



Chain Reactions

Jonathan Calderwood of Almac Group discusses the advantages of having in place a streamlined cold chain process, and outlines methods for achieving this goal

Management of cold chain clinical supplies presents sponsor companies with significant logistical challenges, especially considering the global nature of distribution to many less developed regions and emerging markets. When investigational products are shipped, supplies are subject to various factors which may influence the way in which temperature-controlled shipping systems may operate. These variables include a myriad of external temperature ranges, supply routes, transit time, and availability of stability data and people.

The nature of clinical trial shipments means that they are exposed to more risks than commercial shipments due to the urgency of shipments, diverse destinations, shipping methodologies or routes, and variable shipment quantities. However, the goal still remains to ensure a consistent flow of material, arriving at the site in a condition which is fit for its intended use.

When contemplating cold chain logistics, there are a number of elements to take into consideration:

- Packaging for maintenance of temperature control - active and passive shipping systems
- Use of monitoring devices
- Courier selection and transit time
- Planning for deviations

PACKAGING FOR MAINTENANCE OF TEMPERATURE CONTROL – ACTIVE AND PASSIVE SHIPPING SYSTEMS

There are many shipping solutions readily available in the market that provide a degree of confidence when shipping temperature sensitive products. As indicated above, the vast majority of clinical trial consignments involve relatively small volumes of material shipped with a high degree of urgency. These smaller volume shipments lend themselves to usage of a passive shipping systems, such as an insulated shipping containers, while larger shipments (such as those going to a regional depot) may be more successful if an active shipping system is used. System selection represents just one decision required from sponsor company supply management teams.

Insulated shippers are available in both one-way and reusable forms; selection will depend on specific study requirements. Pack-out configurations often vary seasonally, though this should be determined in conjunction with the manufacturer. Consultation with individual manufacturers regarding their product can also provide valuable insight into the correct preparation and conditioning of specific shippers. It is amazing to see how a seemingly minor deviation from standard conditioning procedures can adversely effect individual shipments.

Qualification and validation of insulated shippers are terms which previously caused a great deal of confusion. A few years ago it was acceptable to discuss validation of shippers openly, however qualification is now seen and the appropriate terms are applied. Validation refers to a highly controlled reproducible process, whilst qualification offers the ability to provide a high degree of assurance within acceptable parameters. Qualification is now the generally accepted term, whether we are referring to prequalified shipping systems (qualification is based on industry standard temperature profiles) or a protocol-specific qualified shipping system. We have seen a



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trend toward the use of prequalified shipping systems which, although costly, do provide a high level of reassurance.

Active (or closed) systems are becoming increasingly popular as a bulk drug shipping solution. Solutions such as the Envirotainer provide a thermostatically controlled environment whereas a Unicooler also provides heating as part of the control process. These products provide a higher level of security, reducing the risk of tampering or theft during in transit. As they are 'closed systems', cooling elements may be replenished without the need to expose product, and an external temperature readout allows immediate determination of the integrity of the product. These systems do have some disadvantages, as they are often larger and more cumbersome to handle, so it is important that the site which has the responsibility of handling such a delivery is able to provide the necessary capacity. Typically, they are not an 'off the shelf solution' so a degree of shipment planning and anticipation is required.

USE OF MONITORING DEVICES

Temperature monitoring of shipments is an area in which 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 units have appeared on the market. These new monitors have improved communication methods such as RFID or USB compatibility. They also boast more sophisticated internal and analytical software. The criteria used by quality departments to judge a products usability, based on stability data, can be programmed directly into the monitor. This reduces the number of quality reviews of temperature excursions, while improving accuracy and turnaround times.

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 judgement in the event of a temperature excursion. This may not be a concern in cases where the shipped product is relatively cheap and readily available.

Often the shipment analysis results are thrown away with the monitor if there are no temperature excursions. Therefore, 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 now making data collection practical and cost effective. There may come a time when regulators will require a record of temperature conditions to which a product has been exposed throughout its life cycle. 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 to facilitate these decisions.

COURIER SELECTION AND TRANSIT TIMES

There are a wide range of courier companies specialising in transportation of cold chain materials. Premium couriers are the most commonly used providers for long distance destinations, due to the small quantities being shipped for clinical trial. However, where the transit times are less than 48 hours, an express service provider is often used. Premium couriers will monitor shipments and provide special handling if the shipping system is not able to maintain



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the correct temperature for the duration of the transit. When the transit time is expected to be less than 48 hours, and a robust shipping system is used, no special handling should be required and an express courier will be sufficient.

PLANNING FOR DEVIATIONS

As we all know, deviations are possible with any shipment; however, with temperature-sensitive shipments, any deviation outside of specified temperature ranges can affect the integrity of the product. On many occasions, fluctuations outside pre-set temperature ranges can be as little as 1°C for only a few minutes. That said, this product still cannot be released or administered unless the site can verify that this deviation has not adversely affected the product. Stability data for temperature-sensitive products is usually available, but this is not provided to the site. Failure to disclose this information to a site could result in avoidable delays or a missed enrolment opportunity, through a lack of visibility of permitted excursions.

Cold chain management is a process that provides many unique challenges; however it is an ever-increasing prerequisite within the pharmaceutical industry. To maximise the success of cold chain management, you should be informed about the shipping process and understand the external factors that could adversely affect your product. Planning and collaboration with shipping solution providers and carriers will improve the chances of success.

CONCLUSION

As with many regulations in clinical trials, the requirements for cold chain 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 improved solutions become available, the expectations for temperature controlled shipping will rise, driving further development. The net result will be improved safety for patients through a continually evolving, fully integrated cold chain network – that is exactly where we want to be.

About the author

Jonathan Calderwood is the Global Marketing Manager for Almac Clinical Services (Almac Group). He was educated in Queen's University, gaining a BSc in Biochemistry, and he holds a Post Graduate Diploma in Computer Science and in Marketing, and is a member of the Chartered Institute of Marketing. Jonathan has extensive experience in clinical trial supply production and project management, as well as in the business development field.

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