UNDERSTANDING THE CHALLENGES OF TEMPERATURE CONTROLLED INVESTIGATIONAL MEDICINAL PRODUCT DISTRIBUTION IN EMERGING MARKETS

WHITEPAPER

WRITTEN BY:
George McAuley,
Product Manager,
Almac Clinical Services

www.almacgroup.com
Temperature Deviation within the supply chain is a complex issue. While the risk of shipments going outside their specifications may never be completely eliminated, it can be minimized by careful planning and control of processes, even in emerging markets.

As clinical trials become more global in nature and the number of biologic investigational products increase, drug developers look to tap into novel patient groups in emerging markets. Exceptional consideration must be given, and a diverse range of challenges must be overcome to effectively forecast, develop, and manage the clinical supply chain in these new markets.

CONSIDERATIONS FOR SUPPLY CHAIN LOGISTICS INCLUDE:

- Varying regulatory requirements
- Depots and supply routes
- Couriers and logistics partners
- Local environmental conditions
- Selection of packaging and shipping containers
- Transporting and storage from site to patient
- Temperature monitoring of supplies

While all of these considerations are standard in traditional markets, they become increasingly critical when distributing in emerging markets.

REGULATORY REQUIREMENTS

Most established markets, and increasingly some developing ones, have very specific and continually evolving regulatory requirements. Knowledge of the requirements in each region, and planning ahead for those requirements, is an essential piece of supply chain management that can save time and help to avoid significant delays during distribution.

The growing focus on additional controls around temperature-controlled distribution of IMP’s is a global trend, shown most recently with the Chinese Ministry of Health and India’s Central Drugs Standard Control Organization releasing guidance on Good Supply Practice and temperature monitoring of supplies in transit.

As regulations evolve globally, the pharmaceutical industry will have to ensure they have robust processes and systems in place, as well as proper regulatory knowledge for effective planning, to manage risk and demonstrate temperature stability throughout the entire supply chain.

DEPOTS AND SUPPLY ROUTES

The location of supply depots and their proximity to key markets are important factors in planning an effective supply chain. Having a shipping depot located close to the point of consumption brings a number of benefits including improved continuity of supply, less risk of stock-out, reduced shipping time, and minimized exposure to environmental conditions.

When choosing a depot, companies must consider: location within the territory; temperature-controlled storage capacity; power failure plans; and shipping and receiving procedures.

An existing relationship with the service provider may permit selection and qualification of the depot based on review of documentation, but for new suppliers it is likely that an on-site audit will need to be performed to ensure that facilities and procedures are of an acceptable standard. All of these activities cost time and money and should be included in budget planning.

COURIER AND LOGISTICS PARTNERS

Choice of courier or logistics partner is no less important than choice of shipping depot. Some depots may be part of a larger service organization offering both storage and shipping, but if not, should be able to assist with courier selection as they will have invaluable local knowledge.

Shipments to depots are likely to cross international boundaries, and partnering with a courier who has experience with managing customs clearance of temperature sensitive material will be extremely important. The possibility of shipment retention by the destination country’s customs agency is highly likely, particularly for IMP’s. Temperature must be controlled even during the retention period. This can be accomplished with either an active or passive temperature control system.
When using passive temperature control units, a courier who has the ability to refresh ice packs while the shipment is retained by customs should be used where possible. Where it is not possible to refresh ice packs, the courier should be asked to arrange appropriate temperature-sensitive storage conditions while the supplies are moving through customs.

Courier service from depot to site or site to patient also needs significant consideration. For example, is the shipment time-sensitive and requiring same day or next day delivery? In some markets, same or next day service may be available in major population centers but not in more remote regions. The infrastructure and operating environment in some developing countries may differ significantly from that in more established territories, and the courier service normally used in a company’s home territory may not be available or may not have the same capabilities in emerging markets.

With these points in mind, choosing a logistics partner with regional experience and storage capabilities will reduce temperature variance and waste, as well as significantly improve trial distribution efficiency.

**LOCAL ENVIRONMENTAL CONDITIONS**

Local environmental conditions will have a major impact on the conditions in which supplies are shipped and how they arrive for use. Temperature differences from region to region and from season to season, even within countries, are common. The graphs in Figure 1 offer a snapshot of the variations that can be present in some markets.

For example, in Sao Paulo we see a temperate climate with little seasonal shift, however for Moscow and Beijing there is a huge swing between summer and winter conditions. For New Delhi, the challenge is the high summer temperatures with a daily mean average of 40° C in June, with peaks of up to 45° C not uncommon.

Although we cannot control the weather in a region, every precaution must be taken, and temperature variations must be managed through careful selection of shipping containers and reliable monitoring. Knowledge of, and planning for, average seasonal climates for each country receiving goods is imperative for an effective logistics plan.

**Figure 1: World mean temperatures**

*Source: worldweather.org*
PACKAGING AND SHIPPING CONTAINERS

An active temperature-controlled system may be employed for delivery to depots; for example, using temperature controlled vehicles or battery powered refrigerated/heated shipping units. Active systems may not be available or may not operate to the same standards in remote markets; and even if available, the systems may be cost prohibitive for the final leg of the supply chain, from depot to site or from site to patient. In these cases, a passive temperature-controlled system must be employed.

Passive systems typically consist of an insulated shipper packed with dry ice for frozen shipments, or gel packs which have been conditioned by heating or cooling. Passive systems are qualified to maintain internal temperature within a given band, for a specified time, based on a set range of external temperatures. These systems cannot react to extreme changes in the external environment, so while having different winter and summer pack-out plans for each region will help, there will certainly be occasions where shipments will go out of specification. Common causes for this are extreme weather events and seasonal anomalies, incorrect packaging of supplies, mishandling of shipments in transit, and delays in delivery of supplies.

Choosing an appropriate temperature-controlled system, proper packing of materials, and understanding and planning for regional weather conditions will decrease the chance of temperature excursions when distributing to emerging regions.

FROM SITE TO PATIENT

If the IMP is to be taken to the patient’s home for administration, the transport of the medication from the site to the patient’s home should also be taken into account. In many situations in remote regions, this will either be via public transport, without air conditioning, or on foot. In these instances, a cooler and ice pack can be provided to enable the drug to stay in a temperature-controlled environment during the transition.

Home storage for temperature-sensitive material also requires planning. Even in the 21st century, there are still homes that may not have electricity or refrigeration. If the product has limited stability data and must stay under refrigeration at all times, this important factor should be considered when enrolling patients into the clinical trial.

TEMPERATURE MONITORING

Temperature monitoring is the only way to ensure excursions are captured and the integrity of the IMP is maintained. There are several options to choose from, depending on distance, time, and region of distribution.

The most basic of these is the indicator-type monitor. These monitors will show if temperature goes above or below a specified threshold indicating the existence of a problem. Some will do this without showing the minimum/maximum temperature, and some will show the range but not how long the supplies were out of specification.

The indicator monitor may be suitable if shipping a low-value/high-volume product. Indicator-type monitors are generally not suitable for use in emerging markets, as they place responsibility on the receiving site to interpret the information provided and make a decision to accept or reject supplies. In the event that an out of specification result is reported, there is no opportunity to review temperature data to establish how long the shipment was out of specification or at what time the result was recorded.

For some time, there have been temperature monitors available which will record and report electronically on temperature, giving a more complete picture of the temperature data. These monitors allow an investigation to be performed to determine when the temperature excursion happened and for how long supplies were outside specification. This information can be compared to stability data and transit information, allowing for an informed decision to be made to either accept or reject materials. This also helps determine at what point the problem occurred and may help with future distribution improvements.

Historically, one drawback was the need for specialized hardware to extract the data from the monitor: hardware which many sites would not have access to. In the past, this was resolved by returning monitors to the shipping depot to extract the report, which was then forwarded to decision makers. Reverse logistics is difficult, slow and expensive, particularly in emerging markets, and should be avoided where possible.
TECHNOLOGICAL ADVANCES

In recent years, a range of USB temperature monitors have become available which can be plugged into any computer with a USB port. Most of these monitors will display a PDF report which can be opened by the site and will typically show a plot of temperatures against time, as well as summary information about the shipment. This is a big advantage as it provides the information immediately at point of receipt. These newer temperature monitors also allow more complex temperature profiles to be created and programmed into the monitor, to better match stability data, meaning fewer false out of specification alarms.

Although these advances in temperature monitor technology are beneficial, managing the return of temperature reports can be challenging. The starting point for maintaining compliance is having visibility of all shipments and a link to the shipping monitors which were used with that shipment. Further decisions will need to be taken on whether to instruct sites to return only reports which have alarmed, so that out of specification shipments can be investigated and remedied, or if sites should return all temperature reports so there is complete visibility of the supply chain.

Either way, an agreed process or system needs to be established for managing the return of temperature monitor reports – this could be via email, or a web interface which allows sites to upload the reports to a central database. Additionally, a process or system should exist for storing and indexing returned monitor reports, and flagging those shipments which need attention. (See Figure 2)

Regardless of the process that is put in place, clear instructions should be given to the site so it understands what is expected and how the decision to accept or reject supplies will be communicated. When dealing with emerging markets, remember that receiving sites may not speak or read English fluently, so additional steps should be considered to overcome potential language barriers.

Undoubtedly, use of temperature monitors will add to the overall cost of individual shipments. However, temperature monitoring of supplies will provide assurance that supplies have been delivered to the site under appropriate conditions, and may, in some cases, save money by allowing the opportunity to review and accept seemingly out of specification products in the event of a false alarm.

Figure 2: High-level view of process for managing shipping temperature data
MINIMIZING RISK, MAXIMIZING EFFICIENCY

The risk of temperature deviation within the supply chain can be minimized by careful planning and control of processes, but it cannot be eliminated entirely. Vendor selection can give assurance that the shipping depot has appropriate facilities and processes to maintain supplies under the correct validated conditions. Likewise, planning how supplies are packed for shipping and choosing the right courier can minimize the risks to supplies during transportation, and use of a temperature monitor coupled with a robust process for return and storage of temperature data will demonstrate that supplies have been maintained within acceptable limits during distribution.

Careful consideration of all these factors and subsequent planning in the supply chain will lead to an improved and more efficient emerging market distribution plan.

GET IN TOUCH

UK
Almac Group
(Global Headquarters)
9 Charlestown Road
Seagoe Industrial Estate
Craigavon
BT63 5PW
United Kingdom
info@almacgroup.com
+44 28 3836 2436

US
Almac Group
(US Headquarters)
25 Fretz Road
Souderton, PA 18964
United States of America
info@almacgroup.com
+1 215 660 8500

SINGAPORE
Almac Pharmaceutical Services Pte. Ltd.
9 Changi South Street 3
#01-01
Singapore 486361
info@almacgroup.com
+65 6309 0720