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What is "Cold Chain"?

 The term "cold chain" or "cold chain management" refers to <u>controlled</u> <u>temperature transportation</u> of pharmaceutical products, biologicals, and active ingredients. It also applies to diagnostics, research and investigational materials that require temperature control.

- Cold Chain and Cold Chain Management (CCM) are often used interchangeably
 - Cold chain also refers to refrigerated and frozen products; i.e. "cold chain products"
 - In general, they are products which have storage temperatures cooler than Controlled Room Temperature (CRT), or are very sensitive to temperature variation, on both sides of the storage range.

The Goals of Cold Chain Management

- Keep the material in the designated temperature range
- Comply with all regulations (GMP and non-GMP)
- Minimize costs
- Increase efficiency

- Why the Interest in Cold Chain?
 - Rapid growth of biopharmaceuticals in addition to complex distribution chains with a variety of transportation modes.
 - Global sourcing and distribution
 - Business Impact
 - High value of products
 - Long lead times/Limited supply

Increased scrutiny of product protection during transport

- Examples of storage conditions commonly referred to as cold chain (from USP, not all inclusive):
 - <u>Refrigerator Storage Statement</u> The storage statement for labeling may be as follows: "Store in a refrigerator, 2° C to 8° C (36° F to 46° F)."
 - Freezer Storage Statement The storage statement for labeling may be as follows: "Store in a freezer, –25° C to –10° C (–13° F to 14° F)."

Controlled Cold Temperature

- Involves use of the Mean Kinetic Temperature (MKT) formula
- 2° to 8° C, with excursions allowed down to 0° and up to 15° during storage, shipping and distribution, as long as MKT does not exceed 8°.
- Transient spikes of up to 25 °C are permitted for no more than 24 hours, unless there is additional supporting data.

Global Regulations

- Many countries have issued regulations that address product integrity during transportation.
- The regulations include temperature-controlled products which have specific storage temperature requirements (List references in PDA Technical Report 39)

Canada, Ireland, UK

WHO, South Africa, Austria

- Australia, Czech Republic, China
- Brazil, Venezuela, Singapore, Spain

- Australia, South Korea, European Union

- FDA has the authority to regulate transportation of products:
 - 21 CFR 211.150 of the GMPs addressing distribution procedures;
 - 21 CFR sections 203 and 205 on good practices for holding drugs;
 - NDA/ANDA labeling requirements; and
 - Application and GMP requirements regarding stability and expiration dates.

- FDA has the authority to regulate transportation of products: (cont.)
 - USP monographs, general notices and information chapters;
 - USP General Chapter <1079> Good Storage and Shipping Practices
 - USP General Chapter <1118> Monitoring Devices – Time, Temperature and Humidity
 - USP General Chapter <1150> Pharmaceutical Stability

- Contributing factors Temperature Excursions During Transport
 - Product transfers many times during transportation
 - Extreme temperatures
 - Tarmac time
 - Containers in extreme temperatures
 - Mishandling
 - Lack of instructions
 - Human error
 - Delays
 - Customs
 - Transportation changes
 - Weather







- How Can We Minimize Risk to the Product During Transportation?
 - Communication with carriers and forwarders

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- Knowledge of product stability
- Appropriate product protection
 - Active containers
 - Passive containers

Considerations in Selection of Shipping Solution

- Temperature profiles of shipping method and route
- Duration length and variability of shipment time needs to be understood
- Vibration effects on material being shipped
- Air Pressure Cycles effects on containers and venting
- Physical stresses crushing, handling, dropping, leakage from/onto, package orientation, package placement
- Security Inspection, tampering, radiation exposure

- Options for protecting cold chain products during transportation
 - Temperature controlled trucks and trailers for ground transportation
 - Temperature controlled ocean containers
 - Active temperature control (i.e. Envirotainers) for air transport
 - Passive temperature control Qualified protective packaging utilized for all modes of transportation

Active Shipper

 System that utilizes a thermostat-controlled container that usually employs fans and dry ice as refrigerant and is powered electronically





- Commercial Passive Shipper
 - Typically consist of a box with gel-packs, freezer packs or dry ice within an insulated box
 - Often sold as pre-qualified stock items by commercial vendors.
 - Example: 48-hour shippers will provide insulation for 2-day shipments.



Seasonal "Pack-Outs"

- Summer Pack-Outs
 - Larger, heavier, and use refrigerated or frozen gel packs
 - Designed to keep material cool
- Winter Pack-Outs
 - Typically smaller and/or use more insulation
 - Designed to keep materials cool and may minimize unwanted freezing
- All Season
 - Designed to maintain a temperature range regardless of ambient temperature

- PDA Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature Sensitive Medicinal Products through the Transportation Environment; Technical Report 39 (Rev. 2007) Supplement Vol.61, No. S-2
 - Purpose is to outline a recommended process for protecting your product, minimizing its exposure to temperature extremes, and understanding the impact of such exposures if they occur.
 - Contains suggested temperature studies to demonstrate "robustness" of the product

Cold Chain Shipping: Protecting **Temperature Sensitive Products** Process to Qualify Protective Packaging Identification of Requirements Identify product, stability data, mode of transportation, and temperature sensitivity Design Qualification Define ambient temperature profile Product shipping configuration Temperature monitoring device location Insulating material

- Process to Qualify Protective Packaging
 - Operational Qualification (OQ)
 - Performance Qualification (PQ)
 - Develop and implement training of stakeholders
 - Develop and implement Quality Systems
 - Ongoing monitoring and auditing of process

Diagram of Gel Pack Configuration



Good Distribution Practices: Cold Chain Management

- Prepare for transportation temperature excursions to minimize product loss and business impact:
 - Evaluate data from long-term and accelerated stability studies, temperature-excursion studies, and/or temperature cycling studies to predict the impact of temperature excursions on product quality during the transportation process.
 - Understand responsibilities of shipper, receiver, and manufacturing site to quickly communicate excursions for resolution as quickly as possible.

- Exception Management of Temperature Excursions (like any other deviation):
 - Documentation and notification Communicate to all involved, i.e. shipper, transportation providers
 - Root cause analysis must include entire chain, from pack-out to delivery
 - CAPA Implementation may impact procedures or transportation selection
 - Monitor to assure effectiveness of actions taken to prevent recurrence

Summary

- Definition of Good Distribution
 Practices of "Cold Chain" Products
- Current Regulations
- Managing Temperature Excursions
- Qualification of Protective Packaging