Developed by

PCI PHARMA SERVICES

In Cooperation with

Life Science Leader

LIFE SCIENCE CONNECT

COLD CHAIN, HOT TOPIC:

The Challenge and Opportunity of Distributing Temperature-Sensitive Biopharmaceuticals and Cell Therapies

A Q&A with Rachel Griffiths, Samantha James, and Rich Nelson, PCI Pharma Services

ABSTRACT

Distributing sensitive biopharmaceuticals and cell therapies is a complex challenge that calls for detailed understanding of the product, access to the latest technologies, and global reach combined with local knowledge.

INTRODUCTION

Pharmaceutical industry interest in biopharmaceuticals, cell therapies and, more recently, biosimilars has increased significantly[1,2]. In addition to targeting and treating disease more effectively than small molecule medicines, such products have the potential to generate higher revenues and are less likely to face competition when they go off patent[3,4].

However, unlike small molecule drugs, which can be easily transported, large molecule biopharmaceuticals are highly sensitive to temperature fluctuations and require special handling[5].

Large molecule drugs are also more expensive to develop and manufacture than small molecule products, which means any lost as a result of problems during transportation have a higher financial impact[6].

Similarly, transporting cell therapies is a challenge[7]. While hydrogel-based alternative technologies are being developed, the vast majority of cell therapies are still shipped as frozen stocks[8].

Failure to protect frozen cells against temperature fluctuations can be disastrous, particularly for autologous therapies derived from cells extracted from the patient.

Effective Cold Chain distribution requires knowledge of the product being transported. Everything from the physical characteristics of the molecule or cell and the temperature range over which it is stable to how it is packaged must be understood. The various touch points within the manufacturing, packaging, and distribution network also warrant considerable understanding to maximize the effectiveness of the successful end-to-end Cold Chain.

But beyond the product, other factors also need to be considered. Choosing the correct container and monitoring technology is vital, as is knowledge of the environmental conditions and customs procedures used at the destination.

A detailed understanding of the regulatory requirements is critical, as is having a courier network capable of ensuring the safe transportation of such high value shipments[9].

Q&A

Understanding the material being shipped is only the start of any Cold Chain project, according to Rachel Griffiths, Samantha James, and Rich Nelson from PCI Pharma Services.

In this Q&A, they explain that successfully transporting sensitive biopharmaceuticals and cell therapies also requires detailed knowledge of complex regulations, established relationships with reliable couriers, and the ability to choose the appropriate technologies.

Cold Chain, Hot Topic: The Challenge and Opportunity of Distributing Temperature-Sensitive Biopharmaceuticals and Cell Therapies

What are the first steps in distributing a biopharmaceutical or cell therapy?

Griffiths: Before we begin any Cold Chain distribution project and before any material arrives on site, we conduct a detailed technical review of the product. We ask the client to share information at the proposal stage to make sure we fully understand the temperature range involved.

James: If we win a proposal, the next stage is to prepare to receive the material, all the materials we receive are packaged in refrigerated conditions or utilizing cold plate technology under temperature-controlled conditions according to validated methods.

Additionally, because the materials we receive can be supplied by the developer directly or from a contract manufacturing organization (CMO), we make sure we engage with clients prior to receipt of the batches in order to develop a bespoke, on-site management plan.

What are the challenges involved in distributing biopharmaceuticals and cell therapies?

Griffiths: For clinical-stage products, how we distribute depends on information collected during the technical review. First we select the packaging and shipping technologies that are appropriate to the particular project.

To provide maximum assurance we test shipping technologies according to our own specifications, as regulatory requirements do not really put them under stress. Our tests are based on real-world experience.

We try to model temperature excursions to see if the technologies can cope. We also provide feedback to technology manufacturers to help guide development of new systems. All of these factors depend on the needs of the product, geographic distribution and trip duration.

The next stage is to identify the couriers we will use to transport the materials.

Nelson: Distribution of commercially approved biopharmaceuticals follows similar lines. However, one of the major differences from Cold Chain distribution for investigational trial materials is that the technologies we use need to be able to cope with larger shipments.

Another difference between clinical trial supply shipments and commercial shipments is the distances involved. In general, trial supplies only travel short distances to local trial sites. Commercially approved products are shipped over much longer distances and distributed to multiple sites. This means that for approved products we have to use systems validated to keep shipments at specified temperatures for longer. This involves accurate monitoring and reporting of data.

For example, we use a software system developed by TrakCel that takes a temperature reading every eight minutes during shipment. This generates thousands of data points that are fed back to customers. This technology can be integrated directly into our Webflow client portal, affording our customers significant supply chain visibility.

Also, echoing Rachel's [Griffiths] comment, most systems have time limitations. For examples, it is a significant technical challenge to keep a shipment at -20° C for three days, which is required by some biopharmaceuticals and cell therapies. We are collaborating with our vendor partners to develop shipping systems that can achieve longer time durations at the specified temperature conditions.

James: In clinical distribution, we are a testing a GPS (global positioning system) from Sensitech that is capable of precisely tracking the temperature and location of shipments in real time.

The pharmaceutical industry is continually trying to access new markets. What impact has globalization had on Cold Chain distribution?

Nelson: Globalization has made Cold Chain distribution more of a challenge. PCI uses couriers, and it is important that we know which organizations are strongest in each market. We actively engage with couriers to follow how they are extending their reach in emerging markets and maintain this information in a database.

Temperature controlled products require end-to-end verification to assure safe medicines are delivered to patients.

It is also important to understand the rules and regulations in the country to which a shipment is being sent. Making sure a shipment passes through customs efficiently and is not impounded is always important; however, it is vital for temperature-sensitive biopharmaceuticals and cell therapies.

A biopharmaceutical shipment left sitting in Customs for two weeks will be ruined, regardless of the technology used. Ensuring paperwork is correctly completed to prevent shipments being impounded is vital. We use a hands-on approach to achieve this, utilizing our own expertise in global shipping as well as diligently working with local agents to gather real time information that is maintained in our global shipping database. To minimize the impact of a Customs delay we pre-clear shipment paperwork prior to dispatching the product, this ensures any questions are clarified and resolved before the product is transported.

James: *More and more clinical trials are being conducted in countries whose airports lack cold storage facilities.*

Knowing, for example, that there is no cold storage capacity at airports in Jordan, Sierra Leone, or Liberia ahead of time is vital. It allows the selection of appropriate shipping technologies, local couriers with capacity, or even the identification of alternative supply routes. Adaptability is very important.

Nelson: *It is important to be able to tailor distribution to specific needs. Sometimes we are called on to really go above and beyond. We once went to the extreme of chartering a plane capable of maintaining a temperature of 2° C to 8° C, as it was the only way of distributing a particular shipment.*

How complex are the regulations that cover Cold Chain distribution of biopharmaceuticals and cell therapies?

Griffiths*: Good distribution practice (GDP) standards are clear and well established. That said, rules governing shipments vary country-to-country. They also change regularly, and, although we track these changes, it is an ongoing challenge to keep up to date in all markets.*

Nelson: *We have had instances in which regulations in place when a shipment left had changed by the time it arrived. We focus on reacting to changes as fast as possible both through our own information gathering and by working with leading third party experts like leading third-party specialty couriers.*

What regulatory pressures and market dynamics are going to impact biopharmaceutical and cell therapy in the future?

Nelson: *From the point of view of investigational medicines, pharmaceutical companies are looking to break away from the traditional distribution model and reliance on a large depot that feeds satellite hubs. Now the preferred model is to ship directly from a central location for reasons of cost and audit burden reduction.*

Whether temperature-sensitive biopharmaceuticals or cell therapies can be shipped using a direct approach remains to be seen. In my view, pharmaceutical companies are going to increasingly rely on distributors with well-placed, temperature-controlled depots located in key markets to ship such products.

Direct-to-patient shipping is another area of emerging demand. The approach has clear application in the field of personalized medicines, particularly for autologous or patient-derived cell therapies. Again pharmaceutical companies are likely to outsource a lot of this type of work, as, in the U.S. and a number of other key markets, sending medicines direct to patient requires an organization to be registered as a pharmacy.

James: *The challenge for Cold Chain distribution of clinical-stage biopharmaceuticals and cell therapies is the global spread of trials.*

Pharmaceutical companies' desire to access treatment-naïve patients and accelerate recruitment means conducting research in regions where research has not been conducted before. Such countries usually lack Cold Chain distribution infrastructure, which means shipping trial supplies relies on local

PCI offers a robust supply chain solution for temperature-controlled products including Cold Chain packaging as well as storage and distribution.

Cold Chain, Hot Topic: The Challenge and Opportunity of Distributing Temperature-Sensitive Biopharmaceuticals and Cell Therapies

couriers with sufficient capacity. PCI's relationship with specialty couriers gives us a head start in many emerging clinical research hubs.

Griffiths: *Speaking more generally about Cold Chain biopharmaceutical and cell therapy distribution, pharmaceutical companies are looking for contractors that provide a full range of services, from clinical-to-commercial.*

Clients value the ability to provide storage and distribution capacity across the full range of Cold Chain temperatures — 2° to 8° C, -20° C, -40° C and -80° C — and the adaptability to cater to therapies requiring conditions outside this range. PCI offers bespoke solutions and we recently constructed an entire facility to accommodate a client's specific needs and supply chain requirements.

Global reach is also a key differentiator. Pharmaceutical companies are increasingly keen to access new markets which, for temperature-sensitive products, means relying on a contract with Cold Chain capacity in hot markets and the ability and local contacts to access emerging markets. PCI supplies products destined to over 100 countries around the world.

The final factor that is going to determine the success of future biopharmaceutical and cell therapy Cold Chain distribution projects is technology. Innovation in Cold Chain distribution is constant, and access to novel technologies through relationships with developers is key to improving efficiency of the process.

REFERENCES

1. www.nature.com/nbt/journal/v27/n3/full/nbt0309-293.html
2. www.bioprocessintl.com/manufacturing/biosimilars/an-analysis-of-the-us-biosimilars-development-pipeline-and-likely-market-evolution-343790/
3. www.future-science.com/doi/pdf/10.4155/ppa.12.34
4. http://content.healthaffairs.org/content/25/5/1353.full
5. http://deutsch.sensitech.com/assets/articles/lsbisharaapr.pdf
6. www.hrpub.org/download/20131107/AEB3-11801011.pdf
7. www.ncbi.nlm.nih.gov/books/NBK208660/
8. www.bbsrc.ac.uk/documents/hydrogels-pdf/
9. www.emeraldinsight.com/doi/abs/10.1108/09600031111147835

Emerging technologies for cell therapy require infrastructure and specialized procedures to support temperatures down to -196° C. PCI offers ultra-Cold Chain expertise at sites in Europe and the United States.

Rachel Griffiths

Rachel Griffiths, Associate Director, Technical Services, PCI UK. Rachel joined the company in 2004 and has held leadership roles in Operations and Technical Support. Her current role involves overseeing the installation and validation of new facilities at the company's Bridgend site and the implementation of new technologies and innovations in controlled-temperature packaging, storage and distribution services. With a degree in Microbiology and Virology, Rachel is the Biological Safety Officer for the Bridgend site and also has previous experience as a development scientist, a technical support scientist and a product support specialist.

Samantha James is Associate Director, Clinical Operations at PCI Pharma Services. Samantha joined the company in 2011 and has held various operational roles across the organisation. Her current role as director of clinical operation services has Samantha overseeing service delivery from Project Set-Up through to Returns and Reconciliation for the PCI facility in Bridgend, UK. Samantha holds a degree in Biology and Forensic Science from the University of South Wales and has over 10 years experience in Clinical Trials

Samantha James

Rich Nelson

Rich Nelson is the Distribution Services Manager for PCI's Clinical Services group, working with clients to provide seamless global distribution for their investigational products. Nelson joined PCI in 2012 after seven years with Fisher Clinical Services, having supported both global distribution for investigational products as well as IVRS solutions. Nelson is certified in Lean Six Sigma/Continuous Improvement including as a Small Group Facilitator/Corporate Trainer. Nelson is a graduate of Monmouth University in West Long Branch, New Jersey.