Introduction to Cold Chain Management—Part II

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“Supply Chain Forum” provides a forum for compliance practitioners to share information about topics associated with the materials quality system. The information provided is helpful and practical so as to enable application in actual work situations.

Reader comments, questions, and suggestions are needed to help us fulfill the column’s objective. Suggestions for future discussion topics and 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.

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KEY POINTS

The following key points are discussed:

• Cold chain is the supply and distribution chain for products that must be kept within a specific temperature range.
• Compliance practitioners must be aware of the regulatory requirements and appropriate practices to ensure that the handling and distribution of drug products and their components are under good control.
• Government agencies and industry organizations intend to assure the quality, efficacy, and safety of the drug products being distributed to the public.
• PDA Technical Reports No. 39 and No. 46 provide guidance for the quality of temperature sensitive drug products through the supply chain all the way through the “last mile” to the actual product user.
• International Safe Transport Association and American Society of Testing and Materials provide methods for testing of packaging.
• United States Pharmacopeia chapter <1079> Good Storage and Shipping Practices addresses storage and shipping practices for pharmaceutical products including standard practices, controls, standard operating procedures, and other systems applications.
• Questions for evaluation of a new storage location are presented. Areas discussed include documentation, receiving and facility, and temperature-controlled storage.
• Several new developments and technology including SenseAware and SMARTemp applicable to pharmaceutical distribution are described.

INTRODUCTION
Cold chain can be defined as the supply and distribution chain for products that must be kept within a specific temperature range. As noted in a previous paper (1), proper control of the supply chain is an extremely important aspect in pharmaceutical and medical device manufacturing. Loss of control of required storage conditions may cause the product to lose integrity, stability, or potency rendering the product ineffective.

Compliance practitioners must be aware of the regulatory requirements and appropriate practices to ensure that the handling and distribution of drug product and their components are under good control. All storage and handling practices for cold chain shipments are regulated per US Food and Drug Administration current good manufacturing practice (CGMP) (2). There are special requirements governing infectious or hazardous shipments as promulgated by the US Department of Transportation (DOT) (3) and the International Air Transport Association (IATA) (4). United States Pharmacopeia (USP) 33 <1079> “Good Storage and Shipping Practices” also provides guidance for handling cold chain pharmaceutical products (5).

A structured approach to cold chain management is recommended including shipping validation. Transport and storage must also be included in the methodology. Written procedures are mandatory. Personnel training is essential. Temperature monitoring during shipping is highly critical.

This discussion continues a review of guidelines and other relevant documentation. Also introduced will be some questions to consider when evaluating a new storage location to determine quality compliance and minimize risk during cold chain distribution. Also discussed are some of the new developments and technology used to monitor the supply chain.

REQUIREMENTS, EXPECTATIONS, AND BEST PRACTICES
FDA, Health Canada (6), European Medicines Agency (EMA) (7), and the World Health Organization (8) all have as their objective the quality, efficacy, and safety of the drug products being distributed to the public. Any facility may be inspected by any or all of these agencies. In addition to the GMP and good distribution practice (GDP) requirements of the regulatory agencies, there are guidelines developed by industrial associations and organizations that have established best practices. Some examples are the Parenteral Drug Association (PDA) Technical Reports # 39 and #46 (9, 10), International Safe Transport Association (ISTA) Standards (11), and USP <1079> (5). Other available guidelines include the International Air Transport Association’s (IATA) Chapter 17 (4) and from the Health Distribution Management Association (HDMA) (12).

PDA Technical Reports
PDA Technical Report No. 39, “Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation Environment,” and PDA Technical Report No. 46, “Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User,” provide guidance for the quality of temperature sensitive drug products through the supply chain all the way through the “last mile” to the actual product user. These reports discuss the processes to consider while developing a distribution chain, and the underlying principles of qualification of the transport methods.

One must have stability data to support the transportation method being used, and the impact on the drug product that may occur due to temperature excursion. The PDA guidance regarding the product stability states the following:

The idea is to evaluate stability data from long-term and accelerated stability studies, temperature-exursion studies, and/or thermal cycling studies to predict the impact of temperature excursions on medicinal product quality during the transportation process.
International Safe Transport Association and American Society of Testing and Materials
In addition to temperature and stability concerns, there are two organizations that provide methods for testing of packaging.

ISTA publishes standards for the testing of packaging for different types of packaging and temperature conditions. They provide test specifications for evaluating the shipping performance of packaging using different transit modes to ensure that packages will perform as expected. These standards describe tests for a variety of attributes in addition to temperature, such as shock and vibration. The American Society of Testing and Materials (ASTM) (13) has also developed test methods and specification for materials being used. Qualified containers are necessary to prevent quality problems during distribution.

USP General Chapter <1079> “Good Storage and Shipping Practices”
Compliance professionals should be very familiar with USP General Chapter <1079>. This chapter is presently undergoing a revision. It addresses good storage and shipping practices for pharmaceutical products. It should be noted that these storage and shipping practices pertain to all drugs, not just cold chain items. The introduction describes the chapter as providing “general guidance concerning storing, distributing, and shipping of Pharmacopeial preparations. It describes procedures to maintain proper storage environments for individual articles and to ensure a preparation’s integrity, including its appearance, until it reaches the user.”

Another purpose of USP General Chapter <1079> is to provide a management systems approach. It recommends standard practices, controls, standard operating procedures (SOPs), and robust processes that should be developed to continuously improve the storage and distribution systems of drug products to the consumer.

In order to maintain drug integrity, the drug product and ingredients must be stored and handled within the appropriate temperature conditions. The chapter provides guidance for establishing temperature profiles and qualification protocols. The shelf life of a drug product is a function of the temperature and humidity experienced within the supply chain as much as a function of the formulation. This chapter also addresses temperature storage statements on labeling and briefly discusses stability requirements. Pharmaceutical stability is more fully addressed in USP <1150> “Pharmaceutical Stability” (14).

All of these standards, guidelines, and regulations must be followed to ensure product quality and a successful defense if audited by a regulatory body.

EVALUATING A NEW STORAGE LOCATION
When considering a new storage location, the following assessment tool questions should be considered, as well as an understanding of the FDA Part 211 requirements for storage and handling; these questions also have a loss control perspective:

- **Documentation**
  - Are there SOPs covering all GMP activities?
  - Are SOPs well written, signed, approved, and available to employees?
  - Is there documented training to GMP principles by a qualified person in relation to function?
  - Is there a quality agreement in place with any sub-contractors?

- **Receiving and facility**
  - Upon receipt, are goods inspected for damage and accuracy?
  - What controls are in place to restrict and monitor access to the product storage area?
  - Who approves receipt of goods?
  - If there is a receipt discrepancy, is there a SOP on how to proceed?
  - How long are the goods on the dock prior to placement in appropriate storage conditions?
  - Are there written procedures in place on how to inspect products upon receipt, including actions to be taken in the event of any suspected or confirmed temperature excursion?

- **Temperature controlled storage**
  - Is the equipment (recorders, etc.) related to temperature-controlled storage calibrated?
  - If it is a cold chain item, are temperatures reviewed and logged at time of receipt?
• Was temperature mapping performed? If controlled room temperature, was mapping done in both summer and winter?
• Do the temperature controlled spaces operate on separate cooling systems?
• Is there temperature control system redundancy?
• Do storage spaces have common or dedicated power supply and backup generators?
• How often are the backup generators tested?
• If diesel powered generators, what is the fuel capacity in days or hours?
• What is the fuel supply monitoring and replenishment program?
• Is the temperature and humidity for each storage space monitored and recorded 24/7?
• Are the doors to temperature controlled spaces alarmed?
• Does the alarm sound if doors remain open for a specific period of time?
• Where are the alarm received and the response procedure?
• Are the temperature controlled spaces protected by an automatic fire sprinkler?

The TSA website states that a key component of TSA’s response to the 9/11 Act mandate is the Certified Cargo Screening Program (CCSP) as follows:

Under CCSP TSA will certify cargo screening facilities located throughout the United States that screen cargo prior to providing it to airlines for shipment on passenger flights. The program is designed to enable vetted, validated and certified supply chain facilities to meet the 100 percent screening requirement.

This program continues the “known shipper” program put in place by the Department of Homeland Security in February 2004.

Certified Cargo Screening Facilities (CCSF) must carry out a TSA approved security program and adhere to strict chain of custody requirements. Freight forwarders and air couriers have approved facilities. An alternative is for a company with large amount of air freight to become certified by TSA and avoid the concerns of expensive temperature controlled materials being opened for inspection. Another alternative is to use all cargo aircraft (e.g., Federal Express) for shipping drug product.

FedEx SenseAware
FedEx has introduced a tracker (SenseAware) (17) to be able to tell you everything about the condition of a package. The tracker can indicate if it has been opened, dropped, outside of temperature range, light exposure, and GPS location to within a few feet. The GPS and cellular signals are used to provide a real-time position, and all that data is fed through a web platform for the sender to monitor. This multi-sensor device is permitted by the Federal Aviation Administration to be used during flights on FedEx aircraft. It lets you monitor in-transit conditions in near real time. You can share near real-time information with your partners about the shipment conditions and location. An example of one application would be to use this tracking device to transport critical medical packages allowing clinics to track the package via the web and know exactly when the shipment will arrive.
APL SMARTemp

Another innovation is a new device to track temperature-sensitive items that uses another type of communication technology to monitor conditions. APL’s SMARTemp (18) uses the low orbiting iridium communication satellite network. The system allows for the remote monitoring of environmental conditions for shipping containers. The refrigerated shipping containers being transported via rail or on trucks transmit the temperature via satellite to the APL center server. Then the information is sent to the customer if the pre-defined temperature limits are exceeded.

CONCLUSION

Proper control of the supply chain is one of the most important aspects of pharmaceutical and medical device manufacturing. Cold chain management requires a structured approach that includes shipping validation, written procedures, personnel training, and temperature monitoring. The review of guidelines presented in this article includes questions to consider when evaluating new storage locations. Developments in technology may be used to ensure compliance with industry regulations.

REFERENCES

15. Code of Federal Regulations Title 49, Transportation part 1549 – Indirect Air Carrier Security
18. APL SMARTemp, www.apl.washington.edu

ARTICLE ACRONYM LISTING

ASTM American Society for Testing and Materials
CCSF Certified Cargo Screening Facilities
CCSP Certified Cargo Screening Program
CGMP Current Good Manufacturing Practice
DOT US Department of Transportation
EMA European Medicines Agency
FDA US Food and Drug Administration
GDP Good Distribution Practice
GMP Good Manufacturing Practice
HDMA Health Distribution Management Association
IATA International Air Transport Association
ISTA International Safe Transport Association
PDA Parenteral Drug Association
SOPs Standard Operating Procedures
TSA Transportation Security Administration
USP United States Pharmacopeia

ABOUT THE AUTHOR

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