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Safe Transportation of Clinical Trial Samples

By Lori A. Ball

With the globalization of clinical research, the safe, punctual and compliant transport of study drugs and other sensitive materials is becoming increasingly complex. Two other trends are also increasing the demand for transporting sensitive materials. First, biotech companies are creating increasing numbers of large-molecule drugs, which are much less stable than most small-molecule drugs. Second, while blood, urine, microbiological and viral sampling has always been common, more and more tissue samples are being collected as biomarkers and for tissue repositories.

"Cold chain management" defines how temperature-sensitive materials are packaged, transported and stored throughout the clinical research process. Any weak link in the chain can compromise drug or sample integrity, breach security, delay shipments, and ultimately result in financial loss or liability. It is therefore vital for clinical trial materials to be packaged and shipped in compliance with industry and government standards and closely monitored by properly trained individuals.

To ensure compliance and diminish both financial and legal risk, study sponsors should take a holistic approach to cold chain management. Factors to consider include:

- Regulations and customs agencies
- Training and compliance
- Packaging and shipping controlled-temperature materials
- Labels and documentation
- Temperature monitoring
- International transportation

Regulations

U.S. Department of Transportation (DOT) Hazardous Materials Regulations (HMR) and International Air Transport Association (IATA) Dangerous Goods Regulations (DGR) specify requirements for the safe transportation of hazardous materials by rail car, aircraft, shipping vessel, and motor vehicles. 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 lack of compliance with HMR regulations.

Personnel should also be cognizant of customs regulations that may impede the transportation of biological materials. Due to possible delays in completing customs requirements, temperature-sensitive material may be consigned with a courier capable of replenishing refrigerant in the event of a delay. As much as three additional days' worth of refrigerant may be recommended for shipments in cases where customs clearance may be difficult.

Training and Compliance

DOT and IATA require organizations and individuals that ship or receive biological materials to undergo formal training to meet their standards in packaging, labeling, documentation, declaration, hazard assessment, and emergency response. Aside from the regulations,

improper packaging and handling are common causes of temperature deviations in clinical trial shipments. Proper training and qualification of all cold chain partners minimizes such problems.

Packaging and Shipping Controlled-Temperature Materials

Sensitive materials are transported in one of three states — frozen, refrigerated or controlled-ambient — through an unpredictable environment of hot and cold temperatures and shipping delays. Structural integrity, insulation and refrigerant (typically dry ice) are obvious elements of suitable packaging, but even the size of the package and the placement of contents are important. If the package is too large, excess air will enter and cause dry ice to dissipate too quickly. Validated packaging solutions, along with IATA- and DOT-approved packing techniques, exist to help safeguard materials in transit.

For dry ice shipments, first put a few inches of dry ice on the bottom of the carton. Then place the sensitive material (in the proper inner packaging) on top of the dry ice. Then add more dry ice around and above the sample until the carton is completely full. The use of dry ice nuggets minimizes air gaps. Note that, as the dry ice dissipates, the sample becomes free to shift around in the package. For liquid nitrogen shipments, the shipper must utilize properly validated dry shipper canisters. Prior to packaging samples into dry shippers, they must first be properly charged in accordance with the manufacturer's instructions.

To avoid compromising the sample integrity of refrigerated biological materials that must be maintained at +2 to +8°C, packaging must be properly pre-conditioned before shipping. To do this, the temperature-control refrigerants inside the shipping carton need to be brought to the specified temperature approximately 24 to 48 hours before packing, depending strictly on manufacturer guidelines. Once the refrigerants are pre-conditioned and placed inside the shipping carton, the carton should rest for one to two hours to ensure that the payload compartment reaches the desired shipping temperature. The payload compartment can then be filled.

Labels and Documentation

DOT and IATA standards for labels and documentation vary by hazard class. Shipments classified as infectious substances must include an itemized list of contents enclosed between the secondary and outer packaging. A completed Dangerous Goods Declaration Form must also be attached to Category A infectious substance (e.g., Bacillus anthracis and Hepatitis B cultures) shipments to avoid shipping delays and the corresponding risks to product integrity. Dry ice, for example, is classified by DOT and IATA as a miscellaneous hazard, class 9 material. As a result, specific procedures must be followed when packaging and shipping materials with dry ice.

In-transit storage conditions, as well as warning statements or content identifications, should be stated legibly on the label. Labels must clearly state that the materials inside are to be transferred to a specified storage temperature immediately upon receipt.

Temperature Monitoring

Temperature indicators typically consist of chemically treated pieces of paper that record the minimum and maximum temperature experienced by the payload. When stringent and detailed tracking is required, reusable data loggers can be placed inside the packaging to monitor temperature and time continuously. This data can be downloaded for graphing, reporting and inclusion in audit trails. If a temperature excursion outside the required range occurs, it must be evaluated and documented. Any corrective action should be promptly

implemented and documented. Clear directions should be provided to the recipient for the evaluation or disposition of the indicators and package contents, depending on the sensitivity of the material or any requirements to prove material stability during transport. In some cases, the material may still be viable, while in others, it must be destroyed, or laboratory analysis may be required to determine disposition.

International Transportation

Shipping across international borders adds complexities above those of domestic transport. Each country has its own regulations, codes, policies, procedures and customs that affect international shipments.

Customs personnel protect their country's population from hazards like infectious materials. They also enforce laws that govern import and export tariffs, quotas and other economic policies to generate revenue and protect local industry.

To protect sample integrity, regardless of the temperature requirement of the samples, study sponsors must ensure that the transportation companies have the ability to maintain the required temperatures while shipments pass through customs and other government formalities.

To help ensure that customs and government formalities are expedited, it is advisable to send copies of all required documentation to the consignee (recipient) prior to shipment for verification and approval. Prior approval of required documentation can help avoid long delays and even possible confiscation.

Shipping within the United States has its own complications. For example, in 2007, Congress mandated that by August 2010, all cargo transported on passenger aircraft must be 100% screened for explosives. These regulations do not apply to shipments on cargo aircraft, but they could in the future. If a cargo plane is delayed, packages could be transferred to a passenger aircraft, which would trigger the screening requirements.

Conclusion

A global clinical trial in 10 countries needs to manage at least 10 cold chains, and probably many more if there are outbound and inbound shipments through multiple border crossings and transshipment points. Packaging, labels, documentation and temperature monitoring vary for different materials, destinations and routes.

Fortunately, developing countries are improving their infrastructure and becoming more familiar with the needs of temperature-sensitive materials. For instance, the ability to re-ice and/or maintain refrigerated temperatures is becoming easier across the globe. Furthermore, by partnering with the logistics industry, life sciences companies today are more knowledgeable about transportation regulations and cold chain best practices. While once an afterthought, logistics now plays a critical role in the clinical research process. It requires not only a profound understanding of shipping and warehousing, but demands adherence to compliant processes and constant awareness of changing regulatory guidelines.

A cold chain is only as strong as its weakest link. A single broken link anywhere in the world for any shipment can have serious ramifications for a pharmaceutical or biotech company.

Author

Lori A. Ball is Senior Vice President at BioStorage Technologies, a dedicated biorepository service provider that stores, ships and manages temperature-sensitive biomaterials for

pharmaceutical and biotechnology firms worldwide. Contact her at 317.390.1866 or Lori.Ball@biostorage.com.

