Logistical Nightmare

Having a huge impact on the success of clinical trials, the shipment of temperature-sensitive pharmaceuticals is a highly complex task, to say the least. By providing controlled facilities, coupled with technological advances in dry vapour packaging and tracking, it is possible to facilitate this complicated process

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Many of the most innovative therapeutics, like regenerative medicines and other advanced cell-based therapies, need to be shipped under very exacting temperature conditions. As companies plan their clinical trials, it is critical to understand the value equation of logistics planning and risk mitigation, the impact of cold chain transportation on biotherapeutic clinical trial results and data integrity, and the regulatory landscape. This article will address considerations in planning cold chain logistics strategies for the successful execution of clinical trials.

Regenerative Medicine

The current focus of regenerative medicine includes cell therapies, tissue engineering and biomaterials, gene and gene-modified cell therapies, and genome editing therapies – all of which require a substantial investment of resources to develop and generate unique, high-value but extremely temperature-sensitive biological products. The risk involved in improper handling of these products is significant.

Regenerative medicine technology companies received about $6.3 billion in financing in 2014; meanwhile, major pharmaceutical companies are forming partnerships with regenerative medicine businesses as it becomes clear that some of these products will come to fruition in the near future (1). In the areas of cell therapy, tissue engineering and gene therapy, there are currently about 600 companies around the world working to bring products to market, with about 66 approved products (1). This means that most of these promising, emerging therapies are still in clinical trials.

The success of these trials critically depends on achieving and maintaining optimal performance conditions for these temperature-sensitive therapies throughout the trial and at all trial sites. Careful planning of all packaging, transport and storage steps, as well as strict adherence to planned processes, is required to make sure that delays and temperature excursions do not affect the quality of any of the materials transported in support of the programme – including the product – and, thus, jeopardise the results of the clinical trial. Manufacturers work very hard to produce high-quality products that meet exacting standards applied to every stage of the production process, and these standards should extend beyond the manufacturing site to the packaging, shipping and storage of valuable, life-saving products.

Packaging and Shipping Advances

For the conduct of clinical trials, there is significant risk associated with temperature excursions and other shipping factors that a clinical sample or product might encounter on its way to a testing or clinical trial site. A number of variables can affect the integrity of sensitive biological samples during transit, including packaging, preservation media, temperature cycling during shipping and transport, the courier chosen, freeze/thaw methodology, seasonal or regional temperature differences and regulatory/customs delays. Any of these can impact the quality and efficacy of the product and, therefore, the quality of data generated by the trial.

Shipping temperatures and preservation media have been shown to significantly affect the integrity of cells. Liquid nitrogen storage and shipment ensure greater stability and higher viability than dry ice shipment or ambient temperature transport media (2). Furthermore, samples shipped on dry ice may have pH fluctuations that could significantly change the activity and safety of the drug product (3).

Liquid nitrogen, although acknowledged as the gold standard for shipping sensitive biological medicines, is treated as a hazardous material, which requires specialised handling. However, developments in packaging technology have resulted in the design of dry vapour dewars that provide sequestered liquid nitrogen in a leak-proof matrix. The dewars extend the temperature stability of shipped materials to 10 days or more and eliminate the risk of temperature cycling. Also important is that this dry vapour shipping method allows clinical trial investigators and logistics managers to ensure their medicinal products are preserved during shipping without the need for hazardous materials documentation and shipping requirements, and without restrictions by airlines and couriers.

The dewars' additional stability also provides the assurance to confidently ship medicines to remote locations around the world or to ship by slower, but potentially more affordable, ground transport. Finally, the new technology allows for stable storage of patient samples at satellite locations prior to shipping to a testing site. This ensures that samples that may have been secured through painful means for the patient are not wasted through improper handling between clinical trial and laboratory testing sites.

Data monitoring is a critical aspect of the shipping process as well. Clinical trial investigators need to know where the product is during shipping, that the proper temperature has been maintained, and that the package has not been tampered with during transit. Specialised couriers that supply advanced software solutions to provide continuous product tracking and chain-of-custody validation are highly recommended to reduce risks associated with temperature excursions and tampering during product transit. The latest data loggers now provide not only temperature and environmental data – such as humidity and barometric pressure – and can tell if a package was dropped, but they can also provide the location of a package in real time.

Logistics Management

As more clinical trial therapeutics are being shipped to more patients in more countries than ever before, it has

Chain of custody	Companies need to have continuous information on the condition of the materials during shipment. One temperature excursion can impact product integrity
Security of the materials	Companies require assurance that the product has not been tampered with
Viability in transport	Advanced cell-based biologics and regenerative therapies should be transported using specialised shock-absorbing packaging to reduce cell membrane-disruptive shipment vibrations that could damage delicate cellular materials
Validation	It is important that manufacturers understand the validation and qualification processes employed to test the shipping containers used for their products. They need to have a formal quality process in place to make sure that shipping containers meet the necessary standards
Customs clearance	Shipping delays can occur if products are not handled properly as they move through the customs process; this can result in temperature excursions
Resource optimisation	Packaging that maintains temperature properly during shipping and movement through customs can allow for optimal use of personnel, while assuring product integrity
International regulations	It is important to understand how international regulations apply to the shipping of biological materials. Regulatory agencies in many countries have guidelines in place for transportation of temperature-sensitive life sciences products
Conditions in emerging markets	Some locations that are desirable for conducting clinical trials may not have appropriate temperature-controlled facilities and infrastructure for maintaining cold chain of biological materials
Transparent shipping process	It is important to know where the shipment is at every step of transport
Risk mitigation	Potential areas of risk must be identified and strategies developed to mitigate these risks in shipping/material handling/transport

Table 1: Challenges of cold chain logistics for clinical trials

become clear that cold chain logistics management is vitally important to preserving the safety of valuable biological medicines and to risk mitigation. Cold chain logistics cost $8.36 billion in 2015, and this number is expected to grow to $10 billion by 2018 (4). However, this is money well spent for clinical trial biological medicines that have no acceptable level of loss, and high stakes ride on the success or failure of new treatments. Maintenance of the cold chain for advanced cellular therapy trials requires well-designed cold chain management solutions that address all aspects of product transport and delivery to ensure maintenance of product quality and efficacy.

Unfortunately, most companies do not integrate logistics planning into their clinical trial design; it is often an afterthought once the product has been manufactured. Adding complexity – such as adding more links to a supply chain – increases the steps that have to be controlled and heightens the risk of a temperature excursion. Companies may grow without considering the increased complexity that this growth brings to fragile biologicals in their existing supply chain. In order to face these challenges, manufacturers must keep abreast of advances in cold chain technologies in order to ensure their products are being shipped with the highest possible safety and quality, and lowest possible risk of loss.

Although logistics will vary according to each company's geographic, product and staffing situation, there are some questions that logistics managers can consider when looking at a new clinical trial site:

- How many additional product movements will be necessary to access the new location?
- Is there access to transportation facilities with cold chain capabilities at the new site?
- Are there proximate access and global access cold storage capabilities that meet your product needs?

It can be difficult, expensive and time-consuming to untangle an existing supply chain that encounters growing pains and starts to show signs of failure. Because of this, the supply chain should be a major up-front consideration along with costs, taxes and talent when assessing the value of new clinical trial sites. Table 1 outlines a range of potential challenges that ought to be taken into account.

Regulatory Environment and Guidelines

As conduct of clinical trials globally becomes more common, regulatory

agencies are responding with guidance for companies that need to ship biological medicinal products internationally. Increasingly, this means shipping, transporting and storing valuable materials in places that might have limited transport infrastructure, or might be in tropical climates. Guidelines relating to cold chain management are in place in many countries around the world, including Argentina, Australia, Bahrain, Brazil, Canada, China, Egypt, the EU, India, Jordan, Mexico, Saudi Arabia, Singapore, South Africa, South Korea, Syria, the United Arab Emirates, the US and Venezuela.

These guidances are designed to protect the safety of patients through assurance that the product is not damaged or compromised during transport in a way that would impact the safety or efficacy of the drug, and to assist companies in documenting transport processes to ensure proper compliance. For example, information is available on how to control pathogens, reduce viral shedding, minimise product degradation, and avoid inappropriate freezing/thawing and damage to packaging that might delay shipments or block customs entry.

Many companies that seek to run clinical trials in which they have to ship materials to various sites or countries are relying on specialised shipping services that understand their needs and the regulations at both local and international levels.

Air Transport and Storage

The importance of cold chain management and the opportunities provided by this growing need have been recognised by airlines and cargo companies around the world. The International Air Transportation Association (IATA) has published internationally approved guidelines for shipping cold chain pharmaceuticals by air, and IATA's Centre of Excellence for Independent Validators in Pharmaceutical Logistics (CEIV Pharma) has developed a certification programme to train and certify handlers in cold chain management. Brussels Airport, Belgium, has just become the first European hub for pharmaceutical freight using the IATA certification programme. Designated workers at Brussels Airport have undergone training, and local freight handlers are encouraged to do so, too.

In Singapore, Singapore Airlines' cargo division operates the Coolport, a purpose-built air freight terminal that handled the transport of 15,200 tonnes of pharmaceuticals last year in its CEIV Pharma- and Good Distribution Practice-validated facility. The Coolport provides temperature monitoring and cold rooms with various temperatures, and ships products to aircraft in on-tarmac coolers (4,5).

In the US, American Airlines' cargo division opened a 25,000-square foot temperature-controlled warehouse in 2015 for cold chain cargo at Philadelphia's airport that is the first of its kind. This "$5 million fridge" is close to Big Pharma companies clustered in the Northeastern US, and is also used for shipping products from Europe that go through Philadelphia on their way to South America. Cargo customers include pharma companies such as Teva, Pfizer, Merck, AstraZeneca, Novartis, Bayer and GlaxoSmithKline, who work with specialised shippers with experience in temperature-controlled shipping and cold chain logistics. American Airlines expects the logistics side of the pharma industry to grow by 25% in the next three years (6).

Necessary Tools

As regenerative medicine therapies move from the bench into clinical trials and finally to approval, the specialised needs of these highly valuable and temperature-sensitive biological materials require advanced technologies for cold chain management to ensure their safety and efficacy when they reach the patient. New dry vapour packaging technologies, advanced package tracking, temperature-controlled facilities and knowledge of international regulations can provide tools that clinical trial investigators and logistics managers need to reduce the risk of compromised clinical trial data due to cold chain logistics issues.

References

1. Lanphier E, Alliance for regenerative medicine, State of the industry briefing, January 2015
2. Kofanova OA *et al*, ISBER biospecimen science working group, Viable mononuclear cell stability study for implementation in a proficiency testing programme: Impact of shipment conditions, *Biopreserv Biobank* 12(3): pp206-216, 2014
3. Murphy BM *et al*, Protein instability following transport or storage on dry ice, *Nat Methods* 10(4): pp278-279, 2013
4. Burnson P, Cold chain: Mitigating risk in a topsy-turvy world, *Logistics Management*, October 2015. Visit: www.logisticsmgmt.com/article/cold_chain_mitigating_risk_in_a_topsy_turvy_world
5. Coolport, Singapore. Visit: www.siacargo.com/hub.asp
6. $5M fridge keeps airline cargo cold. Visit: http://articles.philly.com/2015-06-25/business/63787657_1_american-airlines-cold-storage-cargo-city

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