



## Temperature Challenges in Clinical Supply: Examining the Cold Chain to Ensure the Efficacy of IMPs and Patient Safety

Supply chains for investigational medicinal products (IMPs) are becoming more complex. As clinical trials change rapidly, maintaining product integrity and quality at every stage is challenging. Additional demands are being created by the growing development of biologic and orphan drugs, as well as cell and gene therapies. These temperature-sensitive products are subject to more stringent stability profiles, with strict temperature ranges having to be adhered to. This myriad of challenges calls for the entire cold chain network to be re-examined and potential packaging, labelling, storage and distribution requirements to be considered early in a study's planning.

With this in mind – how can you be sure that the medication is safe to give to the patient? This article looks at the temperature challenges associated with biologic products and addresses how emerging cold chain management solutions are helping sponsors ensure specified temperatures are maintained throughout the supply chain.

### Today's Changing Clinical Trial Landscape

The precision medicine market has witnessed remarkable growth, augmented by a surge in investment into more targeted and patient-centric medicines. Driven by the increasing prevalence of cancer and rare diseases, and ongoing advancements in genome mapping and molecular diagnosis, the global market is expected to reach \$216.75 billion by 2028. Translating developments in precision medicine into treatments is helping to mature the biologics sector, with this market expected to touch \$399.5 billion by 2025.<sup>3</sup> As these therapies become relevant to more disease areas, many sponsors are choosing to populate their drug pipelines through investment opportunities in biologic products and biotech capabilities.

A record number of drug approvals in 2018 saw 59 novel treatments reaching the US market, with almost two-thirds being patented by biopharma companies.<sup>4</sup> The shift towards greater clinical development of biologics and cell and gene therapies has a resulting impact on clinical trials, with completion timelines, costs, resources, and the likelihood of study success, all being affected. Additional complexities are also being introduced by these products, including the need for more frequent re-test dates, changing handling requirements, limited bulk availability, short stability data, and, perhaps, the biggest challenge of all – the complex process of managing cold chain supply.

The globalisation of clinical trials dictates that products travel greater distances, crossing numerous climates and environments, all while maintaining strict temperature controls. By 2020, it is projected that eight of the top 10 pharmaceutical products will require cold chain handling.<sup>5</sup> This has led many sponsors to look to outsourced service

providers to deliver clinical trial materials to investigative sites, while supporting supply planning and forecasting. Establishing efficient supply chain logistics is critical to avoid delayed or failed trials and there is a need for vendors that can achieve this, particularly with mounting concern over costs and patient safety. Rising need for cold chain logistics calls for packaging and monitoring technologies that offer lower-cost solutions, including reusable packaging and phase change materials that allow cooling for more specific temperature ranges.<sup>6</sup>

### Industry Perspectives

A snapshot of industry perspectives pertaining to cold chain management has been captured by a survey of individuals working within pharmaceutical companies, contract research organisations and biotech companies.<sup>7</sup> The survey found that 47% of respondents value reliability as the primary driver for cold chain logistic decisions. This was more than double the percentage of respondents who chose cost (21%) and ten times more than those who selected ease-of-use (5%).

Regarding cold chain management, 71% of respondents stated that their companies either outsource exclusively or do a combination of outsourcing and in-house management. The survey also found that biotech companies are more inclined to outsource certain functions than pharmaceutical companies. 60% of biotech respondents stated that all manufacturing, packaging, storage and distribution functions were outsourced. For pharmaceutical companies, the corresponding figure was 7%.

### Implications for Labelling and Packaging of Cold Chain Products

Failure to consider potential packaging and labelling challenges at a study's planning phase has the potential to compromise the timing, safety and success of a trial. As a result of increased demand for cold chain management capabilities for temperature-sensitive products, new hidden challenges have emerged within the cold chain sub-stream, adding to the existing challenges which apply to all forms of clinical labelling and packaging.

Selection of the right packaging design to withstand and maintain a product within specific limits is critical to ensure stability and integrity within the supply chain. Sponsors should consider several elements prior to defining a packaging and labelling configuration. These include storage and shipping criteria (frozen, ultra-low or cryogenic), ability to have time out of conditions for labelling, blinding requirements, expiration dates, the likelihood of product re-work due to information updates, depot and site storage availability, home storage and patient/physician handling.

Storage criteria will influence how a product is packaged. Biologic products typically sit within three temperature ranges (refrigerated: 2°C to 8°C, frozen: -25°C to -15°C and ultra-low: -25°C and below). The packaging design requirements for 2°C to 8°C products are akin



to those used for ambient medicinal products and usually include solid bleach sulfate (SBS) for the carton material. While cartons for product stored in frozen conditions require a stronger material to prevent damage from moisture, polyethylene one-sided coating is commonly used.

Label design is also influenced by temperature, with consideration required for both processing and storage conditions. When a product is stored below  $-25^{\circ}\text{C}$ , the integrity of paper labels becomes threatened. In this case, a single-panel label is usually the best option over a booklet. The correct label adhesive is fundamental as glues behave differently based on the temperature they are applied at, the temperature they are stored at (and for how long), and the material to which they are applied. If materials are stored in frozen or ultra-low temperatures, cryogenic label stock is necessary.

The amount of time that a product spends out of stipulated temperature conditions will be dependent on the processes involved, the complexity of packaging and the assembly time. If time out of conditions is necessary, then it is advisable to make the best use of this and consider any potential for rework of material or expiry date updates.

If time out of conditions is completely prohibited, insulated containers may be necessary for transportation of material between areas. Alternatively, products can be packaged directly in  $2^{\circ}\text{C}$  to  $8^{\circ}\text{C}$  and  $-25^{\circ}\text{C}$  to  $-15^{\circ}\text{C}$  conditions, or even processed directly out of a freezer for materials stored below  $-25^{\circ}\text{C}$ .

### **Choosing the Most Appropriate Manufacturing Process for Temperature-sensitive Products**

Development of biologic and precision medicines means the industry needs to work in non-traditional ways to mitigate the supply-based risks that these trials pose. There are several methods of manufacturing, packaging and labelling which can be adopted for different demands.

Standard batch manufacturing involves a drug product being made, packaged, labelled and added to inventory to produce a set demand. Favoured for small molecule drugs, this approach can cope with uncertain demand forecast as operations can start and stop as required. While overheads are reduced as one production line can be used for multiple products, lack of flexibility makes the approach unsuitable for biologics and precision medicines.

Lean manufacturing offers a systematic method of minimising waste without compromising productivity. Unlabelled products



held in inventory are packaged and labelled in smaller batches in accordance with short-term forecast. Offering the ability to respond quickly to last-minute scheduling, lean operations can help mitigate the risks of stock-outs, especially in trials where patient enrolment and drug demand forecasts are uncertain. However, the model supports little flexibility as supplies are made in advance.

Just-in-time labelling services offer partial late-stage customisation of clinical kits at the time of distribution. Kits are packaged and labelled in advance of standard batch or lean manufacturing operation. Once a distribution order is placed, kits can be modified with the application of an auxiliary label. This approach can improve efficiency, decrease waste and reduce cost by removing the need for labelling rework.

Just-in-time manufacturing solutions permit the assembly of finished patient kits based on demand. As well as supporting the need for greater flexibility, sponsors are finding that storage costs can be reduced if kits are assembled closer to the point of use. Subsequent changes to study design are also simplified since pre-labelled material is not sitting in inventory. This provides a solution to support patient-centric dosing, which is common in trials involving temperature-controlled medicines.

The benefits of just-in-time manufacturing were realised by an organisation running a Phase Ib trial for a rare paediatric disease which required varied patient dosing. Strict temperature conditions of  $-70^{\circ}\text{C} \pm 10^{\circ}\text{C}$  were necessary throughout the drug's lifecycle and the product was able to withstand only an extremely limited time out of conditions. To overcome the challenges, a custom process was established to enable full late-stage customisation of kits. This condensed the lead-time from the point of drug order to receipt of the shipment at the clinical site from six to eight weeks, to two weeks.

## Temperature Management Solutions for Cold Chain Products

The complexity of clinical trials is driving the need for reliable data management across the supply chain. To ensure products are fit for patients, it is imperative that sponsors are equipped with the ability to track and trace the journey of their IMP, identify issues at the first opportunity and make informed decisions.

Single databases are being introduced that enable temperature data to be tracked from product manufacture right through to the point of patient administration. This not only means that temperature data is held in one place, but also enables a history to be built for every product as it passes through the supply chain, demonstrating that IMPs have been stored within specified temperature limits. Using this type of technology readily alerts sponsors to any pending temperature excursions, enabling preventative action to be taken.

Advances in temperature-controlled shippers are also ensuring the integrity of IMPs in transit. They represent a move away from traditional bulky shippers featuring water-based refrigerants, instead utilising new technology including phase change material and vacuum insulation panels. With the ability to maintain temperature for 96 hours, these shippers bring the flexibility to ship IMPs at any point in the week, as well as mitigating risks associated with potential delays. The shippers can hibernate when stored in an environment that matches their required temperature, effectively 'stopping the clock' and no longer losing the validation period. Reusability also means that the carbon footprint associated with traditional solutions is reduced, as too is the site burden of managing disposal.

An example cold chain distribution which benefited from temperature-controlled shippers involved an IMP that needed to be maintained below  $-60^{\circ}\text{C}$ , with orders processed and shipped





within 24 hours. By using new shipper designs, when a drug order is received the shipper is prepared with dry ice and stored in a  $-70^{\circ}\text{C}$  freezer for approximately 12 hours. Temperature monitors for  $-70^{\circ}\text{C}$  and colder shipments are inventoried in a  $-20^{\circ}\text{C}$  walk-in freezer then moved to a  $-70^{\circ}\text{C}$  mobile freezer when the material is picked. The material is verified and packed into the pre-conditioned shipper, and the temperature monitor is activated. The sealed shipper is placed back into the  $-60^{\circ}\text{C}$  freezer until courier pick-up. The whole pre-conditioning process has eliminated all front-end excursions.

### Final Thought

The packaging, storage and transportation of temperature-sensitive IMPs demands constant monitoring to ensure their stability and viability. Managing product integrity at every point of transfer from manufacture to distribution is imperative in safeguarding patients. As more temperature-sensitive biologic drugs enter the supply chain, innovative solutions are helping to optimise the complex task of tracking temperature excursions. By having a complete picture of an IMP's temperature profile as it progresses through the cold chain, sponsors can have confidence that their product has been maintained within temperature constraints and therefore meets the compliance requirements essential for safe and successful supply.

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