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New Strategies to Increase Clinical Trial Throughput and Reduce Cost

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The pace at which clinical trials are expanding outside the U.S. and into more emerging regions is staggering. Growth in the number of biologics in development, along with lower overall trial costs and access to more diverse patient populations in emerging markets, are contributing to the trend. While international trials offer a number of advantages, companies face numerous challenges when it comes to the transport of investigative drugs and temperature-sensitive samples, including varying regulations, customs delays, required permits, and underdeveloped logistics sources. Organizations like the Parenteral Drug Association (PDA), World Health Organization (WHO) and the United States Pharmacopeia Convention (USP), along with regulatory bodies, are working to address some of these challenges by setting guidelines that aim to standardize distribution practices for pharmaceutical products and study specimens.

In August 2011, PDA released a pair of Technical Reports (TR) – TR-52 on "GDPs for the Pharmaceutical Supply Chain" and TR-53 on "Stability Testing to Support Distribution of New Drug Products" signaling a significant and long overdue step in establishing a more harmonized set of standards for shipping temperature-sensitive drugs and samples. Prior to the release of reports like these, distribution practices have varied greatly from country to country and from company to company. TR 52, which lays out the PDA's expectations for distribution of pharmaceutical products, and TR 53, which defines a "stability budget" concept for ensuring appropriate shipment and storage of temperature-sensitive products, are helping promote a change within the industry that will have a tremendous impact on clinical trial shipping now and in the future.

As a result, new processes and technologies are being developed to comply with these guidelines and assist manufacturers in assuring that quality, integrity, and efficacy of the product are not compromised in the distribution channels. With a number of changes in process expected to abide by these rules, the industry will require additional technology and outsourcing help to put these new recommendations into action.

Trends Impacting Shipping in Clinical Trials

According to ClinicalTrials.gov, there are more than 100,000 trials currently underway in North America and Europe, while close to 40,000 trials are taking place outside of those regions.[1] This translates to an increase in the number of studies involving temperature-sensitive materials being distributed to labs around the world. In fact, the annual market for shipments at or below freezing (0 degrees Celsius) is estimated at more than four million shipments globally.[2]

The PDA's new guidance for GDPs describes its recommendations regarding shipping temperatures and the stability studies needed to address the risks that face drug products during distribution, stating that "pharmaceutical products must be transported in a manner that ensures products will be maintained within an acceptable temperature range."[3] Another key quality component the PDA addresses is regarding the monitoring of these products. It states that "continuous monitoring with calibrated temperature recorders or other devices and/or an active, qualified monitoring system with automated alarming mechanisms to notify of temperature excursions as they occur should be present at all times."[4]

As studies become more global, temperature control and stability during shipping is growing increasingly important and is being seen in earlier phases of drug discovery. For example if phase 2 of a trial does not comply with GDP, then it may impact later phases as well. The complexity of the pharmaceutical supply chain coupled with new regulatory requirements and industry best practices around more complete temperature data create a challenging distribution environment for global frozen shipments.

Most companies recognize that reliability and integrity in the cold chain are important, however, it can be challenging to stay on top of the permits required, customs compliance and the types of packaging needed to give longer, reliable holding times and better stabilities in temperatures. In emerging markets like the Middle East and Asia, the infrastructure needed for typical means of transport are simply not an option for biologics. To stay ahead of the curve, companies are increasingly relying on CROs, central labs and other third party sources to guide them on regulations when shipping to these regions.

Challenges with International Studies

Clinical researchers face a number of challenges when conducting trials abroad, particularly when it comes to shipping temperature-sensitive samples internationally. These challenges include maintaining cell viability and temperature stability in transport, clearing customs in a timely manner, avoiding the risk of counterfeit drugs, and keeping shipping costs down.

- Viability in transport

A paper published in the proceedings of the 6th World Congress of Biomechanics indicates that only 0.1% of the cells obtained from an established cell bank kept at 2 to 8 degrees Celsius and packaged for immediate use, actually survived after 24 hours at that temperature and after vibrations simulating transportation.[5]

While not easy to control, maintaining the viability and integrity of fragile biological materials, like cells or samples, in transport is critical as it can mean the difference between a trial continuing on or being cancelled. Temperature excursions that occur during the storage, handling or distribution process can cause a variety of serious problems for the biologics supplied to a clinical trial, including:

- Unsafe products being administered to patients;
- Increased liability from lack of compliance with global regulatory requirements;
- Inconsistency of results between and within batches;
- Increased complexity and costly delays from shipments being rejected by a quality assurance department

Not only is it essential that materials used in clinical trials stay at a stable temperature, but that there is a record that stability was maintained throughout the entire distribution chain.

- Security

As the pharmaceutical supply chain expands worldwide, so does the problem of counterfeit drugs. More than 80 percent of the active ingredients used in U.S. pharmaceuticals are manufactured overseas. In developing regions like Asia and Latin America, as many as 30 percent of the drugs sold there are fake and in India, that number is 20 percent according to the World Health Organization.[6]

Diverting shipments is one method counterfeiters use to obtain drugs. Fortunately, new technologies such as 2D bar codes and QR codes, anti-counterfeiting and brand protection technologies are becoming more widely available to help curb the spread of counterfeit drugs by monitoring and documenting the temperature inside the packaging to determine when and where a package was opened, and for how long, so shippers can detect and act on any security breaches in each shipment.

- Customs Delays

Samples sent overseas are subject to importation and custom inspections, putting them at an increased risk for temperature excursions. It is therefore essential that fragile materials like samples and cells clear customs in a timely manner. According to the PDA, it is critical to coordinate shipments throughout the supply chain to ensure proper timing for products to be transported and received with regard to holidays, weekends or other forms of interruptions, including customs-related delays.[7] The PDA's TR 52 report includes import/export compliance among the seven pillars of GDPs, however specific guidance is still under development.

Dry ice is regulated as a dangerous good (DG, HAZMAT) and International Air Transport Association (IATA) packing instruction 904 (IATA PI 904) requires that it be properly identified in documentation, markings and labeling. Almost all airlines and couriers limit the amount of dry ice that can be taken on board because of concerns of CO2 buildup in the cargo hold, thus causing delays in transport. Such inevitable, but unpredictable, delays require "re-icing" and put specimen/product integrity at risk. While dry ice can be added during transit to help maintain a stable temperature, adding the appropriate amount without exceeding carrier restrictions or increasing the packaging weight can be difficult to predict and is often cost-prohibitive.

- Shipping Costs

Clinical trials are often constrained with three to four-day weeks because of concern over shipping on weekends with dry ice. That's because dry ice is reliable for only two to three days before risk of temperature excursions or need for re-icing. Temperatures below the glass transition point (Tg) of water solutions (approximately -136 degrees Celsius) are recognized as necessary to stop biological activity, including the biochemical reactions that would lead to cell death. At atmospheric pressure, dry ice sublimates at -78.5 degrees Celsius and consequently does not provide the temperature required to assure the cessation of cellular activity. This can cause tissue samples to degrade and lose viability, and drugs to lose potency, experience shortened effective lifespans or metabolize and become harmful, depending upon the compound.

As a result, overnight shipping is often selected for shipments to avoid the risk of temperature excursions. Compounding the problem are the costs associated with HAZMAT training, insurance

and documentation, monitoring and tracking, re-icing over long hauls or unanticipated delays, all of which are often underestimated.

The Answer: Dry Vapor Shipping

Advanced cold-chain technologies, like dry vapor liquid nitrogen shippers, have recently entered the scene to improve the integrity and reduce some of the risks associated with global frozen shipping.

Benefits of Dry Vapor Shipping

Dry Vapor shipping solutions provide many benefits, including:

- Making it easy for drug trial facilities to organize, manage and gather bio samples from around the globe for testing and valuation at a fraction of the cost, time, hassle and risk of dry ice.

- Eliminating the need for DG or HAZMAT documentation, labeling or extensive HAZMAT training or facilities.

- No restrictions by airlines or couriers due to the ability to maintain a stable temperature below -150°C for 10 days to ensure there is no degradation in tissue samples, cord blood, stem cells or other biologics shipped.

- The ability for clinical sites to consolidate their dry vapor shipping activities. Clinical sites using dry-vapor shipping solutions have a time, flexibility and ultimately cost savings advantage by being able to prepare one or two shipments per week, rather than daily.

The Cryoport Advantage

With guidance for improved distribution practices in the pharmaceutical supply chain in place from PDA and others, the industry requires more innovative technology and logistics expertise to enable the delivery of temperature-sensitive biomaterials in an increasingly complex and time-sensitive global environment. Cryoport has developed a complete solution to address the challenge of shipping biological materials, such as vaccines, cell lines, and specimens, under frozen storage conditions to mitigate temperature excursions and support good distribution practices. This offering that includes dry vapor liquid nitrogen shippers, improves the integrity during transportation and reduces the risk associated with global frozen shipping.

Through a comprehensive frozen cold chain shipping program, which combines a state-of-the-art web portal for a time-saving, hassle-free process with a proprietary dry vapor liquid nitrogen container, Cryoport makes the transport and logistics of sending biological materials easier and more reliable compared to traditional dry ice methods. Its turn-key shipping process uses a new dry vapor container technology that maintains -150 degrees Celsius temperatures for 10 or more days and provides an environmentally-friendly alternative to the current hazards and waste created using dry ice shipping methods.

Now life science companies can outsource the transport logistics to a single company that has both the technical understanding for the requirements of frozen transport and the logistical connections to make it happen in a cost-effective way by offering:

- *Convenient Web-based Ordering and Tracking:* A 24-hour/7-day, web-based order entry and global tracking and monitoring system that allows clients to request a shipment and then follow its progress as it travels from the point of origin to the destination. The Cryoportal™ automates the entry of orders, prepares customs documentation and facilitates status and location monitoring of shipped orders while in transit. This secure client application runs in a normal web browser requiring no software installation.

- *Safe Stable Temperature throughout Transport*: Cryoport's custom-built dry vapor shipper is an aluminum cryogenic Dewar that uses liquid nitrogen (LN2) and is validated to maintain a stable temperature below -150 degrees Celsius for a 10+ day dynamic shipment, which is critical to reducing risk of biological degradation during long holding times. Because of this ability, the Cryoport Express is the safest shipping method for minimizing degradation or loss of viability because it virtually eliminates sample and cell loss that can occur with temperature excursions due to long holding times and materials such as dry ice sublimating.

  Cryoport's shock-absorbing package also reduces cell membrane-disruptive vibrations, delivering cells in the same condition as when they were placed in the shipper. The container is designated as a "dry shipper" because its proprietary design results in the LN2 being fully absorbed in the material that surrounds the specimen chamber. Cold vapor emanating from the liquid nitrogen entrapped within the foam retention system provides cooling for 10 or more days, eliminating the need for intervention and "re-icing" on long haul and cross border shipping lanes. The foam retention system fully absorbs the liquid nitrogen preventing any spilling regardless of orientation. Even when tipped on its side, the liquid nitrogen remains entrapped in the foam and the specimen cylinder stays dry.

- *Temperature Monitoring throughout Transport*: Similar to a chain-of-custody where the person/s and/or party responsible for a drug product at any given time are recorded, Cryoport provides a chain-of-condition so scientists can ensure that their samples and cells were maintained in a frozen state throughout the entire cold chain from the clinic to the laboratory for testing. Unlike conventional data loggers that might measure the temperature of the box, Cryoport's data logger ensures an accurate measure of specimen temperature exposure because the sensor is placed directly in the specimen chamber. The data logger can be set up to report during the shipment and/or after the shipment. For those shipments involving biologics, clinical trials or any other material that needs to be verified before receiving, the data logger can be pulled out and downloaded to the data station. After the shipment, the data logger is automatically removed for data download and analysis.

- *Resource Optimization*: Because Cryoport's dry vapor shipper maintains -150 degrees Celsius for at least 10 days, packages can ship over weekends or holidays safely, without re-icing, enabling researchers to maximize their investment in analytic labs and personnel as well as add days to sample collection. Now patients can be taken 5 days a week, adding 25 percent or more to the trial throughput and significant cost savings.

- *Unmatched Security*: By monitoring and documenting the temperature inside the dewar, Cryoport knows when and where a package was opened, and for how long, so shippers can detect and act on any security breaches in each shipment.

- *Carrier Partnership Programs with Global Resources & Customs Expertise*: Cryoport works with teams to ensure that the correct documentation and descriptions are on every package. If a package is delayed, Cryoport has established partnerships with major transportation companies, like FedEx and DHL, and can work with its shipping partners to get it cleared, even walking it through customs, if necessary.

- *Reusable, Non-Hazardous Dry Shipping Containers:* The Cryoport Express® dry shipper, which uses liquid nitrogen, not dry ice, as the refrigerant, is part of an end-to-end delivery service. By using the solution, clinical researchers eliminate having to manage packaging inventory, insulated boxes or environmentally harmful waste products or the handling of hazardous dry-ice. When the delivery of biomaterials is complete, the dry shipper is returned to Cryoport to be recharged and reused. This simple design allows Cryoport's proprietary container to be designated as a "dry shipper" and to meet International Air Transport Association ("IATA") requirements, including the stringent Packing Instructions 602 and 650, defining internal pressure and drop-performance requirements.

To learn more about how Cryoport's frozen cold chain shipping program and solutions can increase your trial throughput and cost savings, visit www.cryoport.com or call 949.232.1900.

REFERENCES:

[1] ClinicalTrials.gov, http://clinicaltrials.gov/ct2/search/map
[2] *Pharmaceutical Commerce Magazine*, "New Study Sees Double-Digit Growth in Cold-Chain Services for Life Sciences," by Nicholas Basta, April 30, 2010
[3] *Technical Report No. 52*: *Guidance for Good Distribution Practices (GDPs) for the Pharmaceutical Supply Chain*; Parenteral Drug Association: Bethesda, MD, 2011.
[4] *Technical Report No.* 53: *Guidance for Industry: Stability Testing to Support Distribution of New Drug Products*; Parenteral Drug Association: Bethesda, MD, 2011.
[5] 6th World Congress of Biomechanics (WCB 2010), by James Goh Cho Hong, August 1 – 6, 2010, Singapore
[6] *Forbes*, "PharmaSecure Uses Mobile Device And ID Codes To Take On Counterfeit Drug Problem," by Jennifer Hicks, February 16, 2012
[7] *Technical Report No. 52*: *Guidance for Good Distribution Practices (GDPs) for the Pharmaceutical Supply Chain*; 3.2.6: Product Disposition and Distribution, pp. 8-9; Parenteral Drug Association: Bethesda, MD, 2011.