



Temperature Controlled Shipping in Clinical Trials: A Rising Requirement

Temperature control of pharmaceuticals has received an increasing level of attention over recent years. Companies are focusing more on the temperature control of their products during transportation. Regulatory bodies have been further extending their gaze beyond GMP storage locations to the journey in between. This attention is not new but it is becoming more prevalent. The response from industry has been positive. There is an increased awareness of the underlying issues alongside a greater choice of solutions to the challenge of temperature control in distribution. But what has this meant for clinical trial distribution?

Distribution of clinical trial materials has a different profile to that of commercial distribution. The quantities involved are usually very small; perhaps just a few blister packs. The destinations are varied; particularly of note is the rise of the emerging markets in clinical trials such as India and China. There are many individual shipments; a large clinical trial may require several hundred shipments each month. The most critical single point, however, is the fact that the investigational medicinal product is probably a new product with limited information on how stable it is. Determining the thermal stability of a product through a "stability study" takes time so is often not available in the early stages of a trial.

The net result is that there will be lots of small highly temperature sensitive shipments going all round the world. From a temperature control point of view this is a challenging distribution. So how can this be handled?

A typical example of a challenging distribution would be an experimental biotech protein based treatment. Such a product may be slow and expensive to produce, highly sensitive to temperature and needs to be distributed to 50 different countries. The transit time to destination may be up to 10 days if customs procedures are involved. Temperature excursion in any one shipment not only renders that shipped product unusable but can delay or even jeopardise the entire trial. Even more critical is that patient medication may not be available in time potentially resulting in missed dosing. Such a product needs considerable temperature control and close monitoring to ensure safe delivery.

There are three main areas that require attention when shipping temperature sensitive materials: the choice of shipping system, temperature monitoring device to be used, and the courier who will handle it.

Shipping Systems

There are more choices of shipping system available as the requirements become more widespread. Manufacturers are making use of more efficient insulating and phase change materials to deliver shipping systems tailored to suit the product and distribution. Pre-qualified off-the-shelf solutions are often used to reduce the need for specific testing of customised shipping units.

A biotech product that needs careful control would need a high quality shipping system to reduce the risk of temperature excursion. Since the product being shipped cannot be directly probed to check the temperature of the product the air inside the system must be monitored. The shipping system must be capable of maintaining the air around the product in the correct range. This is even more challenging than maintaining product temperature due to the reduced thermal mass. A shipping system that provides good thermal stability in response to shock extreme temperature and that will offer at least 96 hours of temperature control will be required.



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Temperature monitoring

Temperature monitoring of shipments is an area where there has been rapid development. The "template" style of device has been the most commonly used electronic monitor for many years but a new generation of unit are appearing on the market. The new generation monitors have improved communication methods such as RFID (radio frequency identification) or USB compatible. They also boast more sophisticated internal and analytical software. The criteria used by quality departments to judge a product's usability, based on stability data, can be programmed directly in to such monitors. This reduces the number of quality reviews of temperature excursions while improving accuracy.

Simpler temperature monitor devices are also being developed. The electronic indicator type monitors offer a cheaper alternative to the more sophisticated type. They are simple to use both for the sender and receiver. The main drawback is that detailed information may not be available to make any further judgment in the event of a temperature excursion. This may not be a concern in cases where the product being shipped is relatively cheap and readily available, but are unlikely to be suitable for the sensitive product.

Detailed temperature monitors that store every temperature reading that is recorded are more commonly used and would be appropriate for the more sensitive biotech product.

So what happens to all the data that is recorded by the temperature monitors? Often the results are thrown away with the monitor if there are no temperature excursions. Collating and compiling all the information from all monitors has been both challenging and expensive in the past. The electronic communication technology found in the new temperature monitors is making data collection practical and cost effective. There may come a time when regulators will want the temperature conditions that a product has been exposed to throughout its life cycle to be available on record.

The results of a monitor from a shipment of the sensitive biotech product that has shown an excursion will at least need to be recorded. The information can then be reviewed to decide if the product is fit for use. A temperature excursion on the monitor may not always result in the product being unusable. For example, a temperature excursion recorded on a monitor may have occurred after the product had been separated from the temperature monitor and so will not affect the product. Combining the information from the temperature monitor with the transit and receiving information allows decisions such as these to be made.

Courier Selection

There is a wide range of couriers, many of which specialise in transportation of temperature sensitive material. Premium couriers are the most commonly used providers for far away destinations due to the small quantities being shipped for clinical trial. However, where the transit times are less than 48 hours, often an express service provider is used. Premium couriers will monitor shipments and provide special handling if a transit continues for longer than the shipping system is able to maintain the correct temperature. When the transit time is expected to be less than 48 hours and a robust shipping system is used then no special handling should be required and an express courier will be entirely sufficient.

A premium courier would certainly be used for the sensitive product that requires strict temperature control. In this example it is unlikely that the cost saving of using an express courier will offset the increased risk of temperature excursion.



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So far we have been concentrating on one end of the spectrum; the highly sensitive, high value biotech products that must be kept at the correct temperature at all costs. These products are in the minority however. Most products have less strict temperature requirements. How will these products be handled in the new world of complete temperature monitoring and control? A risk-based approach should lead to appropriate solutions to each scenario.

One of the main driving factors for increased temperature control is the simple question: "Should a temperature sensitive product that requires controlled storage conditions be shipped under the same temperature condition?" The logical answer to this question is yes. Why would we transport a temperature sensitive product at anything other than the stated storage conditions? However, the term "temperature sensitive" needs some clarification. A particular product may suffer degradation if it is heated to +100°C, for example, but is stable otherwise. The likelihood of it being exposed to these conditions in transit between sites is effectively zero.

At the other end of the spectrum, another product may be affected by any temperature outside +15°C to +25°C conditions. Both these products will have storage conditions of +15°C to +25°C but it does not make sense to transport both these products with the same level of temperature control. Regulators have hinted towards a position of "Take the necessary action to ensure product integrity is maintained". Hopefully the expectation of the regulators will be clarified as the practices in temperature-controlled shipping continue to develop.

Conclusion

As with many regulations in clinical trials, the requirements in temperature controlled shipping are unlikely to become less strict. Monitor and shipping unit suppliers and couriers are offering ever improving products and services to maintain temperature. As better solutions become available the expectation of temperature control shipping will rise driving further development. The net result will be improved safety for patients through a continually evolving fully integrated temperature control network. And that is exactly where we want to be.

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Almac Clinical Services provides a global service for the manufacturing, packaging, labelling, distribution, returns and analysis of clinical trial supplies.

These services include comparator sourcing, manufacture and blinding, label printing, distribution via a global network of local and regional depots, web-based patient randomisation (WebEZ™), integrated IVRS and clinical supplies management service (with Almac Clinical Technologies), and drug supply management, amongst others.
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