Challenges in International Shipping

Shipping pharmaceuticals from a Canadian winter to an Argentinean summer is one of the sublime packaging challenges. As clinical trials expand globally, as biologics enter the market and as temperature-sensitive vaccines are commercialized, the hurdles only escalate. Governments throughout the world recognize the challenges and are responding with new distribution guidelines that incorporate temperature monitoring and data logging, often along with track-and-trace or serialization guidelines.

Increased Need for Temperature-Controlled Shipping

Likewise, as cell-based regenerative therapies advance through the clinic and into commercialization, cold chain utilization increases. Regenerative therapies will increase as the global population ages. In the process, regenerative medicine is poised to transform health care. According to Gil Van Bokkelen, chairman of the Alliance for Regenerative Medicine and CEO of Anthersys, speaking at the Biotech Showcase 2012 workshop on regenerative medicine January 10, 2012, “Regenerative therapies could save $250 billion per year in the U.S. alone.”

In a recent research report, Transparency Market Research detailed global industry trends from 2013 to 2019 for the regenerative medicine market (bone and joint), the market is estimated to reach USD 6.5 billion in 2019, growing at a CAGR of 12.8 percent from 2013 to 2019. A report by TechNavio, forecasts growth at a CAGR of 20.16 percent over the period from 2014 to 2019. And today, cancer immunotherapy drugs have captured nearly 50 percent of the overall oncology drugs market, generating about USD 41.0 billion in 2014 alone.

The global growth in clinical trials is also spurring the growth of the pharmaceutical cold chain. ClinicalTrials.gov indicates that 211,437 trials are ongoing globally. Of those, 21.5% percent are being conducted outside the U.S., Canada and Europe. Tufts University reports notably smaller numbers, but agrees with the trend. That number is growing continually, as companies move clinical trials to India, China, Brazil and other regions.

Increased Regulation

Against that background, regulatory bodies and industry organizations are framing new guidelines governing the distribution of temperature-sensitive pharmaceuticals and clinical trial materials. Guidelines relating specifically to the cold chain are in place in Argentina, Australia, Austria, Bahrain, Brazil, Canada, China, The Czech Republic, Egypt, the EU, India, Ireland, Italy, Jordan, Mexico, Romania, Singapore, Saudi Arabia, South Africa, South Korea, the United Arab Emirates, the United States and Venezuela. The Food & Drug Administration, the Parental Drug Association, the U.S. Pharmacopeia, the International Air Transportation Association and other organizations also have established guidelines for the transportation of temperature-sensitive life sciences products.

Increased Temperature Monitoring

Despite slight differences in the guidelines, they all typically call for data logging, temperature monitoring and, sometimes, humidity monitoring. Saudi Arabia (http://www.sfda.gov.sa/En/Home) for example, requires temperature monitors and data loggers on all products that are sensitive to temperature changes. The Saudi Food and Drug Authority (SFDA) notes that some data loggers may be turned off when Saudi authorities open the package, and recommend using two data loggers in packages marked for random opening. Other data loggers, like those used by Cryoport, continue monitoring temperatures inside the specimen chamber every five seconds until the package is returned to Cryoport. That not only assures shippers that temperatures were maintained, but provides a record of when and where the dewar was opened.

Cryoport's data station enables clients to download temperature and condition information about a shipment to their desktops, allowing condition confirmation before shipments are accepted and verification of multiple touchpoints during the shipment. A report detailing conditions throughout transit is generated when the shipment reaches its destination. Such chain-of-condition documentation is a valuable adjunct to chain-of-custody validation, supporting claims that a specimen, sample or therapeutic was maintained at cryogenic temperatures throughout shipment.

A temperature-based data logger also alerts shippers to potential tampering. Because the temperature probe is inside the specimen chamber, a temperature spike is recorded whenever that chamber is opened. Then, when that data is compared with carriers' transportation records, shippers know when and where the breach occurred. This type of security, along with documented temperature maintenance, is among the chief concerns of regulatory bodies and transportation specialists as they develop and implement cold chain governance regulations.

The guidelines are driven, at least in part, by concerns for patient safety. In India, for example, the number of children who died because of immunizations has climbed from 111 in 2008 to 128 in 2010, according to India's Union Health Ministry. The logistics industry speculates that poor cold chain practices caused the increase.

For vaccines and biologics in particular, temperature is critical, and temperature excursions can dramatically decrease shelf life, reduce potency and in some cases harm the patient. Heat exposure can reduce stability for live attenuated cholera and typhoid vaccines, for example, from one year at 2-8° C, to 7 days at room temperature (20-25°C) and a mere 12 hours at 37°C. Some other therapeutics are equally sensitive. For them a temperature excursion could doom a small trial to failure, thwart further research and potentially harm patients.

Shift from Dry Ice to Dry Vapor

Experience shows that with a global supply chain and a global marketplace, dry ice may be insufficient to safeguard temperature-sensitive products. Although dry ice shippers have been in service since the 1960s, they can only hold a temperature of about -80C° for two to three days. Long hauls or diversions require re-icing in route. For today's emerging products and clinical samples, colder temperatures and longer hold times are preferred.

To get those lower temperatures and longer hold times, many shippers turned to liquid nitrogen. Although it kept samples at -150° C, the initial packaging materials leaked. Advanced phase change packaging technology has resolved that challenge by sequestering liquid nitrogen in foam-like material that holds the liquid nitrogen without leaks. Now, regardless how the package is situated, it will not leak. Cooling occurs as the liquid nitrogen changes phase into a gas, maintaining a constant -150°C. Cryoport's dry vapor shipper holds that temperature in the dewar for 10 days or more.

That lengthy hold time allows the shipment to reach the country, clear customs and be delivered even to rural areas without temperature excursions that can damage or even destroy valuable specimen, therapeutics or samples. The technology also avoids the expense and inconvenience of re-icing. Consequently, shippers can send vaccines and cell therapies into remote locations and can get clinical samples out safely, without compromising viability.

Challenging Shipping Lanes

As the life sciences industry expands into emerging markets, infrastructure challenges become increasingly significant. Whether airports have cold storage facilities and personnel trained to actually transport temperature-sensitive shipments to the proper temperature-controlled holding areas can make the difference between success and failure for dry ice shipments.

Likewise, customs inspectors' familiarity with accepted handling procedures for life sciences product inspections is also important. Additionally, improperly labeling the shipment may delay customs clearance. China, for example, has strict controls regarding the movement of human cells, and how they are labeled matters. Cryoport helps minimize customs delays by working with our network of global carriers to stay current with regulations throughout the world. Our network knows the regulations for the countries we serve, and knows when something changes. Therefore, our clients gain the benefit of our global logistics expertise as well as our own significant experience in the life sciences industry.

Challenging Infrastructure

The challenges extend beyond clearing customs. Developing markets generally have inadequate transportation infrastructures as well as security issues and bureaucracies with sometimes unique interpretations of regulations. Although the infrastructure in and around the major cities may be substantial, it generally does not extend throughout the country, logistics experts say. Moving product from the airport to the customer over an often underdeveloped highway system may cause delays that require dry ice shippers to re-ice or risk temperature excursions.

Advanced deep frozen packaging technology helps overcome these challenges. Cryoport's network of carriers and specialty couriers know their markets and can create solutions based on their knowledge of transportation lanes, best practices and local customs to maximize safety and security and minimize costs. Our partners include some of the world's largest carriers, who are now applying their depth of knowledge to life science shipments.

As shippers become more familiar with the capabilities of deep frozen packaging and liquid nitrogen dry vapor shippers in particular, they are identifying opportunities throughout their supply chain. For developers, the ability of the cryogenic packaging to maintain -150° C temperatures for 10 or more days enables clinical trials to occur throughout the world. Consequently, developers can access treatment-naïve populations for trials and also reach populations with great needs, which often are considered orphan conditions in industrialized nations.

Opening New Markets

Accessing a global population also provides drug developers with the genetic variability that otherwise only comes after commercialization, in post-marketing studies. Conducting trials in emerging therapeutic markets lowers clinical trial costs while providing advanced medications to underserved populations, thus helping them live healthier lives.

Trials, regardless of where they are conducted, remain expensive. As personalized medicine advances and as drug developers devote more attention to orphan diseases, trial sizes necessarily shrink. One failed shipment, if undetected, could sabotage a trial and cause an effective drug to be abandoned before completion. Liquid nitrogen dry vapor shipping, therefore, provides assurance that materials used in trials arrive in the same condition in which they left, thereby minimizing the risks of trial failures because of improper cold chain handling.

This technology also expands the potential pool of physicians willing to participate in clinical trials. Because the dewar can be used as a temporary freezer, physicians can collect patient samples throughout the week, store them in the dewar and ship them together in one or two weekly shipments. For patients, this enhances their ability to access cutting-edge therapies and provides the assurance that samples — sometimes taken painfully — arrive at the lab in viable condition.

Applying advanced liquid nitrogen dry vapor technology allows life sciences organizations to reach clinics and patients that previously were beyond their reach. And, just as importantly, it ensures that therapeutics, samples

and specimens arrive in the same condition as when they were packed, with temperatures monitored throughout the shipment with a data logger inside the specimen container. This holistic approach to good distribution practice is being embraced by regulatory bodies globally to help solve some of the ongoing challenges in global frozen shipping.

To find out how you can better navigate these challenges and to find a logistics partner who also offers customs and documentation expertise, visit cryoport.com or call +1 949.232.1900.