An Introduction to Cold Chain Management

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Welcome to “Supply Chain Forum.”

Control of the supply chain is an extremely important topic in pharmaceutical and medical device manufacturing. Supply chain involves all aspects of product manufacturing to some degree. Raw materials, intermediates, bulk product, packaged product, auxiliary materials such as filters and lubricants, and other myriad materials all come through the supply chain. The 2008 China heparin incident and the global diethylene incidents attest to the challenges and criticality of control of the supply chain and the material quality system.

This feature provides a forum for compliance practitioners to share information about topics associated with the materials quality system. The information provided will be helpful and practical so as to enable application in actual work situations. “Supply Chain Forum” will address successful strategies, approaches, and practices associated with this important aspect of pharmaceutical and device manufacturing. We intend “Supply Chain Forum” to be a useful resource that provides valuable information and enhances compliance performance.

Reader comments, questions, and suggestions are needed to help us fulfill the column’s objective. Case studies illustrating actual experiences associated with supply chain management and control are most welcome. Please send your comments and suggestions to column coordinator Ernest Castiaux at Ecastiaux@hotmail.com or journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS

The following key points are discussed:

- Cold chain can be defined as the supply and distribution chain for products that must be kept within a specific temperature range.
- Loss of control of required storage conditions may cause the product to lose integrity, stability, or potency rendering the product ineffective.
- All storage and handling practices for cold chain shipments are regulated per US Food and Drug Administration current good manufacturing practices. There are special requirements governing infectious or hazardous shipments as promulgated by the US Department of Transportation and the International Air Transport Association.
• United States Pharmacopeia 33 chapter <1079> “Good Storage and Shipping Practices” also provides guidance for handling cold chain pharmaceutical products.
• A structured approach to cold chain management is recommended including packaging process and shipping validation. Transport and storage are also included in the methodology.
• Written procedures are mandatory. Personnel training is essential. Temperature monitoring during shipping is highly critical.
• Case studies demonstrating deficient cold chain control practices illustrate key points.

INTRODUCTION

Cold chain can be defined as the supply and distribution chain for products that must be kept within a specific temperature range. The shipping of a drug product that requires temperature controlled packaging is a challenge.

Environmental conditions are critical to ensure drug product quality. If there is a loss of control in the cold chain at any time during the process, a temperature sensitive drug may lose its integrity, stability, or potency. A temperature sensitive drug may become ineffective if exposed to inappropriate temperatures within the supply chain. Frequently, this means that during storage and transport the drug temperature must be held between refrigeration temperatures of 2°-8° C.

The number of temperature-sensitive products is rapidly increasing. Most shipments of biologics are transported via cold chain. The Biotechnology Industry Organization (BIO) has estimated that the average growth of temperature sensitive products will be 15% per year and that this growth exceeds that of the rest of the pharmaceutical industry (1).

Regulations

All storage and handling practices for cold chain shipments are regulated per US Food and Drug Administration current good manufacturing practice (CGMP) guidelines. 21 CFR 211.142 and 21 CFR 150 outline the basic requirements for the storage and distribution of drug products (2). This regulation also pertains to clinical sample shipments. The distribution of clinical kits while ensuring that they maintain proper temperature is just as critical as for commercial drugs. Medical devices containing a drug or biologic product in combination will also fall under these sections of the CGMPs.

Additionally, there are special requirements governing infectious/hazardous shipments as promulgated by the US Department of Transportation (DOT) (3) and the International Air Transport Association (IATA) (4). They pertain to protecting the product container from damage that could result in leakage and human exposure. There are many cold chain drug products that are governed by these requirements.

USP

In addition to the FDA Part 211 requirements and possible hazardous materials requirements, the United States Pharmacopeia (USP) 33 chapter <1079> “Good Storage and Shipping Practices” provides guidance for handling cold chain pharmaceutical products (5). This chapter provides the requirements for ensuring a product’s “identity, strength, quality, and purity” across the entire distribution channel—from manufacturer to end user covering the handling and storage of products in warehouses, during transit, and in pharmacies.

USP 33 <1079> “Good Storage and Shipping Practices” states that “Operational and performance testing should be part of a formal qualification protocol.” This thermal testing qualification may be performed using a validated controlled temperature chamber or actual transit testing using the expected transport method and shipping lanes (origin to destination). Certified test labs use validated environmental chambers to simulate the ambient temperature that the package may encounter using standard profiles. These profiles simulate the transit of the package through the distribution channel with changes in temperature and duration. The profiles are established by the International Safe Transport Association (ISTA) and cover both land and air transport of various times and package configurations (6). Detailed test reports are neces-
sary in order to demonstrate support of the regulatory requirements.

AN APPROACH TO COLD CHAIN MANAGEMENT
The need for special handling, regulatory considerations, and the increase in the quantity of items being shipped requires a structured approach in order to ensure that the drug product moves from the manufacturing point to the patient under the correct environmental conditions. The packaging process must be qualified via documented testing to ensure that the packaging configuration and transit method being used meets pre-determined acceptance criteria with a high degree of assurance. There have been several FDA 483 citations issued for deficient shipping validation.

The cold chain system consists of not only the packaging of the insulated container with the appropriate proven quantity of refrigerants, but also the transport and storage of the drug product. All of these elements should be analyzed, measured, understood, and qualified to ensure that the quality of the product and patient safety is not compromised.

There must be written procedures in place that describe proper handling of the drug product when it is being stored and transported. Personnel should know how to monitor temperatures and how to respond to conditions when the desired temperature is outside the allowed range. The method of monitoring the temperature of the drug product during storage and in transit is critical.

The following two cold chain case studies exemplify failures in the respective firm’s approach to cold chain management.

Case Study Number One
The temperature monitor for a shipment indicated, upon receipt, that the drug product exceeded 8°C for the duration of the shipment. The subsequent examination found that the shipment was packed into the correct container configuration according to the approved standard operating procedure (SOP). All prior shipments were received with the temperature monitor indicating the product had remained within the desired 2°-8°C temperature range.

An investigation revealed that the qualification of the insulated container and gel pack configuration had been performed retrospectively using actual transit data from shipments that had occurred during the winter. The temperature data for the product shipments was within range and, therefore, the configuration was qualified. When this shipment was made during the late spring, at a much higher ambient temperature, the configuration did not have enough cooling capacity to hold the temperature and lacked sufficient insulating capacity to prevent the conduction of external heat to the drug product payload. Thus the validation lacked a formal qualification that took into account all of the conditions expected during transit to demonstrate that the packaging configuration met pre-determined specifications.

Validation protocols for cold chain supply chains should require representative worst-case maximum temperature exposure situations. When challenging the transportation of products that require controlled moderate temperatures, worst-case high temperatures (summer conditions) and worst-case low temperatures (winter conditions) should be utilized.

Case Study Number Two
A shipment was prepared using a qualified container and an approved SOP. The configuration was validated by following Center for Drug Evaluation and Research’s (CDER) General Principles of Process Validation (7), yet the temperature monitor indicated that the shipment never achieved a temperature of less than 8°C (temperature was high). The proper product temperature range requirement was 2°-8°C.

An investigation indicated that the correct quantity and type of refrigerants were used and properly configured within the insulated container. The research determined that a pallet of refrigerants (gel packs) had arrived the day prior to the day of shipment and were placed in the cold storage area. The refrigerants had felt cold to the individual packing the container, so it was not noticed that the refrigerants were not thoroughly chilled and, therefore, did not have the cooling capacity required. The root
cause was determined to be that the refrigerants had not been held long enough at the desired low temperature.

If refrigerants are not held at the desired cold temperature, either frozen or cold, for a sufficient amount of time, then the outer layer of the gel may feel cold, but the gel will not be at a uniform temperature. When cases of refrigerants are received and stored on a pallet, several days in cold or frozen storage are required to ensure complete chilling throughout prior to use.

Procedures describing the preparation of refrigerants must be clearly specified. This includes the specific temperature range at which refrigerants are stored, and the length of time refrigerants are stored to prepare refrigerants for actual use in shipping. Simply feeling the refrigerants without documented storage conditions traceability is not adequate.

CONCLUSION
The special requirements for handling cold chain pharmaceutical products can be challenging. However, they are manageable with proper preparation, using qualified processes, and ensuring that procedures are being correctly followed.

REFERENCES
5. USP, USP 33, <1079> “Good Storage and Shipping Practices,” US Pharmacopeia.

ARTICLE ACRONYM LISTING
CGMP  Current Good Manufacturing Practice
DOT   US Department of Transportation
FDA   US Food and Drug Administration
IATA  International Air Transport Association
SOP   Standard Operating Procedure
USP   United States Pharmacopeia

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