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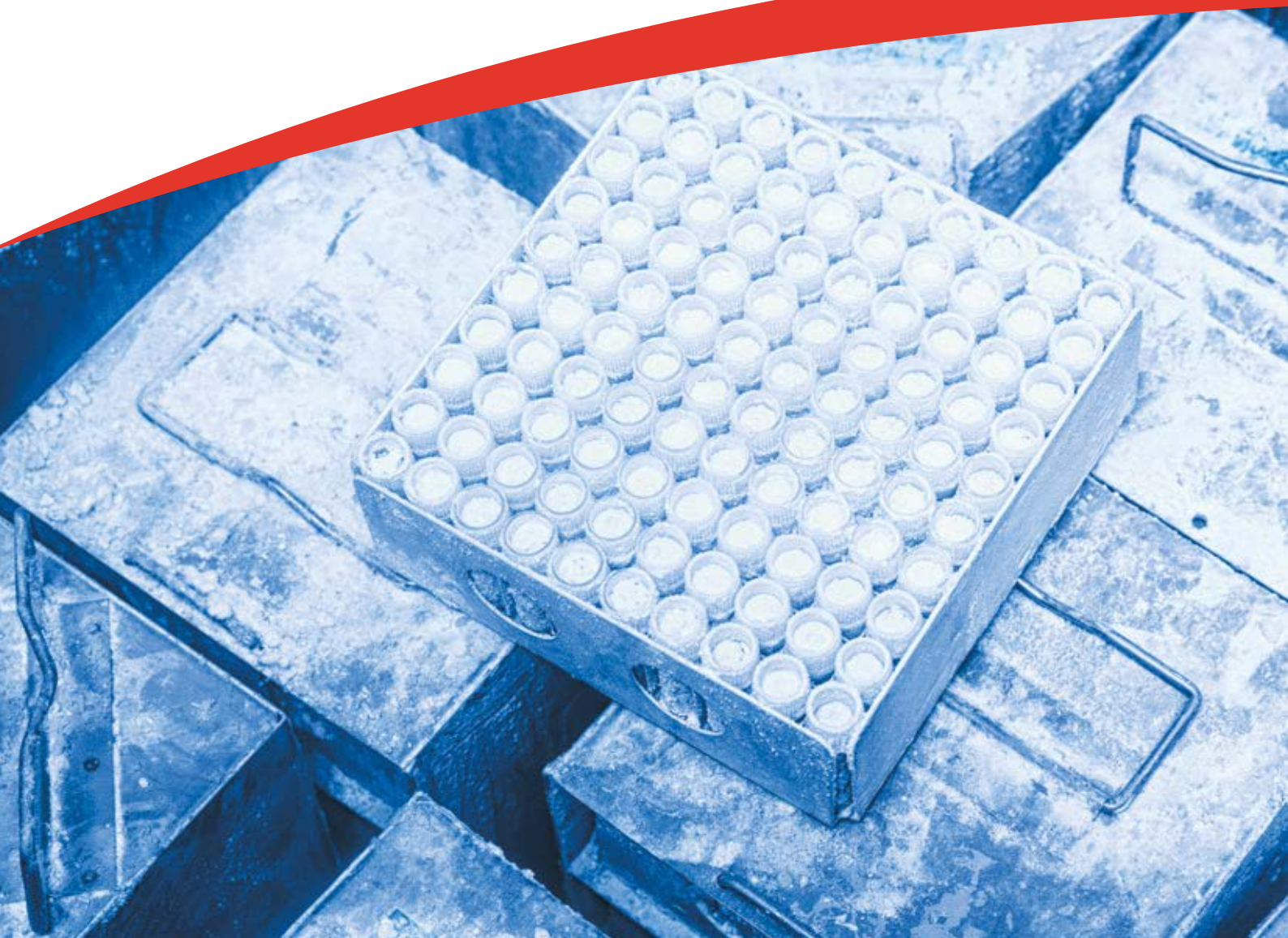
The journey from production line to patient: exploring the end-to-end requirements of a successful cold chain operation



The clinical trials landscape is evolving. Pharmaceutical and biotechnology firms, and the contract research organisations often operating on their behalf, must contend with a myriad of new challenges.

In recent years, the shift from small single-arm trials to larger, more complex studies has been notable. The globalisation of clinical trials has had a big impact on the industry, with the average Phase III trial now spanning 34 countries. This has created the opportunity for sponsors to deliver drugs to market faster than ever before, but has also introduced additional clinical supply complexity, cost and compliance responsibility.

The increase in large molecule and rare disease therapy trials is another game changer. Global sales of biologics are estimated to tip $350 billion by 2021 and biologics are predicted to replace 70% of small molecule drugs over the next two decades[1]. As such, an ever-increasing number of drug consignments will need to be shipped greater distances, across borders and through varying climatic zones, while maintaining strict temperature controls.

Running globalised trials involving temperature sensitive products magnifies the need for sponsors to operate efficiently and weed out risk. One of the most high-risk areas of managing such trials is the clinical cold chain; where failure to consider potential packaging, labelling and distribution challenges at the study's planning phase can compromise a trial's timing, safety and commercial viability.

To avoid this fate, greater awareness of the risks and requirements present at each stage of the cold chain journey – from production line to patient - is essential. Without this, it is impossible to develop effective mitigations that safeguard product integrity and promote patient safety. As clinical trial complexity grows, as does the need for reliable data across the complete supply chain. Data that provides the bigger picture and empowers sponsors to identify issues quickly and take informed, preventative action to demonstrate supplies are fit for patients and to drive continuous improvement.

[1]"Global biosimilars market could be worth US$55bn by 2020, says new report," Manufacturing Chemist, July 2015.

Mapping specific requirements

To best manage temperature-controlled drug consignments on their journey to patients, each link in the cold chain warrants careful consideration. As with all journeys, the best place to start is usually at the beginning. This means reviewing the drug type and looking at its specific set of processing requirements. Is it oncology-based or gene therapy? How has the drug been manufactured? What's the drug substance? Is there a blinding requirement? What impact does this all have on how the product needs to be packaged, labelled and stored?

For instance, many temperature-controlled drugs are presented in innovative dose formats, such as auto injectors, syringes and patches, and packaged in small containers that can be difficult to label. Not only do these drugs need to be processed, stored and shipped in controlled conditions, usually in refrigerated or frozen temperature ranges, they are more complex to manufacture, which can result in limited stock availability. When these factors combine, sponsors may be faced with labelling a small, fragile product, in cold conditions, with a complex multi-language label.

Add to the fragility of primary packaging, the incredibly expensive nature of biologics and the margin for error typically associated with clinical supply chain management is vastly reduced. This also raises the stakes for sponsors when it comes to selecting appropriate packaging design that will limit the risk of costly breakages and not inadvertently heighten the risk of unblinding.

Temperature range challenges

Once processing requirements of temperature sensitive drugs are understood, specific parameters and protocols can be developed. To protect drug integrity, it's important that sponsors understand the challenges associated with the three temperature ranges applicable to processing biologics materials (2°C to 8°C, -25°C to -15°C and ultra-low: -25°C and below).

Drugs processed in ultra-low temperature conditions are only able to withstand a very limited time in ambient exposure so sponsors may need to introduce innovative operating practices, such as the use of dry ice, in order to meet packaging and labelling objectives.

De-labelling or rework of materials stored in ultra-low conditions can also be incredibly difficult, if not impossible. However, sponsors can overcome these issues by adopting a product-first approach and utilising flexible secondary packaging options.

Conditions between -25°C to -15°C present problems too, such as difficulties in application of tamper seals. This is because most tamper evident seals are ineffective when applied to plastic in such temperatures. However, a plastic coating is needed to prevent moisture from eroding the carton, so designs must be adapted that enable the carton's structural integrity and tamper evident seals to co-exist. One solution available to sponsors is to apply a plastic coating to the inside of the carton to prevent moisture damage and affix the tamper seal to the outside of the carton.

Glues also behave differently in extreme temperatures. Very few adhesives are capable of bonding labels to packaging in temperatures below -20°C, with most freezing solid before a bond can form. Sourcing specialist, hard-to-come-by adhesives, or adapting packaging design so cartons can be assembled without glue, may be necessary tactics.

Understanding the limitations of working with temperature-controlled products will help sponsors select the most appropriate materials and processing protocols. Yet, when it comes to defining packaging design and labelling strategies for a cold chain operation, it's important to look at the big picture and consider the process from start to finish: shipping, depot storage, site storage, home storage and patient and/or physician handling. How can packaging and labelling best support drugs on their cold chain journey and be cost-effective for sponsors at the same time? For instance, at face value, introducing custom designed components to meet specific needs may seem like a cost centre. However, if approached strategically, it could provide a return on investment by facilitating improved flexibility and savings in shipping costs.

Breaking with tradition

When processing requirements are established, appropriate materials selected and temperature-based parameters understood, the next action is to determine how traditional manufacturing methods and facilities must adapt.

If time out of refrigeration is restricted or not permitted, adjustments will need to be made to maintain the drug's integrity. Products that are sensitive to light will also require modified environments and the use of light filters, window films or black-out boxes.

Expiry date management is a core part of any clinical supply chain, but the vials and prefilled syringes used for biologics products typically have a shorter expiry date, compared with tablets or capsules. This increases the pressure to effectively plan but also to cater for the need to conduct several expiry updates of labelled inventory.

This can also limit choice of manufacturing strategy, as late stage customisation of kits kept in inventory can quickly prove a false economy, depending on projected demand vs. expiry date specifications. That said, Just in Time Manufacturing (JTM) can sometimes be an effective tool to support patient-centric dosing – common with trials involving temperature-controlled drugs, while offering enhanced cost control and flexibility. This is achieved through assembling kits much closer to when they are needed, in response to immediate user demand that is often triggered by patient enrolment; resulting in reduced waste and storage costs. Sponsors may also need to accommodate longer packaging durations, reduced operation sizes and enhanced PPE for operatives, as a result of dealing with temperature sensitive products.

Selecting the best strategy can be a minefield for sponsors keen to balance drug availability and integrity with the need to minimise waste. Yet, by exploring requirements at the onset of a trial and partnering with experts to devise bespoke, agile and effective operational strategies, the right approach can be found.

Maintaining control in transit

Understanding how temperature sensitive drugs need to be processed, creating the right operating procedures and environments and selecting capable materials is half the battle. Ensuring that appropriate temperature controls are maintained once drug consignments begin their journey to patients is the other, much more difficult, half – as visibility and control typically diminishes.

Products are transported around the world and stored in various facilities, at the mercy of multiple third parties. Yet, avoiding temperature excursions matters more than ever with enhanced regulatory demands, such as the recently revised Good Distribution Practices (DDP) guidelines, placing greater compliance pressure on sponsors.

Indeed, distribution is the cold chain's danger zone, with data suggesting that most breaches occur at custom clearance in the country of destination.

To minimise the risks to drug supply during the distribution process, it is important to have a structured and well-developed distribution strategy firmly in place. The distribution strategy should consider key factors, such as the use of approved couriers, assessment of the shipping lanes at a country level, import documentation requirements, facilities at the destination, as well as determining whether to ship direct to site or via a local depot.

The decision to ship direct to site or to utilise a local depot will frequently be driven by whether the country has long and cumbersome import requirements. In cases where this is not an issue, sponsors will have to decide upon the most effective strategy for their study. Ultimately this decision usually comes down to weighing drug conservation against cost. For instance, with a local depot strategy, there is often less risk to temperature-controlled supplies and the distribution will be supported by in-country resources and shipping networks. However, sponsors will see an increase in set-up, storage and management fees.

Contrastingly, a direct to site distribution strategy is less likely to result in overstocking of drugs, which can reduce costs and simplify expiry date planning. Sponsors must remain mindful that the decreased set up and storage fees, are typically countered by increasing freight and courier costs, due to smaller and more frequent shipments.

There is no 'one size fits all' distribution strategy for clinical trials involving temperature-controlled products. It is therefore vital that sponsors assess the unique specifications of their study and work with experts to determine the most appropriate course of action.

Whichever strategy is selected, there remains a constant need to reduce the risk of temperature excursions throughout the distribution process. One way sponsors can better meet this need is by adopting thinner, more flexible and reusable storage solutions that incorporate innovative materials and technologies.

A combination of vacuum insulation panels (VIP) and phase change materials (PCM) are acknowledged as the most reliable shipper solution for safeguarding the integrity of temperature-sensitive drugs in transit. This is due to the shipper's ability to change phase slowly, maintaining the midpoint of selected narrow temperature ranges for long periods. The shippers can also 'stop the clock' when stored in an environment that matches the specified temperature range, reducing the risk of temperature excursions, even if consignments are removed from specified conditions between depot and physician.

However, these shippers only represent a value proposition for sponsors if the are easily and cost-effectively reusable. When sponsors are required to manage return shipping and shoulder responsibility for quality control and reconditioning independently, the benefit on offer is quickly outweighed by the surge in risk.

Sponsors can take advantage of shippers that incorporate VIP and PCM, meet 96-hour qualification and provide robust temperature control, without introducing excessive cost or logistical complexity. Leasing PCM and VIP shippers, via a GDP-compliant service solution,

supported by a global network of approved couriers, reduces risk, removes complexity and delivers complete cold chain oversight and control.

To bolster the protection of drugs in transit further, these intelligent solutions can be integrated with IRT technology to provide real-time visibility over temperature data and alert sponsors to pending excursions, so preventative action can be taken. This integration also automates product approval, based on the temperature data captured by the shipper's monitors. Furthermore, by combining transit and site temperature data, sponsors can strengthen compliance and build a complete temperature history of their products; demonstrating drugs have been stored within the label claim throughout their journey through the cold chain.

The same, just different

Despite the clinical trials landscape evolving rapidly in the past decade, the overarching objectives of meeting the varying needs of individual trial protocols, upholding the integrity of products and supplying patients with safe and compliant IMP remains unaffected.

By breaking down the cold chain journey, from production line to patient, exploring end-to-end requirements at the earliest opportunity and adjusting manufacturing materials and strategies accordingly, safe, agile, optimised and effective cold chain operations can be crafted. Cold chain operations that not only help individual studies perform like clockwork but make a meaningful contribution to the advancement of global human health.

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