

## Mitigating Risk in the Biomaterial Cold Chain

Cold chain management is essential in biopharma development

**By Jeff Clark**

As clinical research continues its migration towards globalization, expanding into such regions as Latin America, Eastern Europe and East Asia, the process of transporting human clinical trial samples has become increasingly complex. For example, China reported a four-fold growth (982 trials in 2001, growing to 4,307 in 2003) in ongoing clinical trial projects from 2001 to 2003<sup>1</sup>. As a result, the biomaterial cold chain has become as critical as any element in the pharmaceutical and biotherapeutic development processes.

Cold chain management defines how temperature-sensitive products and biomaterials, such as clinical trial samples, APIs and microbiological and viral samples, are packaged, transported and stored throughout the R&D process. Weakness or failure at any point in the chain can compromise sample or product integrity, breach security, delay shipments and ultimately result in financial loss or liability.

### Role of Cold Chain Management in Biopharma Development

The biotech industry is expanding at a rapid pace. U.S. biotech sales grew 20% to \$40.3 billion in 2006, while pharma sales grew 8% to \$275 billion, according to IMS Health<sup>2</sup>. Because biotech drugs are made out of living cell cultures, instead of the simple molecules used to create traditional pharmaceuticals, much of this development as well as other research initiatives rely on the safe, on-time and compliant shipping of biomaterials.

Unfortunately, these valuable and sometimes irreplaceable materials are often handled precariously while in transit. For instance, at various phases in development, biomaterials are transported between collection sites, analytical labs and biobanking facilities. These locations are often spread out over several different geographical areas, which, among other variables, have varying temperatures. This can have a negative effect on samples and compromise integrity.

Consider what would happen if a clinical trial samples thawed out before it reached the testing lab. This compromise could cost the sponsor hundreds of thousands of dollars to repeat the trial. Moreover, if samples are delayed at customs and don't reach their destinations on time, it could have a ripple effect throughout the development process.

From a regulatory perspective, lack of compliance can delay biologic shipments at inspection points or subject drug developers to fines, ranging from a few hundred to thousands of dollars. Even specific individuals can be fined or, in extreme cases, imprisoned. It is in the best interest of the drug or biomaterial developer to build a reliable, efficient cold chain that protects the company's biological assets and helps bring products to market faster.

To ensure compliance and mitigate both financial and legal risk, biopharmaceutical developers must take a holistic approach to cold chain management. Specific factors to consider include:

- Training and Compliance
- Packaging
- Labeling and Documentation
- Tracking and Monitoring
- Transportation (Domestic and International)

### Training and Compliance

The importance of training site personnel in correct shipping and receiving processes for temperature-sensitive



materials cannot be overstated. Set-up and handling are a common cause of temperature deviations; therefore, it is crucial that all cold chain partners are properly qualified and have been adequately instructed in handling these materials. In fact, the International Air Transport Association (IATA) and the U.S. Department of Transportation (DOT) require organizations and individuals that ship or receive biological materials to be trained formally in packaging, labeling, documentation, declaration, hazard assessment and emergency response<sup>3,4</sup>. As a result, many corporations have established in-house training programs specific to their shipping needs. Also, service firms are available for companies that do not have on-site expertise. These companies offer in-depth assistance with training to make certain proper instructions are communicated and standard procedures are followed.

### **The Role of Packaging**

Packaging solutions are becoming more technologically advanced and sophisticated as the demand for temperature control increases. Because the external environment cannot be controlled during shipping, biopharmaceutical firms maintain the viability of their temperature-sensitive biological materials with specialized packaging. Validated packaging materials and effective packing techniques will protect products during transit and unexpected delays. Packaging that includes insulation, temperature-tracking devices and some form of refrigerant creates additional insurance throughout the cold chain.

To ensure materials are maintained properly, logistics personnel must first adhere to the carton manufacturers guidelines. They must also be aware of the temperature requirements of the products being transported and understand the unique packaging challenges presented by different temperature requirements (i.e. controlled ambient, refrigerated or frozen). It is the logistics professional's responsibility to package products appropriately, document the specifications for each package and ensure that the shipping company can accommodate and maintain these requirements throughout the entire shipping process.

### **Best Practices for Frozen & Refrigerated Shipments**

For frozen and refrigerated specimens, each detail is key. Blood and other biological materials are commonly shipped with dry ice or liquid nitrogen to maintain their frozen state. For dry ice shipments, the size of the packaging (payload compartment) is key. Packaging that is too large allows for an excess of air space, which causes dry ice to dissipate at a higher rate and decreases the temperature hold time. Another common refrigerant used to ship biological material is liquid nitrogen. Logistics personnel must adhere to best practices associated with using these sub-zero substances to maintain the integrity of perishable biological materials. When shipping samples that require liquid nitrogen temperatures, the key is to use proper validated dry shipper canisters and precharge them according to manufacturers instructions.

For biological materials that must be refrigerated and maintained at +2° to +8° Celsius, packaging must be properly preconditioned prior to shipment to avoid compromising sample integrity. To precondition packaging, refrigerants used to maintain temperature inside the shipping carton must be brought to the specified temperature for 24 to 48 hours before packing, based on stringent manufacturers instructions. To avoid potential risk, on no account should personnel deviate from manufacturer guidelines. Once the refrigerants are preconditioned and placed inside, the carton should rest for one to two hours to ensure that the internal compartment reaches the desired shipping temperature.

Strategic packing techniques bring an added measure of temperature control to the shipment. For instance, proper placement of the refrigerated or frozen gel packs within the payload compartment can prevent fluctuation during transportation.

Common issues that can impact biomaterial integrity during transport include prolonged delivery delays caused by transportation glitches, security inspections or customs scrutiny; temperature fluctuations inside shipping vehicles; and seasonal or climate differences between origination site and destination.

### **Labeling and Documentation**

Rigorous demands from authorities and industry associations worldwide require that standard operating procedures be set in place not only for shipping, but also for labeling and documentation. Any controlled transport storage conditions, as well as warning statements or content identification (i.e., flammable or infectious substances), should be clearly stated on the label applied to shipping containers. Labeling should be securely attached and clearly state that materials must be transferred to a specified storage temperature immediately upon receipt.

Additionally, logistical personnel must be properly trained to understand the characteristics of the materials being shipped and applicable regulations to avoid delivery delays, liability and financial penalties. They must determine the appropriate hazard class and shipment description to establish the required packaging, markings, labels and documentation.

For example, any shipment classified as an infectious substance — any viable microorganism that is known or reasonably believed to cause disease in humans or animals — must include an itemized list of contents enclosed between the secondary and outer packaging<sup>5</sup>.

The return of clinical samples to central laboratories for testing is another key component in clinical trials conducted internationally. In some regions, doctors and nurses are becoming involved in clinical trials for the first time and are shipping hazardous and temperature-sensitive materials to central laboratories. Without appropriate training, this can have serious legal and cost ramifications.

The DOT's Hazardous Materials Regulations (HMR) and IATA Dangerous Goods specifies requirements for the safe transportation of hazardous materials by rail car, aircraft, shipping vessel and motor vehicle. These

regulations dictate specifications for classification, packaging, hazard communication, shipping papers, incident reporting, handling, loading, unloading, segregation and movement of hazardous materials. Fines and shipping delays often result from non-compliance and lack of awareness of HMR requirements.

### Tracking and Monitoring

Beyond selecting the proper packaging and using it correctly, there are additional steps logistics personnel should implement to confirm that shipments maintain the contents at the desired temperature throughout the shipment. Effective cold chain practices incorporate continuous monitoring and tracking systems to ensure that sample integrity is not compromised at any stage.

Temperature monitors are used to track the temperature of materials being shipped. If temperature excursions outside the previously determined temperature range occur, they must be evaluated and documented. Corrective action should be implemented where necessary, and documented. Clear directions should be provided to the recipient for the evaluation or disposition of the indicators and products. A variety of factors, including regulations and internal guidelines, must be considered when situations require the use of temperature monitoring devices.

### Transportation (Domestic and International)

As clinical trials evolve and continue to expand globally, more rigorous controls and restrictions have been set in place that, if not adhered to correctly, can cause delays in delivery of biological materials. For pharmaceutical and biotech firms that conduct clinical trials outside the U.S., receiving and shipping temperature-sensitive materials can be a challenge. With a growing number of regulations, cold chain logistic personnel must be conscious of custom regulations, in addition to codes and restrictions imposed by various industry entities. The U.S. Customs and Border Protection has dictated that it is the responsibility of the importing company to ensure that U.S. import shipments meet admissibility requirements and that proper permits are obtained in advance of the goods' arrival in the U.S.<sup>6</sup> Personnel should also pay close attention to new rules and regulations that may impact their cold chain process. Current rules and regulations include:

**Known Shipper Program:** This program is a comprehensive set of mandates that applies to transporting cargo by air. Under the current regulations, all indirect air carriers (IACs) — entities that arrange air transportation shipments — are required to establish "known shipper programs." Only known shippers are authorized to place freight in passenger aircraft; all others must transport freight on cargo aircraft. Limiting the types of flights on which shipments can be placed greatly limits options for cost-effective and timely transportation<sup>7</sup>.

**Indirect Air Carrier (IAC) Standard Security Program:** To avoid delays due to extensive inspections, IACs must have a Transportation Security Administration-approved Indirect Air Carrier Standard Security Program and a designated IAC Security Coordinator. IAC employees who need a Security Threat Assessment must also obtain one.

**The U.S. Food and Drug Administration Good Importer Practice:** This guidance provides recommendations to pharmaceutical and other manufacturers on possible practices and procedures they may follow to increase the likelihood the products they import are in compliance with applicable U.S. safety and security requirements<sup>8</sup>.

Transporting biomaterials domestically throughout the U.S. is not without its complications and difficulties. In 2007, Congress mandated that by August 2010, all cargo transported on passenger aircraft must be 100% screened<sup>9</sup>. This doesn't effect integrated carriers such as FedEx, which are moving on cargo aircraft (CAO) only, but for those organizations using common carriers it adds yet another hurdle in the biomaterial cold chain.

While emerging markets across the globe offer significant advantages in terms of large populations, increased speed of recruitment, and cost, they also bring additional complexities to the drug development process. Staying ahead of regulations will help ensure temperature-sensitive biological shipments are not jeopardized during shipment. This is especially important today as the recent focus on molecular therapies, personalized medicine and biomarker discovery in medical research has placed an increased emphasis on quality samples.

Failure to reinforce all of the links in the cold chain can have serious ramifications for firms competing for market share, as a lost day in development is a lost day in the marketplace. As globalization continues and effective cold chain management makes its way to the forefront of life sciences, drug developers should remember one crucial point — a chain is only as strong as its weakest link.

### References

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