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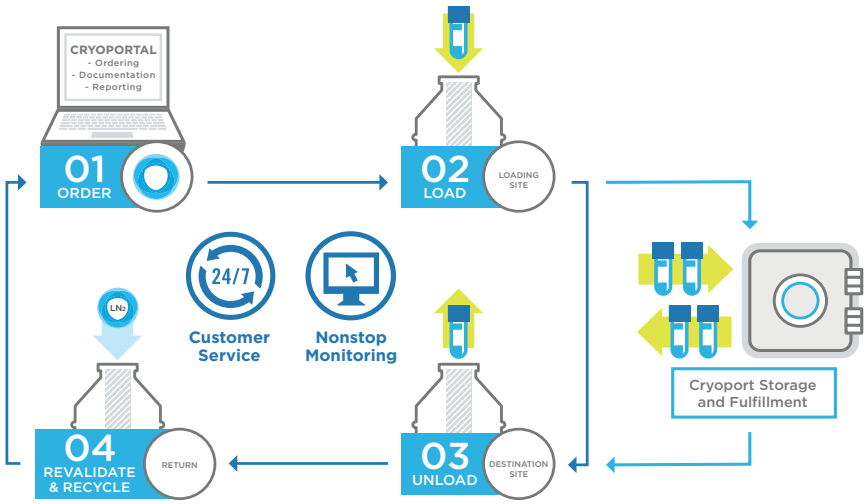
CRYOPORT BIOSTORAGE:

MEETING THE CHALLENGES OF MOVING AND STORING REGENERATIVE MEDICINES



New systems allow biopharmaceutical companies to make data-driven logistical decisions.

Shipping and storing clinical trial therapeutics and biospecimens involve more than moving materials from Point A to Point B. In the biopharmaceutical industry, material transport and storage are especially complex operations because the materials cannot be exposed to temperatures outside the range(s) prescribed for storage and/or transport — a phenomenon known as a "temperature excursion." While frozen materials are shipped and received every day, the logistics surrounding their storage create new challenges for even the largest and most experienced clinical trial networks and supply chain managers.

The most challenging aspect of storing and shipping biopharmaceutical materials — a category that includes bioanalytical samples, clinical trial samples, vaccines, stem cells, biomarkers, immunotherapies and regenerative medicines — is maintenance of the chain of condition and chain of custody. As a logistical consideration, complete information on the chain of condition (encompassing metrics such as temperature, handling and shock/tilt of shippers) and the chain of custody (e.g., geographical location, lane mapping, carrier performance) is critical to ensure the integrity of products during transport and storage. Improper handling, shipping and storage of biopharmaceuticals greatly affect the quality of the material, stability of the analytes/drug product and, by extension, bioanalytical assay outcomes.

Moreover, undocumented freeze-thaw cycles, thermal cycling and pH changes due to improper storage/shipping conditions can lead to the loss of millions of dollars' worth of biopharmaceutical product and clinical samples. Similarly, analyte instability can negatively affect bioanalytical assays and undermine the robustness of clinical data. It can take months or even years to troubleshoot the problems resulting from poorly performing assays and inconclusive data, not to mention the re-manufacture of biopharmaceutical products. Such challenges thus can greatly affect the development timeline of a new drug at immense cost.

Within the biopharmaceutical industry, the importance of a sound storage/shipping logistics strategy — and the economic ramifications of not having such a strategy — are greatly underappreciated. Alarmingly, it is still common practice to place biologic material in a Styrofoam box with an unmeasured amount of dry ice and to hope for the best. Fortunately, advanced data monitoring and logistics systems are available that facilitate chain-of-condition and chain-of-custody maintenance. These newer systems allow biopharmaceutical companies to make data-driven logistical decisions, much as they do for drug development and commercialization.

What to Look for in a Biostorage Partner

There are numerous factors to consider when selecting a storage partner for biopharmaceuticals. Chief among these is compliance with current Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), Good Distribution Practice (GDP) and International Society for Biological and Environmental Repositories (ISBER) guidelines. GLP/GMP/GDP/ISBER compliance means having validated cold storage equipment and freezers that are temperature-mapped and connected to backup generators, as well as temperature monitoring and alarms. Storage systems should also incorporate accessioning and inventory management systems that comply with Part 11 of the U.S. Code of Federal Regulations Title 21 (21 CFR, Part 11), which governs electronic records and electronic signatures. There are a number of IT systems available with differing capabilities; some integrate with robotic automated accessioning systems, others integrate with laboratory information management systems (LIMS), and some provide fulfillment capabilities as well.

A second consideration is capacity and, more importantly, capacity within the required temperature bands. For example, large projects for -20°C storage may require a cold room, whereas cell lines or infectious material may require segregated cryogenic storage.

It is also important to consider sample recovery capabilities and fulfillment logistics management. When materials are ordered out of storage for analysis, the conditions in which those materials are extracted and transported are of utmost importance. Storage providers must therefore accession and transport materials using “cold-carts” in order to limit thermal cycling and analyte degradation.

Other considerations come into play when biopharmaceuticals must be routed under extreme conditions, such as in cold weather or tropical climates. Key factors include packaging design and performance, particularly in terms of whether performance has been validated at extreme temperatures; refrigerant volume and rate of evaporation/sublimation at given temperatures; time exposed to extreme temperatures; and a logistics and interdiction strategy to move the shipper to a less hostile environment and/or to secure the biomaterial in the event of a shipper failure. In this case, one may choose to expedite delivery, replenish the refrigerant or move the material to a newly conditioned shipper.

In recent years the biopharmaceutical storage and shipping field has benefited from technological advances that have greatly improved the performance and efficiency of freezers and the IT systems that support them. To a great extent, sample accessioning and inventory management have been automated and directly integrated into a broader IT-based logistics solution, allowing for comprehensive fulfillment, shipment tracking and data monitoring/management from a single location.

Basing logistical systems on the cloud enables transparency throughout an entire supply chain while eliminating much of the "busy work." Such advances are facilitating the design of systems that can develop data chains to track entire histories of specific lots of drug product, while linking those histories to that of a specific patient sample, thereby enhancing data integrity and the targeting of drugs to patients who are most likely to benefit from them.

Adherence to Best Practices

Numerous organizations — including the World Health Organization (WHO), the U.S. Food and Drug Administration (FDA) and the International Society for Biological and Environmental Repositories (ISBER) — have issued standards and guidelines for the collection, storage, retrieval and distribution of biologic samples. When selecting a provider of storage and fulfillment services, biopharmaceutical companies should vet suppliers for adherence to the following best practices:

- **Business continuity and security**
  - Appropriate environmental controls (24/7), including monitoring and records
  - Proactive calibration and preventive maintenance
  - Redundant freezers and/or backup power — uninterruptible power supply and backup generators
  - Access policy
  - Security systems
  - Fire prevention/detection plans
  - Emergency response planning
  - 21 CFR, Part 11-compliant monitoring

- **Quality systems**
  - Documentation of current Good Practices
  - Audits: records of temperature, access and inventory control
  - Adequate safety measures for the type of materials stored: biological, chemical electrical fire, physical, liquid nitrogen
  - Training program and documentation
    - Training records documenting frequency of training
    - Cross-training to adequately train employees on security, continuity, inventory policies and procedures

- **Record retention**
  - Availability for audits and inspection

- **Inventory systems**
  - Current GMP-compliant storage
  - Location system
  - Lot control
  - Audit trail/tracking
  - Labeling
  - Barcoding
  - Temperature/humidity tracking and records

- **Shipping conditions**
  - Comprehensive data monitoring
  - Availability of data records to validate temperature controls

Cryoport Biostorage and Fulfillment Capabilities

Cryport offers secure temperature-controlled storage, fulfillment and transportation of all valuable and often irreplaceable time- and temperature-sensitive biologic material including therapeutics, reproductive materials, vaccines, cells and tissues. We offer these services, made possible through a strategic partnership with Pacific Bio-Material Management, Inc., in response to a clear demand from our customers to complement our leading temperature-controlled logistics solutions with advanced storage and fulfillment capabilities. Our end-to-end solutions ensure that every shipment reaches its destination securely, and our strategically located depots allow our clients to reach emerging markets around the world faster and more cost-effectively.

Cryoport's end-to-end solutions ensure that every shipment reaches its destination securely.

With GDP-compliant facilities and knowledgeable staff, and through strict adherence to generally accepted best practices, Cryoport's technology and processes deliver reliability, security and flexibility — whether you're shipping a single package or a whole sample store.

Cryoport's biostorage and fulfillment services are designed to help customers maintain product quality while accommodating shipping timelines and workflow management for sponsors, investigators and researchers. Our capabilities include:

- Full GLP/GMP-compliant storage facilities with GDP fulfillment capability
- Dedicated multi-temperature warehousing, from controlled ambient to deep frozen
- Packaging and radiofrequency identification (RFID) label application
- Labor management systems and processes
- Open pallet storage
- Independent temperature detection data loggers
- Commercial drug storage
- 21 CFR, Part 11-compliant accessioning and inventory management
- 24/7 on-site security

Cryoport offers storage solutions that include GDP-compliant biorepositories at controlled temperatures and climatized systems with effective redundancies such as backup freezers and power. Our extensive management and monitoring offerings include controlled access to commodities and periodic temperature and activity reports, as well as 21 CFR, Part 11-compliant monitoring with 24/7/365 alarm response.

Your Comprehensive Biostorage Solution

Cryoport combines detailed logistics, biostorage and fulfillment capabilities to enable complete control and transparency of material shipment and storage. Our team of experts can assist your organization in planning for an end-to-end solution and compliant workflows that protect materials and patients while providing the information to validate clinical trial data. To learn more, contact us at **+1 949.232.1900** or **info@cryoport.com**.

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