ThermoFisher SCIENTIFIC

THE CHALLENGE OF KEEPING COOL

END-TO-END TEMPERATURE MANAGEMENT FOR THE CLINICAL SUPPLY CHAIN

patheon

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Introduction

From manufacturing through delivery to the patient, pharmaceutical drugs must be maintained within strict temperature guidelines to protect the efficacy of the product. This level of protection is not exclusive to refrigerated and frozen product. Even ambient product (generally 15°C to 25°C) needs protection in climates where it can be at risk of becoming too warm or cold.

Temperature management is not just about storage conditions

Manufacturing processes need to ensure the product remains within stated guidelines.

Packaging and labeling needs to be efficient so that materials stay within required thresholds.

According to **EU GDP guidelines**, "the required storage conditions for medicinal products should be maintained during transportation within the defined limits as described by the manufacturers or on the outer packaging."

Finally, once the product arrives at an investigator site and, in some cases, as it travels to a patient's residence for ongoing administration, **it needs a controlled environment.**

End-to-end temperature management is critical and requires detailed quality oversight. Any deviation must be documented with a supporting Corrective Action–Preventative Action (CAPA) process to mitigate future risk.

Recall requires item-level control & tracking

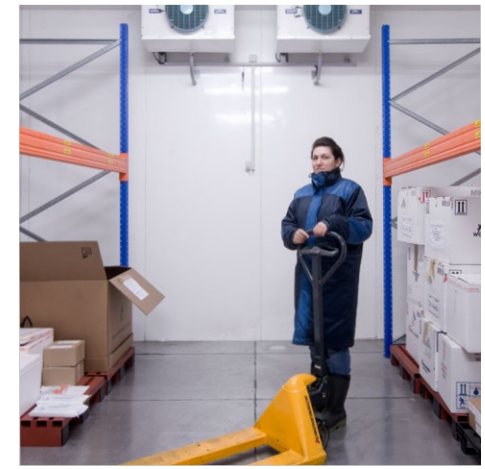
US FDA issues recall for product which is a 20% IV Fat Emulsion, in 100mL dose, distributed between 8/11/17 and 8/31/17 to hospitals and healthcare providers in the United States, to the user level. The product was exposed to subfreezing temperatures during transit to a distribution facility. The subfreezing temperature was outside of the acceptable storage range listed on the product labeling. If accidentally frozen the emulsion droplets would increase in size leading to potentially serious and life-threatening health consequences

Managing the storage environment

Pharmaceutical product requires a controlled environment at all temperature ranges. Terms such as “ambient”, “room temperature” and “cold chain” are too general and subject to interpretation. For example, World Health Organization, U.S. Pharmacopeia, European Pharmacopeia and Japanese Pharmacopeia have four different temperature ranges when referring to “cold” storage. So when referring to storage conditions, it’s always best to state a defined temperature range e.g. 2°C to 8°C.

When materials arrive at their destination, whether that is a manufacturing facility, large distribution center or an investigator site, they must be moved into the required environment with minimal delay. At a manufacturing or distribution center, shipping paperwork has to be verified and materials transferred into the required environment to complete the receiving process as quick as possible. In some situations a facility that is specialized for cold temperatures may have a refrigerated dock so materials always stay within environment. At an investigator site, inbound shipments should be clearly labeled as cold/frozen so they can be expedited into appropriate storage and not risk sitting in a centralized shipping/receiving room for an extended period of time.

Storage areas must be equipped with temperature and humidity monitoring systems that provide continuous data logging. Additionally, these systems should include configurable thresholds that, if reached, trigger an alarm that initiates an immediate response by the facility staff 7/24/365. Recent natural disasters have reinforced the need for redundant systems, backup generators, as well as adequate supply of on hand fuel and coolant reserves in the event of power outages, flooding etc. While sophisticated systems may be common in large pharma-specific manufacturing and distribution centers, it is less likely that an investigator site has similar equipment. A trial sponsor should verify the refrigeration equipment that is in use, possibly making temperature loggers and alarms a requirement where their Investigational Medicinal Product (IMP) has strict guidelines. In a similar fashion, if the trial allows patients to self-administer at home, the sponsor might supply a small refrigeration device with appropriate monitors. While this may not be necessary for every trial, in some situations with high-value product, or where there is potential of critical adverse effects, it is likely well worth the investment.



What are the regulatory definitions for “ambient,” “room temperature” and “cold chain”

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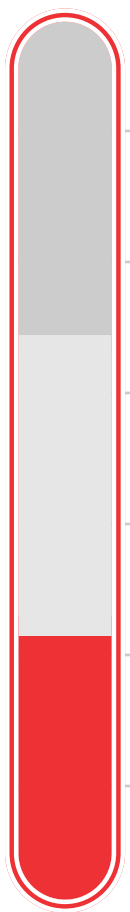

	European Pharmacopoeia (Pharm.Eur.)	World Health Organization (WHO)	U.S. Pharmacopeia (USP)	Japanese Pharmacopeia (JP)
Frozen/deep-freeze	Below -15°C	-20°C	–	–
Refrigerated	2°C – 8°C	–	–	–
Cold	8°C – 15°C	2°C – 8°C	<8°C	1°C – 15°C
Cool	8°C – 15°C	8°C – 15°C	8°C – 15°C	–
Room temperature	15°C – 25°C	15°C – 25°C	temperature prevailing in a work area	1°C – 30°C
Controlled room temperature	–	–	20°C – 25°C excursions between 15°C and 30°C are allowed	–
Ambient temperature	–	15°C – 25°C or 30°C depending on climatic conditions	–	–

Packaging and labeling in environment

If the packaging and labeling process takes place in a separate facility, it is important to understand the storage environment at that location. Product will need to be transported to that facility in vehicles and/or containers that maintain the required temperature. Just as with the primary distribution center, special care must be taken to provide appropriate interim storage at the packaging provider until the job is complete and materials are transported back to the primary distribution center.

Temperature management is important even when packing at the same facility. Product must move from refrigeration / freezer units to the packaging room. Specialized containers that will maintain product temperature are typically used for protection during transit from the warehouse storage to the packaging room. In some situations smaller freezers with short-term battery power can be used to minimize time out of environment.

Labeling product stored refrigerated frozen or deep frozen involves special considerations. Adhesives behave differently at different temperatures. Selecting the right material is dependent on the temperature the label is applied at, the temperature it will be stored at (and over what period of time), and the material it is being adhered to. In some situations it may be possible to “warm” the product for a short period of time in support of running a packaging and labeling job. In other situations, the temperature guidelines are so strict that it requires packaging in a cold environment.

Completing a packaging and labeling process in a 2°C – 8°C environment isn’t uncommon amongst experienced clinical supply providers. However, packaging product that needs to be maintained in a -20°C environment is an entirely different matter. Many providers address this need by packaging over dry ice. The product is moved from the refrigerated / frozen storage into a well-ventilated work area where staff completes the process using specialized tables with dry ice baths. Timers are used to ensure they perform the job within allowable thresholds e.g. 8 minutes or less. The process is manual with limited controls and without validation.

There are providers that will pack at -20°C so the product never leaves the required environment. Needless to say staff is in protective clothing, and multiple teams are used to allow the staff to rotate into / out of environment. A clear advantage is that the product never leaves the environment and, as such, standard quality assurance and validation controls are in place.

Managing the transportation environment

Any time product is moved it requires protection to ensure it stays within defined limits. When product is moving in bulk, such as from the batch drug manufacturing to distribution facility, refrigerated trucks can be used to avoid using specialized packaging material. These trucks would be equipped with temperature monitors and should have backup systems in place. If materials are to be shipped via air or ocean cargo, 'active shippers' can be leased to create a temperature managed environment for palletized materials.

When dealing with smaller shipments, such as those to an investigator site, it is more typical to use thermal packaging material ("passive shippers"). In this situation an insulated container with preconditioned coolant material is used for the individual shipment. Passive shippers are available with different 'hold times' to provide protection for 24, 72, 96+ hours. Temperature loggers can be placed inside the shipper and, upon delivery, the data can be reviewed to ensure there was no excursion throughout the shipment life cycle. For high-value shipments, GPS loggers can introduce additional visibility to enable proactive redirect in the event of an unexpected delay.

Recent advances in technology have introduced shippers that, for the same internal capacity, have smaller external dimensions while reducing the likelihood of temperature excursions significantly. These shippers use phase change material (PCM) rather than traditional water based coolants. An important advantage to PCM is that when the container is placed into the required storage environment, the coolant maintains the thermal performance, effectively 'hibernating' and extending the overall hold time. When dealing with international shipments that are subject to Customs clearance, this offers significant advantages. Where a Customs office has refrigerated storage, it eliminates the need to replenish water/ gel-based coolants if there are unexpected delays. Overall, high performance, re-usable shippers can reduce the temperature excursion rate by up to 80% as seen within the clinical trial industry based on the extended overall hold time.

All transportation service providers are not equal in their capabilities. In the context of a global trial where shipments may travel to remote locations with limited infrastructure, it's important to investigate if there's a track record of success for shipping on time, in full, and at temperature. Working with an experienced 3rd party logistics provider can offer significant advantages for the clinical supply team. They can make recommendations on the type of packaging that is most appropriate and, in many cases, can also supply the preconditioned shipper. They work with a network of established, quality-vetted suppliers and can recommend the best mode of transportation and also the best supplier for the given origin and destination point. In some situations the logistics provider can also offer invaluable support when it comes to preparing the required import/export documentation.

Planning for end-to-end temperature management

The most important aspect of dealing with temperature managed product is making sure every step in the journey is subject to detailed quality oversight. Establishing the requirements up front is essential.

Clearly define guidelines that govern the environment your product must be handled at and, if possible, the maximum time it can be out of environment and at what temperature ranges.

Perform transportation lane mapping to know where the risks are within the supply chain and which are the worst-case routes for external temperatures. Ensure qualification encompasses these.

Ensure there are Standard Operating Procedures for every aspect of the product handling.

External providers can be invaluable resources to provide input and to share their own best practices.

Clearly defined communication protocols must exist throughout the supply chain to ensure any excursion is immediately documented and reported.

Planning early and minimizing the number of providers and handoffs will help to ensure zero excursions and maximum product integrity.

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