Cold Chain Outsourcing: A Simple Answer to a Complex Question?

PEER REVIEWED

Pharmaceutical manufacturers are facing a new challenge. The recent patent cliff and the exponential growth in the development of high-value pharmaceutical products, biologically developed therapies and live vaccines in the last ten years has resulted in a greater need for temperature-assured handling of drug product, from active ingredients to finished dosage form. This can be demonstrated by the fact that in 2013, seven of the top ten highest-selling pharma products were biologics[1], with global sales contribution from biologic drugs forecasted to jump from 23% in 2014 to 27% in 2020[2].

Side-effects of Growth

There is a growing side-effect from the global expansion in demand for cold chain services for the pharmaceutical industry: a supply chain which is becoming more and more demanding and complex.

Causes for this increase in demand include the previously identified growth in the biopharmaceutical sector, driven by the industry's technological breakthroughs, resulting in more effective treatments by virtue of more effective mechanisms of action. This is further complicated by industry trends in the size and complexity of clinical trials, and greater regulatory demands for safety and efficacy data prior to drug approval. In particular, the growth in the biologics sector has increased the importance of robust and carefully managed global supply chains. These temperature-sensitive biological products often have shorter shelf-lives than small molecule therapies and therefore require specialist handling. With cost pressures and readily available patient populations, clinical investigator sites are increasingly in developing markets and remote locations; geographies such as Ukraine and Russia, Asia Pacific, and Latin America.

Biologics add an increased complexity to the supply chain and require specialist handling during packaging, labelling, storage and distribution to ensure the product remains within its specific temperature range, which can vary from controlled ambient to cryo-store at -196 degrees Celsius.

This is a crucial issue because biologics are of extremely high value in terms of supply and cost, and are vulnerable to minor temperature deviations. Failing to maintain specific temperature ranges can have a negative effect on the efficacy of the drug. Additionally, the timescales for manufacturing these materials are often very long and replacements for damaged products may not only be costly, but could take many months - causing shortages in the supply chain.

This can potentially have a significant impact on the clinical trial supply chain and, most importantly, there is the ultimate consideration of the risk to the patient.

The Outsourcing Trend

Historically, the pharmaceutical industry has taken a short-term tactical approach to outsourcing clinical supply chain services by managing specific peaks in demand. This is now changing to align with the biotech sector, which has developed a very different strategy: a large number of biotech companies have been founded on a 'virtual' model; outsourcing all manufacturing and distribution activities. This often leaves the organisation with little supply chain experience and no in-house clinical supply teams and services to support their requirements. They have had to rely extensively on external service providers to develop clinical supply chain strategies for the manufacturing, packaging (primary/secondary), labelling, storage and global distribution of high-value biological products. This outsourcing trend is being continued by pharma companies who want to concentrate on what they do well and leave the specialist handling to the specialist outsourcing providers.

Greater Opportunity; Greater Risk

There is a lot at stake. To put it into figures: a recent Visiongain report highlighted that the global clinical trial supply and logistics market was estimated to have been worth $11.6 billion in 2013 and is predicted to increase to $16.34 billion in 2019 and further projected to grow to $22.08 billion by 2025. Analysts attribute this strong growth to increased outsourcing of clinical trial supplies and distribution, which is expected to drive the market at a compound annual growth rate of about six per cent from 2015-2025.

However, this globalisation of the clinical trial supply chain and increased access to new markets could increase risk to the supply chain. It will demand the development of distribution strategies to mitigate this risk of potential loss of often high-value product and, as a practical matter, effectively considered invaluable due to its limited supply. A key part of this strategy would be a fully audited global supply chain with a consistent approach to managing shipments via both standard operating and specialist training procedures.

At the moment, for example, a temperature excursion during shipment is only recognised when the investigational product is received by the clinical site/end user and the temperature monitor graph is downloaded and reviewed. If there is an excursion, the product will remain quarantined until the sponsor confirms whether the temperature excursion is within allowable limits. If there has been a deviation and the product is deemed not suitable for use, this can result in a delay in patient dosing, postponement of patient enrolment, loss of the patients from the trial and/or trials to be delayed. Depending on scope and available supply, it may also warrant costly new manufacturing activities to feed the supply chain for resupply to the investigator sites. With the high cost and often limited availability of biopharmaceuticals, entire shipments may need to be rejected.

The development of truly strategic partnerships, including a robust and simplified supply chain, is crucial to limiting risk. The aim is to reduce the number of 'touch points' where things can go wrong. Selection of an outsourcing vendor is an important consideration in the clinical supply chain. Importantly, this relationship should be evaluated in the context of a trusted strategic partnership. There are a number of questions to ask to verify their expertise in cold chain management and distribution:

- Are they a specialist in this area?
- Do they offer a range of shipping solutions?

- Do they conduct their own shipper validation or do they rely on data provided by the shipper supplier?
- Are they capable?
- Do they have capacity, even at short notice?
- Are they flexible?
- Do they contract out to any third-party vendors and how are these relationships managed?
- If shipments have deviated from specified temperature ranges, how will this be managed and how will it be addressed to reduce risk with future shipments?
- In the spirit of a true partnership model, what ownership and accountability do they take to ensure safe packaging, labelling and effective logistics to the patient?

Responding to Change

The response to the new pressures on cold chain services can be demonstrated by the drive of sponsor companies turning to specialist outsourcing providers to fulfil the needs of their temperature-sensitive materials. Proactive and collaborative management of service level agreements and key performance indicators is key to ensuring the patient receives the right product, at the right time and in the right condition (temperature maintained through the supply chain). Such performance indicators include operational metrics such as on-time despatch, on-time delivery, volume of temperature deviations, and gauging the overall safety and reliability of their logistical operations.

An additional strong focus is the financial analysis in terms of spend on individual clinical trial activities. Setting and managing a clinical trial supply budget is an ever-evolving task, especially for global studies with distribution strategies which are focussed on responding to the requirements of patient enrolment.

Online portals integrated into supply chain operations present opportunities to extend visibility to sponsor companies into logistical touch points. This visibility can help foster a partnership model by providing real-time information about inventories and locations, shipment status, and acceptance at the investigator sites, thereby reducing study lead-times and consolidating communication channels. Software can be extended to electronic document approvals and sharing, order transactions, integration into IRT technologies, and so many other facets of business integration. This integration fosters a more effective supply chain and ultimately more effective study execution.

Smarter Technology

A smarter supply chain has many facets, but central to the entire process is the refrigerated packaging and labelling of products that have limited stability data outside of refrigerated temperatures, and when refrigerated room space may be at a premium.

When packaging and labelling cold chain products, it is crucial that the total time the product is outside of the appropriate storage temperature is minimal. The preferred packaging option delivered by the majority of vendors offers limited packaging suites for refrigerated labelling and packaging operations. Cold room space is often at a premium. To address this and to ensure secure and efficient packaging, the industry must look for innovative and smarter ways to address these challenges. One such method is the use of a fully validated cold plate technology in which the product is stored whilst being packed and labelled. This method offers a unique solution to overcome the standard hurdles. This is specifically favourable when a just-in-time service is required and removes the need for personnel to physically conduct labelling and packaging in a dedicated 2-8°C packaging room.

Investigational therapies can be extremely invaluable, or practically immeasurable, in the case of cell therapy. Supply chain visibility can help mitigate risk. Technologies exist for an integrated electronically monitored platform that orchestrates supply chain activities for advanced therapeutic medicinal products, utilising a single, compliant and FDA-validated technology platform. These combine proven technologies that economically and effectively integrate and risk-manage the cell therapy supply chain. Any paper-managed cell therapy supply chain quickly becomes inefficient and risk-prone due to shifting regulatory requirements and linear complexity as demand scales up and scales out. A successful and scalable cell therapy supply chain demands standardised processes, automated electronic records, integrated temperature-sensitive logistics, real-time visibility and end-to-end traceability to ensure final product quality.

In some instances, reversing the logistical order of standard practices can help mitigate risk and drive efficiencies. For example, storing vials at temperatures as low as -196°C also presents huge challenges for ensuring the all-important labels are able to be applied. Bespoke solutions have been developed by working with the product manufacturer to design, print and pre-label vials prior to filling and freezing.

As another example of adding visibility and safety to the supply chain, bespoke barcoding systems have also been developed to incorporate cold chain traceability during the picking and packing of products and reduce errors. This forces the operator to scan individual identifiers, ensuring the correct kit is picked at every stage of the shipper packaging process and confirms the 'start' of the temperature monitor.

Partnerships leverage innovative logistical models to ensure success. Flexible and just-in-time strategies must also be applied, taking into account the availability of the product, multiple protocols and the possibility of additional countries being added after the trial has commenced. For example, multi-language booklet labels can provide flexibility, but are typically produced based on the countries planned at the commencement of the study. If unplanned countries are introduced during the trial, this can make the existing labels redundant and add time and expense due to requiring updated booklets and the subsequent relabelling of inventory. An alternative strategy is to label supplies on a just-in-time basis, whereby supplies are labelled with country-specific labels only after distribution orders are received for shipments to clinical sites. Just-in-time labelling can be performed as either a discrete labelling operation in a packaging suite, or may be integrated into the distribution process, in some instances in an approved regional depot closest to the remote investigator site.

Non-standard Temperatures

The growth of the pharmaceutical industry has brought with it the development of new drugs which may require non-standard storage temperatures, for example -40°C. The requirement for this temperature range is increasing as biologicals are inactive below -35°C and it is possible to build pallet storage warehousing at this temperature for the

storage of bulk materials prior to fill finishing and therefore maximising the shelf-life of these expensive products. These very specific product needs may warrant construction of a bespoke solution from the outsourced partner in the form of a tailored stand-alone facility.

Speed and Control

The emerging need to improve distribution strategies is why cold chain specialists are striving to identify innovative methods to improve temperature-controlled shipping systems. Instead of relying on validation data from the traditional suppliers of shipping containers, logistics providers are looking at their own methods of validation of shippers to ensure the integrity of the cold chain under 'forced' demanding conditions.

For example, a new phase-change frozen shipping system (-15 to -25°C) has been recently validated, which involved extended conditioning times for the frozen plates, requiring one-month storage at -30°C. The clinical market is so fast-paced, dynamic and difficult to forecast that actually one month's conditioning is completely inefficient.

With the aim of speeding up the process, suppliers' validations are being challenged and new custom methods for conditioning these systems have been created, which enable a significantly reduced conditioning process for the frozen shipping systems: from one month to 48 hours. This can be achieved by employing ultra-low temperature conditioning of the plates at -70°C for 48 hours, compared to the supplier's method of one month at -30°C. Coupled with increasing the conditioning time at ambient (in order to expel the required amount of energy prior to pack-out), this ensures controlled frozen temperatures are maintained during transit.

This ability to continually challenge the supply chain by qualifying shipping systems at-site and utilising bespoke test environments may prove to be a crucial capability for successful operators in the future, and result in completely removing temperature deviations from incorrect packaging of shippers. These solutions continue to be developed in the spirit of partnership and prevention.

An Ongoing Challenge

Although the cold plates are currently validated for refrigerated packing at 2-8°C, there are still more processes that can be developed to reduce timelines. This would include developing a method to adapt the cold plates to support validated packing on dry ice, maintaining temperatures below -20°C and containing CO_2 levels to a minimum for a safe working environment.

Other innovative developments could include a method which enables the utilisation of automated labelling equipment within a large 2-8°C environment to support high-volume packing runs, which cold plate technology is unable to support.

To meet the challenges of the future, the industry requires a shift towards real-time 24/7 monitoring of the temperature of specific shipments, involving faster processes and new strategies. Stocking strategies at central hubs, depots and clinical sites may be designed to conserve valuable inventory by shipping little-and-often, but this in turn can result in higher shipping costs.

More cost-effective solutions are forecast to be in increased demand; met through new packaging and monitoring technologies, including reusable packaging and phase change materials that allow cooling for more specific temperature ranges. There is also speed. Innovative operational and logistical concepts for those studies requiring a rapid start-up have been developed to further accelerate products through the supply chain, without compromising quality and regulatory requirements.

Cold Chain Conclusions

An increasing proportion of worldwide drug sales are forecast to be derived from biological products. As the biopharmaceutical market is growing rapidly, outsourcing/partnering cold chain activities to specialists is critical as a result of the increasing complexity of the biopharmaceutical supply chain.

In an industry where the patient is at the forefront of everything that we do, developments in activities such as packaging, storage and shipping technologies will continue to be made in response to the unique challenges this sector provides - to ensure that the right drug gets to the right patient at the right time, and within the right temperature range.

Longer-term Development of the Biologics Supply Chain?

As we have seen, the current supply chain is constantly evolving to cater for – and predict – the pharmaceutical industry's developing technology and requirements. We are currently seeing the trend towards custom parenteral delivery forms, such as the auto-injector to aid patient convenience for injectable medicines. This trend further complicates the temperature-controlled supply chain for biologically developed medicines because of the unique nature of these devices.

On the horizon, however, is the even longer-term prospect of a radical upheaval that could bring a step-change in the supply chain – the oral biologic. If injectable biologics – with all their cold chain supply implications – are replaced by tablets which are able to be packed and shipped at room temperature, that would be a revolution which would provide the possibility of a vastly less expensive supply chain, faster, and easier to manage.That is some way off. One of the problems that must be solved is that, unlike current methods, orally delivered biologics break down in the gastrointestinal tract and become inactive.

But if this roadblock is cleared, it would remove the need for cold chain packaging, labelling storage and distribution strategies, and eliminate associated complexities. It would be the ultimate simplification of the supply chain. Just as biologics are now enabling new research and treatments, new developments could utterly reshape the supply chain. For progress to continue, each side must keep pace with the other.

Adapted from the CPhI Annual Report 2015.

References
1. The Global use of Medicines: Outlook through 2017. Report by the IMS Institute for Healthcare Informatics
2. EvaluatePharma, World Review 2015, outlook to 2020, June 2015

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