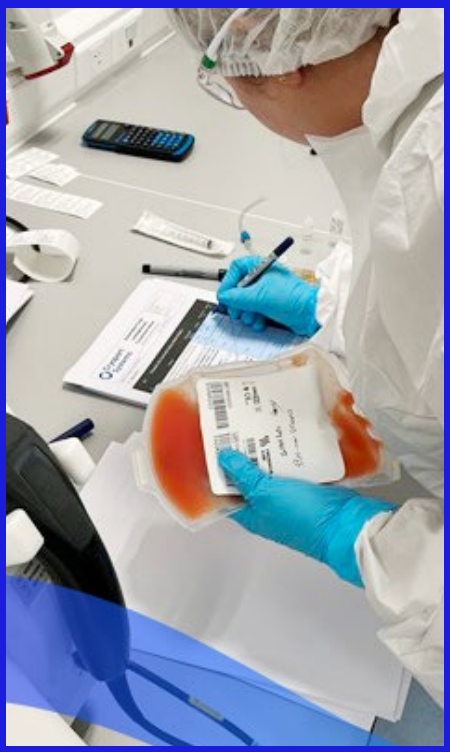
Introduction

Cryoport Systems is a global market leader in temperature-controlled supply chain solutions for critical materials in the life sciences industry.

With the introduction of IntegriCell™, Cryoport Systems is advancing the cell therapy landscape by incorporating cryopreservation services into our industry-leading supply chain platform. This whitepaper outlines an innovative approach to the delivery of high-quality, consistent cryopreserved leukapheresis, which is commonly used as starting materials for many cell-based therapies.

By leveraging the principles of distributed manufacturing, Cryoport Systems ensures that cryopreservation processes are robust and reproducible across multiple facilities, optimizing scheduling and capacity planning while delivering certainty and scalability.

> Cryoport Systems addresses the challenges associated with utilizing fresh leukapheresis by standardizing the cryopreservation process across multiple centers in the US and EU through IntegriCell™.”



The Need for Standardized Cryopreservation

Chimeric antigen receptor (CAR)-T cell therapies are being increasingly adopted in earlier lines of treatment of hematologic malignancies and being evaluated in solid tumor cancers and autoimmune diseases[1,2,3]. As these therapies expand to treat a larger patient population, the consistent production of high-quality CAR-T cells becomes critical. The quality of leukapheresis is a pivotal factor and can impact the final drug product.

Fresh leukapheresis presents several challenges[4]:

- The supply chain is complex and risky, leading to potential quality degradation.
- Increases the risk of underutilized manufacturing slots due to potential logistics delays and timing mismatches.
- Logistical challenges are prominent, particularly those related to the distance between patient collection centers and centralized manufacturing facilities.

Specifically, the rapid decline of the starting materials’ stability and quality once collected is of major concern. The decrease in viability means the cells can change or die, which ultimately leads to a negative impact on the quality of the end product. Extending the materials’ effective shelf life is no longer possible at this point, even when transferred to short-term storage solutions at low temperatures (≈ 4°C). The metabolic decline and disruption can contribute to cellular apoptosis, leading to a loss of cell viability and cell count while also impacting critical quality attributes. In turn, this can hinder downstream processing, and even more concerning, the ultimate end goal of increased patient health.

Alternatively, cryopreserved leukapheresis material offers substantial advantages. It extends the time window between collection and manufacturing and ensures cell viability and function are maintained despite potential delays[4,5,6]. This flexibility is crucial as the production of CAR-T cell therapies expand globally, reducing the risk of supply chain disruptions and improving manufacturing efficiency. The adoption of cryopreservation, which has proven efficacious through global clinical trials[7,8], helps overcome the challenges associated with fresh leukapheresis and ensures a reliable supply of high-quality starting material for successful therapeutic advancement. Multiple commercially available CAR-T cell therapies have incorporated leukapheresis cryopreservation into their manufacturing process, and global supply chain management teams have begun integrating this approach to facilitate robust drug product manufacturing and support an increasing number of patients.

Cryoport Systems addresses the challenges associated with utilizing fresh leukapheresis by standardizing the cryopreservation process across multiple centers in the US and EU through IntegriCell™. IntegriCell™ provides cryopreservation services to uphold the safety, quality, consistency, and viability of critical manufacture-ready cryopreserved leukopaks no matter the collection date to support the treatment of patients with today’s most advanced cell therapies. By integrating cutting-edge bioprocessing technology and cryopreservation methods and leveraging state-of-the-art GMP-compliant cryogenic storage and transportation, Cryoport Systems streamlines the traditional fragmented cell therapy supply chain and effectively mitigates risks associated with the supply and transportation of critical starting materials.

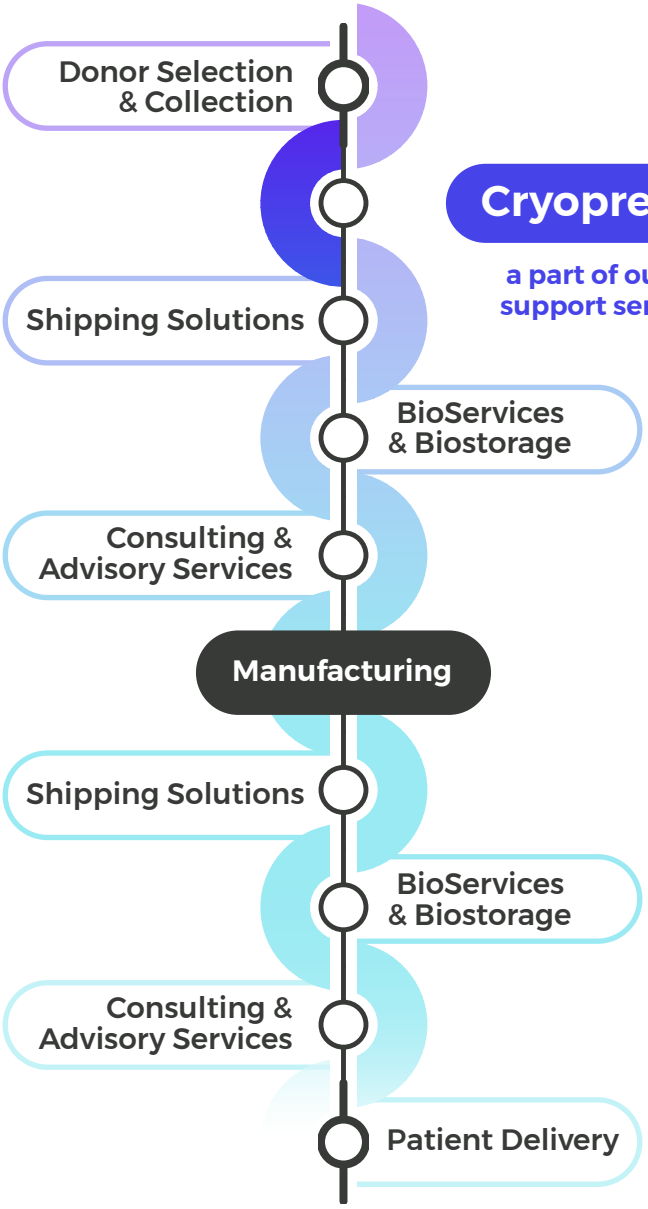
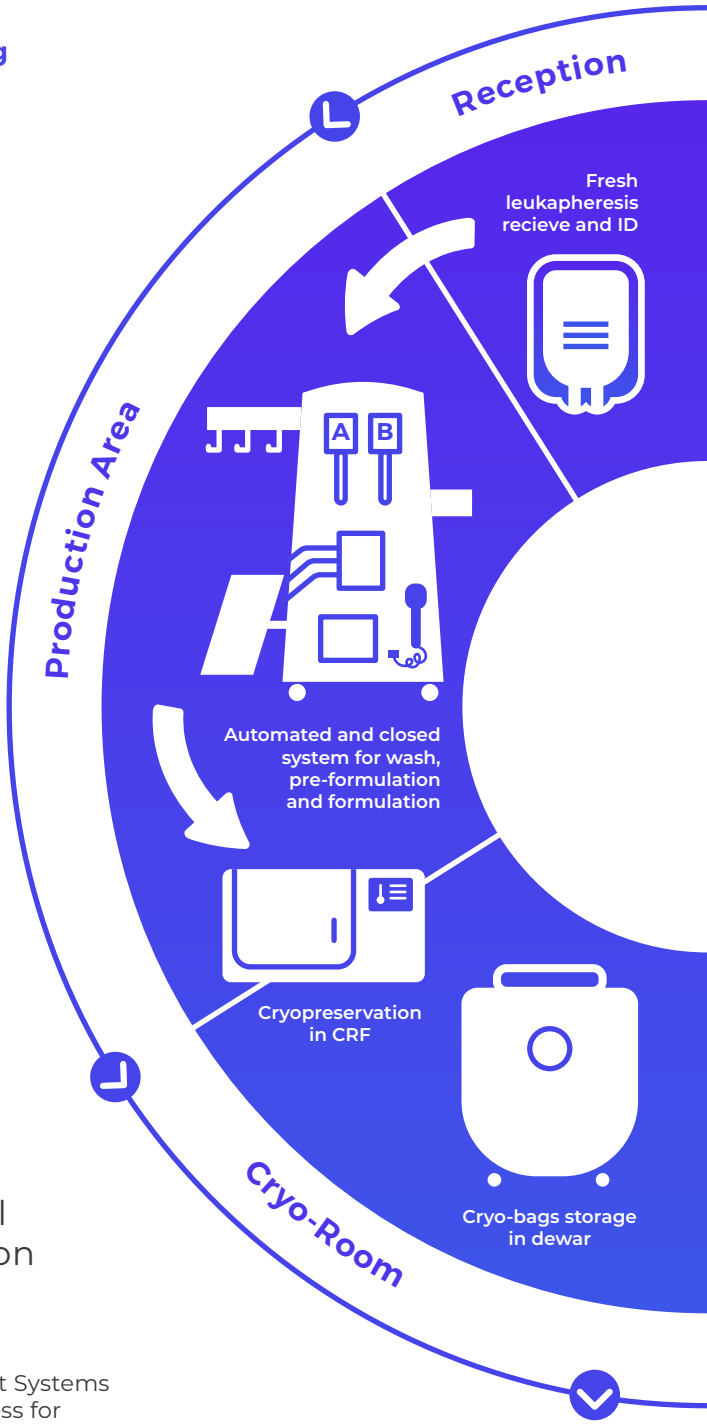


Figure 1.

Cryoport Systems' automated closed process for leukaphereses cryopreservation



Automated Closed Process for Cryopreservation

The IntegriCell™ automated closed process (ACP) for cryopreservation incorporates several critical steps to ensure high-quality preservation of leukapheresis materials.

This approach is designed to minimize contamination risks, enhance reproducibility and consistency, and maintain superior quality. Cryoport Systems aims to deliver a clinical and commercial-grade cryopreservation process for fresh leukapheresis, supporting the successful manufacturing of cell and gene therapies. The IntegriCell™ cryopreservation process incorporates an automated closed system, which isolates it from the surrounding environment. Thereby, the need for critical interventions in the BioSafety Cabinet (BSC) is reduced while associated contamination risks are mitigated.

As illustrated in Figure 1, the automated closed cryo-process encompasses five steps:

1. **Leukapheresis Preparation:** Fresh material is visually checked, transported at verified temperature, and documentation is controlled for release.
2. **Washing:** Leukapheresis volume is measured, and cells are washed using spinning membrane filtration. In-process control sampling is performed for cell count measurement, allowing the cell concentration adjustment to occur at the next process step.
3. **Pre-formulation:** Based on post-washing cell count measurement, cell concentration is automatically adjusted in pre-formulation buffer to reach appropriate cell concentration.
4. **Formulation:** A cryoprotectant is added to reach a target cell concentration, and cells are transferred to Cryo-bags, including both product bags and QC bags. Final QC sampling is performed.
5. **Freezing:** The cells are frozen using an automated Controlled Rate Freezer that ensures freezing cycle parameters are performed in a reproducible and controlled manner.

Performance Evaluation

The performance of the IntegriCell™ ACP was rigorously evaluated using multiple healthy donor samples. Key findings include:

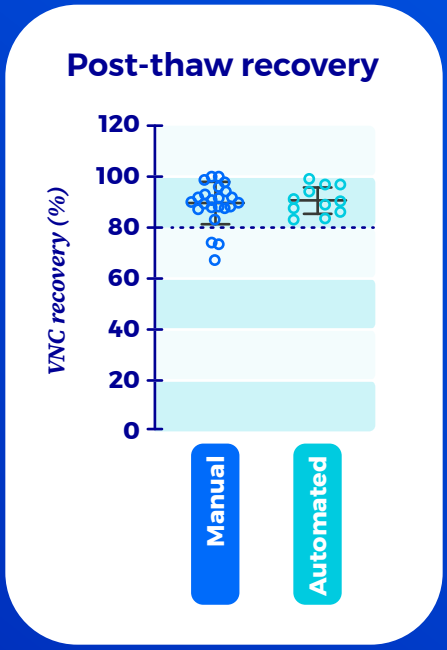


Figure 2.

Performance of post-thaw recovery, manual versus automated

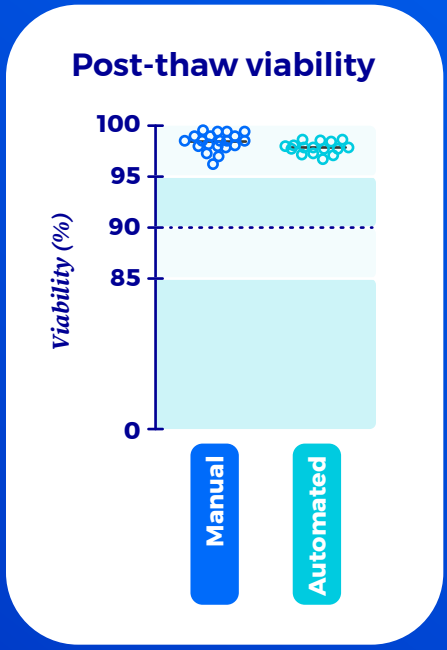


Figure 3.

Performance of post-thaw viability, manual versus automated

Consistency in Cell Recovery and Viability

A standardized, automated closed process consistently achieves high post-thaw cell recovery and viability. This method reduces the incidence of outliers compared to a manual processing approach (Figure 2. & 3.). The comparison was conducted against manual processing performed at a single site using one specific protocol. It's important to note that manual processing across multiple sites could result in even greater variability and a higher occurrence of outliers. This underscores the reliability and reproducibility of the automated closed cryo-process in maintaining cell quality post-thaw.

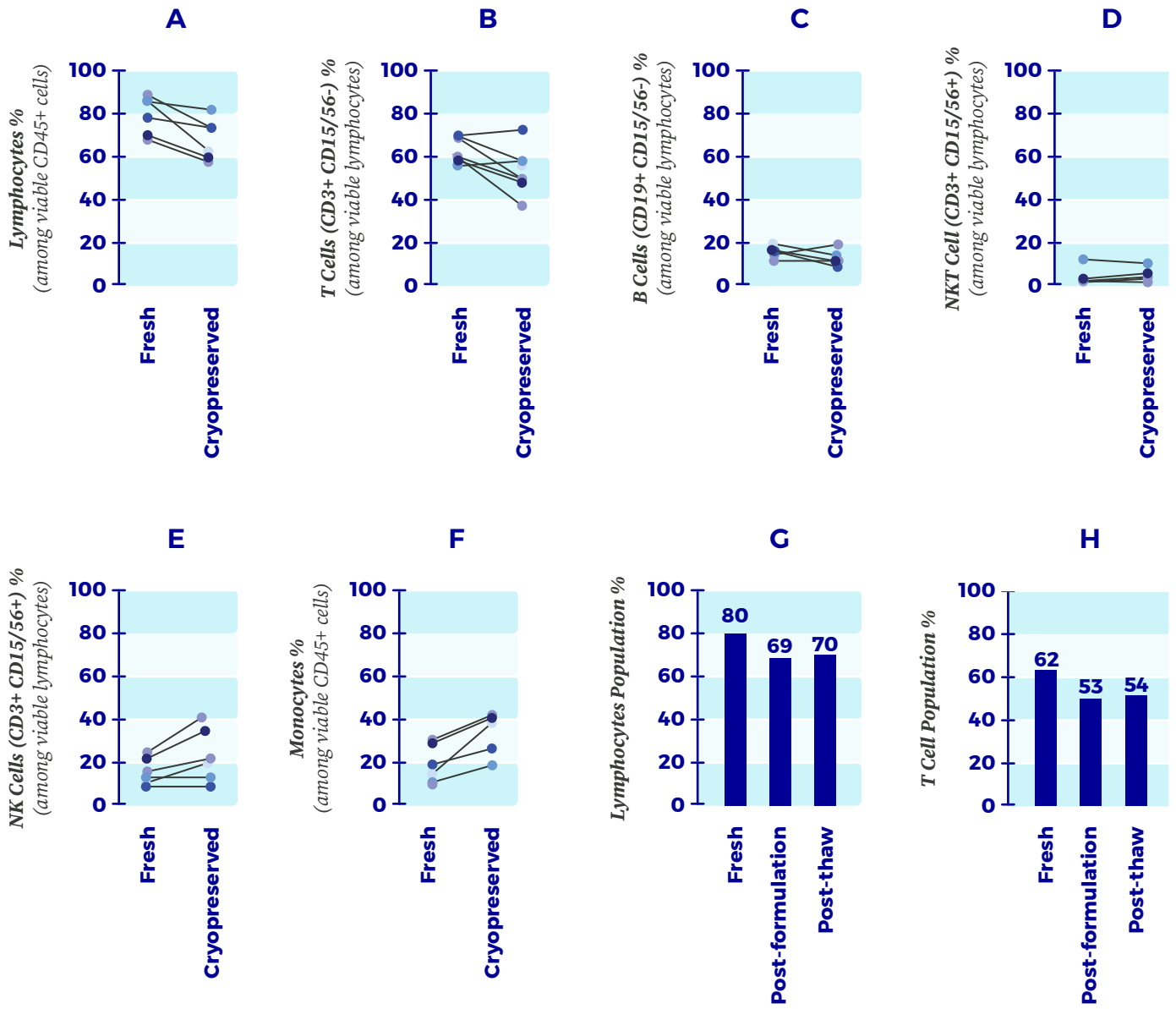


Figure 4.

Flow cytometry analysis comparing viability of fresh starting material versus cryopreserved

Preservation of Immune Cell Composition

In addition to the consistent high cell recovery and viability observed between multiple donor-derived leukaphereses, flow cytometry analysis (Figure 4. A-H) confirmed that the immune cell composition was well maintained in the cryopreserved leukapheresis via our automated closed process as compared to the fresh counterpart from the start. Specifically, there was an average recovery of 87.6±2.8% for lymphocyte population post-thaw (Figure 4. A), which includes a crucial 86.9±4.9% preservation for T cell subpopulation (Figure 4. B). The observed cell loss primarily resulted from the processing during cell washing while the cell formulation and freezing procedures did not impact the cell population (Figure 4. G-H). This high level of preservation ensures a reliable supply for use in cell therapy drug production. With a commitment to quality, Cryoport Systems' IntegriCell™ team is continually developing improved processes to ensure the highest performance of cryo-processing with the IntegriCell™ solution.

360° Support with the IntegriCell™ Model

Cryoport Systems' IntegriCell™ cryopreservation services expand into an end-to-end model that supports clients' entire temperature-controlled supply chain. The IntegriCell™ model combines Cryoport Systems' standardized cryopreservation services with our world-renowned logistics and supply chain expertise to facilitate the timely delivery of manufacture-ready cryopreserved leukopaks to manufacturing sites. The solution includes several critical components that ensure the integrity and quality of the therapy throughout its journey.

Leukapheresis Transport

The IntegriCell™ model supports the transportation of leukapheresis from collection centers to our cryopreservation sites housed in our specially designed Cryoport Express® shipping system. Like all our diverse shipper fleets, the Cryoport Express® temperature-controlled shippers include our best-in-class condition monitoring system, Smartpak™, that tracks each shipment's location, temperature, orientation, and other critical aspects. This technology enables constant coverage, and the metrics are accessible to clients within our innovative logistics management system, Cryoportal®. With this insight, clients can ensure their transported materials remain viable from initial collection to our cryopreservation facilities.

Cryopreservation Process

IntegriCell™ applies a standardized cryopreservation process of fresh leukapheresis within an ideal 24 hours of collection, coupled with rigorous quality control measures. This robust and reproducible cryopreservation process maintains the viability and potency of the cells, which is essential for the efficacy of the final therapeutic product. The cryopreservation process is automated and conducted in a closed system using the Cue® Cell Processing System from Fresenius Kabi. This method adheres to the principles of Quality by Design, where the cryopreservation process has been meticulously developed, identifying and optimizing Critical Process Parameters (CPPs) with a thorough risk assessment. Key CPPs, such as the content of the wash buffer solution, cell concentration during processing, and spinning membrane wash flow rates, are fine-tuned to ensure consistency and quality of the cryopreserved cells.

Storage and Distribution

IntegriCell™ features an integrated storage and distribution network that ensures controlled, worldwide transportation of the cryopreserved cells to their manufacturing destination. This network exists within our Global Supply Chain Centers (GSCC), which house our logistics, biostorage, and cryopreservation processes from a single location. The cryopreserved material can be stored for both long and short-term durations within our GSCCs then distributed to manufacturing facilities on a scheduled or last-minute timeline to accommodate client needs.

Conclusion

Cryoport Systems' IntegriCell™ solution represents a significant advancement in the cell therapy supply chain by providing an automated, closed, and standardized cryopreservation process.

Leveraging distributed cryopreservation services, IntegriCell™ guarantees high-quality, consistent leukapheresis starting material and facilitates global clinical and commercial manufacturing. The integration of IntegriCell™ into Cryoport Systems' logistics and GMP-storage network boosts standardization and reliability, thereby advancing the effectiveness and reach of cell-based therapies.

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About Us

Cryoport Systems is a comprehensive supply chain partner for the life sciences industry focused on meeting the challenges of the global cell and gene therapy market. We excel in the specialized management of the biopharma supply chain through our comprehensive offerings in logistics, BioServices and biostorage, cryopreservation, and consulting. With our expansive platform and decades of temperature-controlled supply chain expertise, Cryoport Systems helps Enable the Outcome™ for advanced therapies programs, safely and securely guiding critical therapies to patients in need.

For more information about IntegriCell™ and how it can support your cell therapy supply chain needs, please scan the QR code.

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Americas
EMEA
APAC
info@cryoport.com
+1 949.232.1900
cryoport.com