ISO 21973: A LEAP FORWARD IN STANDARDIZING THE REGENERATIVE MEDICINE SUPPLY CHAIN

HOW TO ENSURE FULL COMPLIANCE AT EVERY STEP OF THE JOURNEY

A NEW STANDARD ENABLING STANDARDIZATION AT SCALE

The pressure to move regenerative medicine beyond clinical trials and into the commercial market is intensifying and accelerating. By 2025, the Food and Drug Administration (FDA) predicts the industry could have as many as 20 new commercial regenerative medicine therapies coming to market each year,[1] requiring safe and effective delivery of multiple-thousands of individual doses.

If the FDA is accurate in its predictions, the regenerative medicine industry is on the cusp of a period of significant growth and rapid innovation. As the pace of growth increases, the complexities and risk 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. 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.

In June 2020, the ISO/TC 276 Biotechnology Technical Committee defined a new standard for the transportation of cells for therapeutic use.

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THIS NEW STANDARD, ISO 21973[2], ARRIVES AT A CRITICAL MOMENT, WHEN THERE IS MUCH AT STAKE

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 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 and is crucial for viable scalability.

This white paper will help explain the new requirements of ISO 21973, why it matters, and what steps developers should take to drive compliance.

WHY ISO 21973 IS SO SIGNIFICANT

While some existing standards (e.g., 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, recognizing that these products are significantly more fragile and valuable than most small molecule and biological medicines. Damage to products during shipping is not always evident. 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 varies significantly, resulting in considerable risk and potential loss of irreplaceable therapies. Quality systems, validation, and traceability are mandated to mitigate risk and ensure safe delivery of cell and gene therapies in a zero-failure environment.

THE SIX KEY AREAS OF ISO 21973 – A CLOSER LOOK

This outlines the requirements of the six main sections to the ISO 21973 standard that must be met for the Chain of Compliance®.

1. Cell Transportation Specification
2. Shipping Container & Labelling
3. Operation
4. Organization
5. Storage
6. Documentation

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1. CELL TRANSPORTATION SPECIFICATION

This specification provides product-related information, from 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 specification.

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 segregation of human- and animal-derived materials to prevent any potential cross contamination.
- The TSP should also establish the optimal shipping routes and methods to reduce risk and time in-transit (taking into consideration that airline schedule may change, and 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 – ensuring correct identification of package labelling, documentation, and personnel to maintain chain of identity.
- Throughout the transportation process, risk must be managed and mitigated. Examples of how this may be done include, 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 in the supply chain. Data for this may come from shipping lane validation, simulated shipments, historical data, and GPS data monitoring of specific routes.

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2. SHIPPING CONTAINER & LABELLING

Best practice 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 into 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 labelled 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. It is important that all labels are removed from reusable shipping containers to prevent confusion on subsequent journeys.
- In addition, if a shipping container is reusable, it should also be labelled 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 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 labelled correctly, and data loggers set appropriately.

Requirements

- Transportation should be performed according to the Transportation Specification to maintain chains of custody and identity. Once sealed, the shipping container should not be opened. The records of all processes in transportation should be retained – including time of collection and delivery, 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 by using GPS location monitoring; dynamic monitoring of critical parameters such as 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.
- In addition, all shipping containers, accessories, data loggers and shipper performance data should be controlled using an appropriate recording system.

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Incidents and emergencies

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

These plans should include:

- all relevant emergency contact details of personnel at the site of origin and site of delivery.
- the TSP should be able to conduct an investigation, in association with the client, to determine the cause of any incident and should have a system to immediately notify clients of any exceptions and deviations in the transportation process.
- all investigations should be adequately documented.

4. ORGANIZATION

It is expected that the TSP will have a suitable Quality Management System (e.g., ISO 9001) in place.

Requirements

The Quality Management System should include, minimally:

- 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 be appropriate 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 cleaning of equipment and premises, to prevent any form of contamination.
- There should also be a procedure in place to address any malfunction or failure of equipment or shipping container while at the facility.

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6. DOCUMENTATION

All documentation generated during the transportation process must be properly maintained for every 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 ISO 21973 standard seeks to mitigate the risks associated with fragile material movement by considering packaging and transportation as an integrated quality process that must be risk assessed, using validated shipping equipment with known historical data, validated shipping lanes and IT systems to ensure the chain of custody and identity are maintained for each unique shipment.

THE CHALLENGE FOR VENDORS WILL BE TO GET IT RIGHT FOR EACH SHIPPING EVENT AND TO MAKE IT BETTER FOR EVERY SHIPPING EVENT THAT FOLLOWS.

This requires a cycle of continuous improvement that anticipates and enables progress rather than simply catching up, after the fact.

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.[4] Only by doing this can a high level of confidence be achieved that the product will be protected in transit and that the shipping container will perform as expected.

Process Qualification should also 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 determine and address 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.

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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 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 the provenance and performance of the shipping container is known before every shipment. It should also be mentioned that any cleaning process needs to be suitably validated to ensure efficacy.

More than ever before, the emphasis will be on data.

In the world of quality, the phrase "what gets measured gets managed" is well known – and for the advanced therapy supply chain it is particularly relevant. The ability of vendors to validate before, during, and long after a specific shipping event will be critical to the industry's ability to create a cycle of continuous improvement.

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.

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)
- shifts to shipper packaging orientation
- the time and location of shock events — this is critical to monitoring the condition of the product en-route and to ensure therapeutic suitability of the commodity upon arrival

What gets 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 gets captured, analyzed, and mined will support timely decisions for patients around the globe, 24/7/365.

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THE POWER OF THE NEW ISO 21973 STANDARD IS ITS DEVELOPMENT OF A CLEAR PATH TO OPTIMAL EFFICIENCY AND RISK MITIGATION.

As this new 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 in ensuring that these drugs arrive on time, in the best condition, at the most important destination – the waiting patient.

We hope this white paper helps. If you'd like more information, please contact: info@cryoport.com.

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