Biostorage: Closing the Loop in Biopharmaceutical Supply Chain Management

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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.

In the rapidly growing markets for immunotherapies as well as stem cell and other regenerative medicines, one of the most challenging aspects of storing biopharmaceutical materials is the maintenance of the right conditions, especially temperature - which is also important when storing bioanalytical samples, clinical trial samples, vaccines and biomarkers. As a logistical consideration, complete tracking of the condition is critical to ensure the integrity of products during both storage and transport, as improper handling or storage can 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 packaging, 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.

"Storage is a critical element of supply chain management. By adding storage services to cold chain shipping and tracking, the best of the logistics management companies create a more comprehensive, end-to-end service offering for clients of any size," notes Michael Lebbin, president and CEO of Pacific Bio-Material Management, Inc., a provider of regulatory-compliant storage, transport, management and cold chain logistics of biological materials.

"Increasingly, small and mid-tier biopharmaceutical companies are outsourcing cryogenic supply chain management to logistics partners as a means to preserve their capital for therapeutic development," Lebbin adds. "At the same time, large biopharma companies are outsourcing cryogenic supply chain solutions to access specialized expertise in cold chain supply, tracking and monitoring, inventory control, quality systems and equipment management, a practice that allows them to focus their internal resources on drug development."

Considerations for Selecting 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 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 or damaged 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 "cryo-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

In addition to the ISBER, numerous organizations - including the World Health Organization (WHO) and the U.S. Food and Drug Administration (FDA) - 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
    - Equipment system validation IQ/OQ/PQ
    - 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

Verifiable Biostorage and Fulfillment Capabilities

When planning for commercialization of a cell-based therapy, a biopharma company should confirm that a prospective logistics management partner has advanced, GMP-compliant cryogenic storage and fulfillment capabilities, as these are essential to maintaining product quality while accommodating shipping timelines and workflow and inventory management for sponsors, investigators and researchers. GMP-compliant facilities and knowledgeable staff can facilitate the transportation of valuable and often irreplaceable time- and temperature-sensitive biologic materials, which may require dedicated shipment and storage to ensure that every shipment reaches its destination securely. Additionally, suppliers with strategically located depots around the world can allow drug developers and marketers to reach emerging markets quickly and cost-effectively.

For many biopharmaceutical companies, the outsourcing decision rests on identifying a full-service provider. When vetting a potential biostorage and fulfillment partner, biopharmaceutical companies would do well to consider the following capabilities:

- Dedicated multi-temperature warehousing, from controlled ambient to deep frozen
- Packaging and radiofrequency identification (RFID) label application
- Quality control systems
- Open pallet storage
- Independent temperature detection data loggers
- Periodic temperature and activity reports
- Controlled access to commodities
- Commercial drug storage
- 21 CFR, Part 11-compliant accessioning and inventory management
- Capabilities to segregate approved, quarantined and damaged materials
- Kitting services, if required
- Storage capacity for apheresis materials, collection kits and final dose
- Inbound and outbound shipments and tracking
- Documentation for shipping and receiving
- Agreement on shipment notification periods and lead times
- Availability of long-term storage, if required
- Protocols for shipment method and agreement on qualified vendors
- Adequate reporting (at the customer's required frequency) of:
  - Lot numbers
  - Expiry information
  - Quantities by category; released, quarantined and damaged materials
  - Temperature deviations
- Ability to integrate with customer's proprietary information systems for real-time tracking and reporting
- Labor management systems and processes
- 24/7/365 on-site security and alarm response

Suppliers that combine detailed logistics, biostorage and fulfillment capabilities can enable complete control and transparency of material shipment and storage. Those making use of advanced technologies can facilitate planning for an end-to-end solution and compliant workflows that protect materials and patients while providing the information to validate clinical trial data.

"The future is in the technology," says Lebbin. "Companies seeking to outsource supply chain management should look for logistics and biostorage partners that leverage technological advances to facilitate complete visibility of the entire chain of custody and chain of condition. As the market for cell-based therapies continues to expand, end-to-end biostorage and fulfillment services will become increasingly vital to ensuring successful drug development and commercialization."