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Cold Chain Planning for Clinical Studies of Regenerative Medicines

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Biopharmaceuticals are inherently fragile and temperature-sensitive, requiring exacting control of environmental conditions to maintain product efficacy. The need is especially acute for regenerative therapies: gene therapy, gene editing, stem cell therapy, and immuno-oncology.

Clinical trials of regenerative therapies depend on cold-chain management solutions involving suitable packaging, storage, data collection, and logistics. Any temperature excursion — exposure to temperatures outside the range prescribed for storage or transport — can alter product quality and efficacy. Such practices can lead to product degradation or a change in the characteristics of the shipped material, potentially affecting the integrity of data gathered during a trial or, worse, the efficacy or safety of a drug candidate. Nevertheless, biological materials for clinical trials are often transported and stored in suboptimal packaging and temperature conditions.

Recently published data have shed light on the risks associated with the transport of biologic materials.[1] The use of inappropriate preservation media, poor maintenance of shipping temperatures, or inadequate freeze/thaw methodology can profoundly reduce biologic material viability and functionality.[1-3] Additionally, inadequate review of primary packaging properties (i.e., those pertaining to a temperature-controlled package placed within another type of insulated packaging, such as a box with foam) can undermine the viability of tissues, proteins, cells and other materials being transported or stored.[4]

ISBER Guidelines

The International Society for Biological and Environmental Repositories (ISBER) has published "Best Practices for Repositories." This document addresses numerous areas of concern for proper handling of regenerative therapeutic materials for clinical trials.[5]

Quality management requires documentation of compliance with current Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and Good Distribution Practice (GDP). GLP/GMP/GDP compliance requires validated cold storage equipment and freezers with temperature recording ("temperature mapping") and connection to backup generators, as well as having temperature monitoring and alarms, to ensure an uninterruptable power supply and 24/7 environmental control.

Quality management also requires auditing of records pertaining to temperature, access and inventory control, as well as documentation of training programs, including cross-training of employees to ensure adequate training in security, continuity and inventory policies and procedures.

Companies must document implementation of measures that ensure biological, chemical, electrical, fire, physical and radiological safety, as well as safety measures applicable to the types of materials stored (e.g., liquid nitrogen (LN2), dry ice, and carbon dioxide).

Guidelines for business continuity and security apply to materials in transit and in storage. The guidelines require monitoring and documentation of environmental controls, proactive calibration, preventive maintenance, access policies, security systems, fire prevention and detection plans, and emergency response planning. (Continuity and security considerations include compliance with 21 CFR Part 11 (Subpart B 11.10 and Subpart C 11.100), which

subjects accessioning and inventory management systems to regulations pertaining to electronic signatures and record-keeping.[6])

Guidelines for record retention cover availability for audits and inspection; inventory systems management, including location systems, lot control, audit trail/tracking, labeling, bar coding, and documentation of temperature/humidity control; and shipping conditions, including comprehensive data monitoring, as well as availability of records documenting temperature control.

ISO Guidelines

The International Organization for Standardization (ISO) is developing standards for the storage and distribution of these types of therapies. ISO/TC 212 is under review. It outlines testing requirements for evaluating the quality and potency of regenerative therapies. ISO/TC 276 will define standards for storage and distribution of these therapies, including storage and packaging validation, comparability and metrology (measurements).

These ISO standards will likely define the acceptable limits of environmental excursions during distribution and the level of detail required for packaging qualification and validation.

Logistics

Biopharmaceutical companies should integrate logistics considerations into the clinical trial planning process, especially for regenerative medicine trials. Planning should start by addressing the following logistical considerations:

- Specialized packaging needs
- All legs of the journey
- Storage and administration capabilities of investigative sites
- Advance testing of shipping routes ("lanes"), import/export and other logistical features
- Visibility, tracking and reporting of chain-of-custody (e.g., geographical location, lane mapping, carrier performance) and chain-of-condition (e.g., temperature, handling, package orientation (e.g., "This Side Up")
- Ease of shipment handling at manufacturing location and investigative sites
- Reverse logistics for cleaning, revalidating and recharging packaging

Data Monitoring and Recording

Maintaining proper temperatures is essential for fragile biologics during transit and storage. Many biopharmaceutical companies therefore ship their materials in temperature-controlled LN2 dry vapor packaging ("shippers").

Proper use of these shippers requires observable, recordable data that document temperature maintenance. To that end, a condition monitoring system or data logger that works in conjunction with a logistics management platform can provide real-time information about condition and location that could impact the quality and/or timing of a delivery, such as location, temperature, pressure, light, orientation, humidity, shock and battery life.

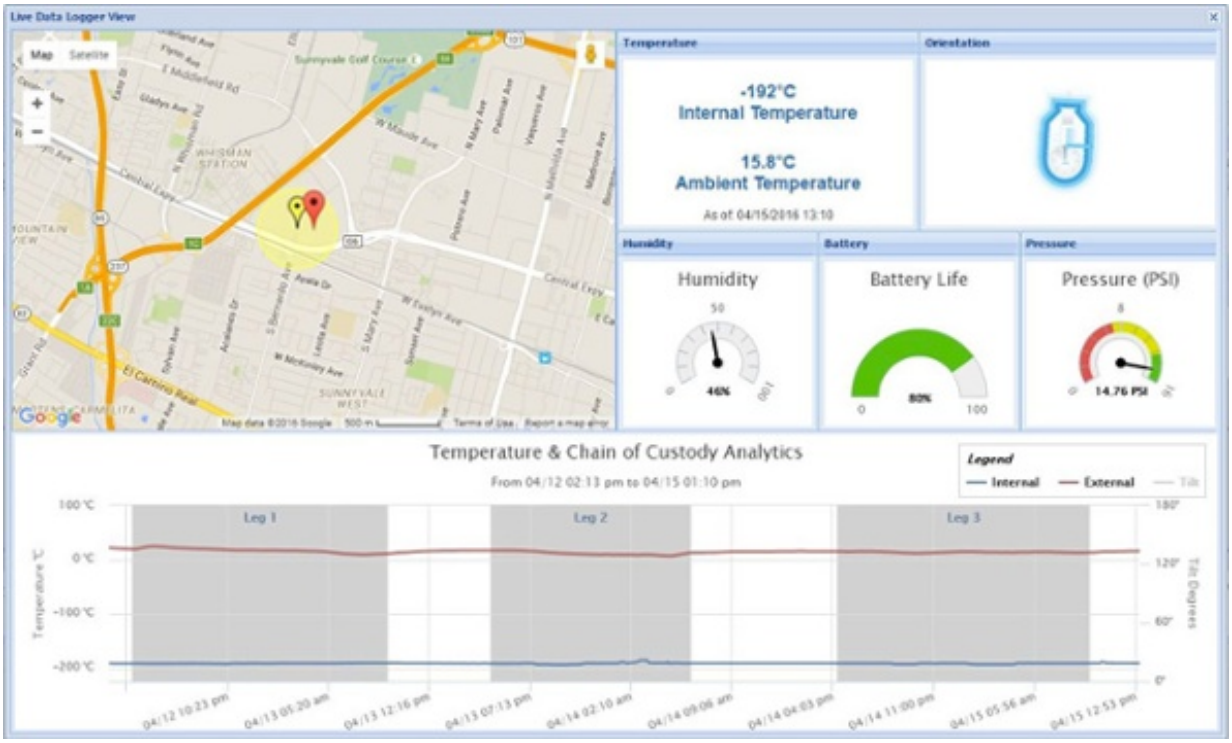
Recent advances have greatly improved the performance and efficiency of freezers and packaging technologies and the information technology (IT) that supports them. Automation of sample accessioning and inventory management systems — and direct integration of these systems into a broader IT-based logistics solution — can enable comprehensive

fulfillment, shipment tracking, and data monitoring/management from a central location or multiple locations. Cloud-based logistics systems can make the entire supply chain more transparent, while eliminating much of the manual paperwork.

Such advances facilitate the design of systems that can track the history of a specific lot of drug product and link that history to specific patients, thereby enhancing data integrity.

IT systems are available that integrate with robotic automated sample accessioning systems. Other IT systems integrate with laboratory information management systems (LIMS), and some provide fulfillment capabilities as well. These systems can facilitate data collection via wireless communication, as well as transmission and reporting of data to the vendor and customer on a dashboard (Figure 1).

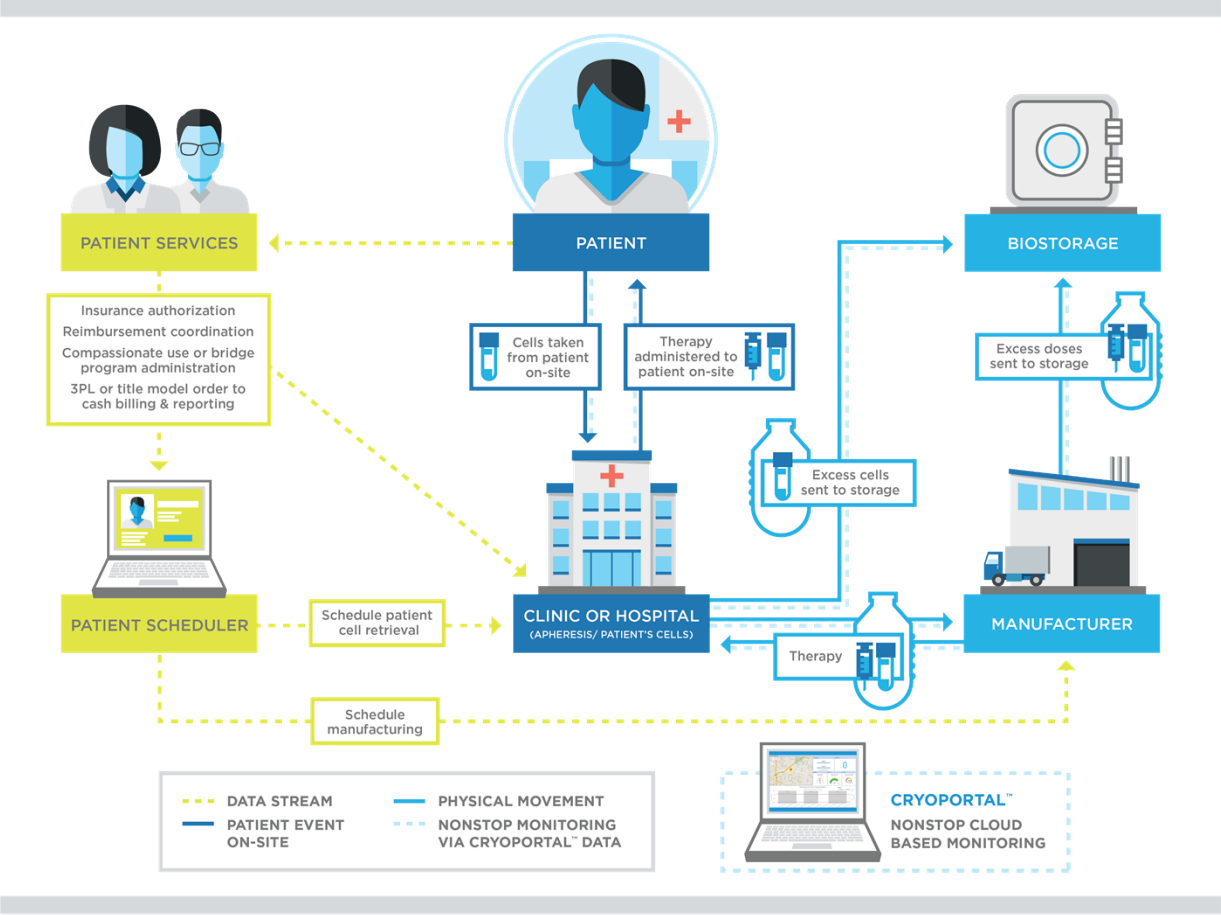
Figure 1. Example of Logistics Dashboard



Autologous Therapies

For a developer of regenerative medicines, every shipment is unique and, in most cases, irreplaceable, leaving no room for error. That is especially true for transport and storage of autologous therapies (i.e., treatment with the patient's own cells or tissues), as patients receiving this type of personalized medicine are often very ill and can tolerate only one apheresis (reintroduction) process. For such therapies, there are logistics systems that provide verified chain-of-custody and chain-of-condition transport from (a) the collection of the patient's cells in a hospital setting, to (b) a central processing facility, where the cells are processed into a personalized medicine, to (c) the research site (Figure 2). If required, the vacuum-insulated container ("dewar") can then serve as a temporary freezer/repository at the research site — a benefit that is also available for allogeneic therapies (i.e., treatment with someone else's cells or tissues).

Figure 2. Example Schematic for Shipment of Biologic Materials for Autologous Therapies



Conclusion

Regenerative medicine, especially autologous therapies, require the highest standards for the transportation and storage of medicinal products. To protect the safety and welfare of study subjects and the integrity of study data, study sponsors should plan the logistical elements well in advance, employ best practices for transport and storage — including a rigorous quality management system — and take advantage of technologies that best meet the needs of the study.

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