ISO 21973:

How to Ensure Full Compliance Throughout Every Step of the Journey

Cryoport Systems

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

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A New Standard Enabling Compliance at Scale

The pressure to move regenerative medicine beyond clinical trials and into the commercial market is intensifying and accelerating in today's industry landscape. According to research from MIT NEWDIGS, the current pipeline of US-targeted cell and gene therapies could see 54 to 74 product-indication approvals by the year 2030, garnering a mean $24.4 billion list price for product revenues. If this prediction comes to fruition, the regenerative medicine industry will experience a period of significant growth and rapid innovation from the starting average product revenue of $15.2 billion in 2023[1].

As the pace of growth increases, the complexities and risks will rise as well. This growth will place unique pressure on the regenerative medicine supply chain to standardize processes and become far more agile while continuing to maintain operational excellence in a zero-failure environment.

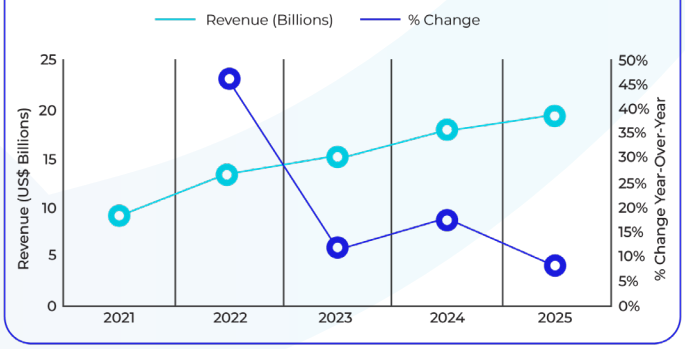
However, the ability to deliver on this promise depends entirely on the industry's ability to deliver these inherently fragile therapies to patients at speed and scale with absolute consistency.

A New Standard When Much is at Stake

In June 2020, the ISO/TC 276 Biotechnology Technical Committee defined a new standard for the transportation of cells for therapeutic use. The cell and gene therapy industry requires end-to-end precision and traceability — everything from chain of custody to chain of condition and chain of identity. ISO 21973:2020[2] extends the chain by focusing on the complete traceability of the equipment, processes, and logistics used in managing the environmental control of the therapy while it is in transit.

This extended "Chain of Compliance®" provides complete traceability, control, and oversight of the entire transportation process, which is crucial for viable scalability.

MEAN PROJECTED ANNUAL CELL & GENE THERAPY PRODUCT REVENUE GROWTH 2021-2025



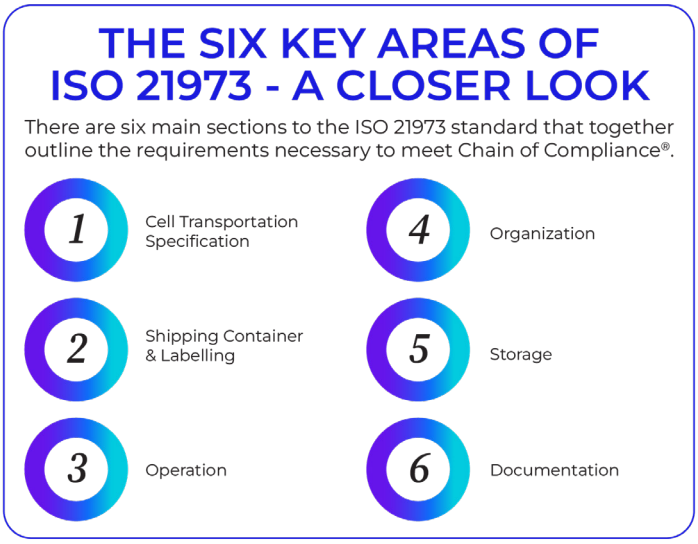
Reference 1 – Drug Discovery Today

> As the cell and gene therapy supply chain continues to mature, the inherent lack of standardization threatens to increase the risks and costs of handling these unique therapies.

Why is ISO 21973 so Significant?

While some existing standards (for example, USP 1044[3]) reference the shipping of advanced therapy products, ISO 21973 is the first standard to specifically address in detail the requirements for the cell and gene therapy supply chain with a focus on transportation while recognizing that these products are significantly more fragile and valuable than most small molecule and biological medicines. Damage to sensitive material products during shipping is not always evident, especially as damaged cell and gene products do not change in smell, color, or other physical ways that are immediately apparent. Slight temperature deviations can render the product ineffective, and minor physical damage can also make the product unusable.

In a global environment, the specification and diligence in the packaging and transportation of these therapies vary significantly, resulting in considerable risk and potential loss of irreplaceable therapies. Quality systems, validation, and traceability are mandated to mitigate risk and ensure the safe delivery of cell and gene therapies in a zero-failure environment.



1. Cell Transportation Specification

This specification provides product-related information provided by the client or manufacturer that determines the requirements for transportation. This information must be shared with the transportation service provider (TSP) who will then conduct the transportation in accordance with the specifications.

Requirements:

- Specification information should include:
  - The appropriate regulatory classification (e.g., infectious, genetically modified).
  - Storage and handling conditions (e.g., temperature range, shelf life).
  - Shipping information (e.g., description of goods, commercial value, weight, consignor/consignee information).
- The TSP must also ensure they (and any third-party partner) can meet the requirements of the specification (in terms of transportation means, equipment, and resources).
- The shipping containers must be suitable to meet the temperature requirement of the product, ensuring the container will remain at temperature for the duration of the transportation.
- There should be systems in place to ensure the segregation of human and animal-derived materials to prevent any potential cross-contamination.
- The TSP should also establish optimal shipping routes and methods to reduce risk and time in transit while taking into consideration that airline schedules may change and that regulations may differ between countries.
- The TSP should monitor and mitigate critical risks such as vibration, shock, tilt, package opening, and X-ray imaging (although this cannot be guaranteed).
- The TSP should also define specific procedures for pickup, handling, and delivery, including correct identification of package labeling, documentation, and personnel to maintain chain of identity.
- Throughout the transportation process, risk must be managed and mitigated (e.g., establishing alternate transportation solutions and emergency procedures as well as the monitoring of additional parameters such as GPS location, shipper integrity, and external conditions).
- Verification and validation of the transportation routes should be considered to mitigate potential risks throughout the supply chain. Data for this may come from shipping lane validations, simulated shipments, historical data, and GPS data monitoring of specific routes.

2. Shipping Container & Labeling

Best practices should be used to guarantee safe transportation and optimal product quality and integrity.

Requirements:

- The shipping container should be designed to protect the payload and anyone who comes in contact with the container.
- The functionality of the shipping container should be adequately validated and documented to ensure the product is maintained at an optimum temperature throughout the transportation process.
- The shipping container should be suitably labeled with consignor/consignee information as well as emergency contacts. The appropriate shipping codes must also be present to prevent avoidable delays at security/border checks. All labels must be removed from reusable shipping containers to prevent confusion on subsequent journeys.
- If a shipping container is reusable, it should be labeled with a unique serial number, making it possible to trace any product throughout the supply chain and to maintain the entire history of use for the shipper.
- For reusable shipping containers, records should be maintained relating to the equipment's performance, commodity, cleaning, and maintenance.
- Reusable temperature-controlled shipping containers should be adequately validated to ensure functional performance and requalified before each use.

3. Operation

The client or TSP should make sure the shipping container is prepared and labeled correctly and that data loggers are set and working appropriately.

Requirements:

- Transportation should be performed according to the transportation specification to maintain chain of custody and identity. Once sealed, the shipping container should not be reopened. The records of all processes in transportation should be retained, including the time of collection and delivery plus the signatures of consignor, consignee, and transportation personnel.
- Visual inspection reports at each hand-off point should be documented. These checks should include any physical damage to the shipping container, any obvious liquid leakage, and any damage to the tamper-evident seals. Once delivered, further checks to the primary container and analysis of data from the data logger should be carried out.
- Full traceability of the shipment should be ensured by the TSP with GPS location monitoring, dynamic monitoring of critical parameters (temperature, shock, orientation, and atmospheric pressure), as well as documenting all pickup locations, times, and signatures. In addition, data should be recorded and managed using appropriate IT systems.
- All shipping containers, accessories, data loggers, and shipper performance data should be controlled using an appropriate recording system.

Incidents and Emergencies:

The TSP should also prepare for incidents and emergencies that may occur. They should have plans in place to mitigate such risks. These plans should include the following.

- All relevant emergency contact details of personnel at the site of origin and site of delivery.
- The options for TSP-conducted investigations in association with the client to determine the cause of any incident (including a system to immediately notify clients of any exceptions and deviations in the transportation process).
- The adequate documentation of all investigations.

4. Organization

The TSP must have a suitable Quality Management System (e.g., ISO 9001[4]) in place.

Requirements:

- The Quality Management System should minimally include:
  - A documented Quality Policy
  - Organization structure
  - Appropriate processes and procedures
  - Training programs with certification
  - Performance monitoring
  - Continuous improvement plans
  - Corrective and preventative actions
  - Controlled documentation

The Quality Management System and all associated documentation and records should be readily available for audit by relevant personnel.

5. Storage

If it is necessary for the shipment to be temporarily stored during transportation, the facility should meet the appropriate requirements for the storage of cells for therapeutic use.

Requirements:

- The facility should be secure with suitable access control. Procedures should be in place for pest control and the cleaning of equipment and premises to prevent any form of contamination.
- A procedure must be in place to address any malfunction or failure of equipment or shipping containers while at the facility.

6. Documentation

All documentation generated during the transportation process must be properly maintained for every scheduled or unexpected event.

Requirements:

- These documents should be readily available and signed by the appropriate personnel. They should also be kept for a period of time defined by relevant regulations or agreed upon by the TSP and client in the transportation specification.
- The history of any reusable shipping containers should be documented and retained.
- All documentation should be regularly reviewed and updated using a version-controlled document control system.
- All documents should be made available for audit to all relevant personnel.

The challenge for vendors will be to meet these requirements for each shipping event while enhancing their processes for every shipping event that follows.

The evolution of process enhancement requires a cycle of continuous improvement that anticipates and enables progress rather than simply catching up post-factum. Shipping containers should be validated according to standard IATA and ISTA testing protocols to ensure the product will be kept at the specified temperature in varying environmental and handling conditions.

A suitable qualification protocol should include both operational and performance testing with actual field testing based on the anticipated transportation route. These tests should reflect actual load configurations, conditions, and expected environmental extremes.[5] Only through this achievement can a high level of confidence be attained that the product will be protected in transit and that the shipping container will perform as expected.

Additionally, process qualification should be performed to ensure reproducibility of the methods used and to ensure consistent outcomes. Vendors can also provide shipping lane validations in a quality technical report that proactively determines and addresses threats that could negatively impact biological products or product integrity during transportation. This validation protocol and report should characterize and be performed on critical shipping lanes using real test shipments. However, information from a single individual journey validation may not be sufficient, so ISO 21973 recommends using data from past transports as additional objective evidence for verification. Data collected for every journey made should be captured for continuous analysis of route and packaging design evolution.

Another consideration is the segregation of human therapeutic materials from non-human materials that could cause potential cross-contamination.

This consideration is especially important for reusable shipping containers where the previous commodity history may not be known. The standard specifically recommends the unique serialization and retention of use-history of these containers to mitigate this risk.

The serialization of reusable shipping containers also enables the recording of cleaning and maintenance histories as well as shipping and qualification histories. This ensures that the provenance and performance of the shipping container are known before every shipment. It should also be mentioned that any cleaning process needs to be suitably validated to ensure efficacy.

Furthermore, having a constant “real-time” recorded view of the journey activity enables the service provider to fully anticipate unexpected deviations and take action to prevent a failed delivery. What data is measured while the product is en route to its destination is what enables timely interventions to ensure consistent quality and risk mitigation. The current and historical data that is captured, analyzed, and mined will support timely decisions for patients around the globe.

This data should include:

- Location tracking using GPS, cellular, and Wi-Fi triangulation.
- Internal and external temperature monitoring.
- Barometric pressure and humidity changes.
- Light monitoring (to measure security breaches, compromised packaging, or premature openings).
- Shifting of shipper packaging orientation.
- The time and location of shock events (which is critical to monitoring the condition of the product en route and to ensure therapeutic suitability of the commodity upon arrival).

Conclusion

The power of the new ISO 21973 standard is the development of a clear path to optimal efficiency and risk mitigation. As the regenerative medicine industry expands and matures with cell and gene therapies being used for an ever-increasing list of indications, reducing risk in the supply chain will become crucial to ensure that these drugs arrive on time, in the best condition, and to the most important destination – the waiting patient.

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. Our expansive industry expertise was integral to the development of ISO 21973:2020, and our experts personally contributed to outlining the necessary protocols to form this compliance standard.

Our platform of risk-mitigating supply chain solutions was built to uphold the strict standards of ISO 21973. We excel in the specialized management of the biopharma supply chain through our comprehensive offerings in logistics, BioServices, cryopreservation, and Consulting Services.

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.

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About Us

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