

Title: Cold Chain Management of Biopharmaceutical Materials					
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Introduction

The risk of compromising biopharmaceutical materials in internal shipping and external distribution is relatively high, as these materials are particularly vulnerable to degradation when exposed to various environmental and handling conditions. The risks can be managed effectively through qualification of transport packing systems, handling, and transport procedures. This guidance summarizes suggested considerations in the cold chain management (CCM) of biopharmaceuticals

Recommendations & Rationale

The quality of biopharmaceutical materials can be protected during storage and shipping/distribution through well-considered planning, selection of appropriate protective packing and qualification testing of the shipping solution.

This Guidance provides strategies and recommendations for designing studies that cover a broad range of conditions. Planning for worst-case environmental conditions and unexpected transit delays when designing qualification studies can prevent loss of valuable biopharmaceutical materials.

The following topics are covered in this document:

- Biopharmaceuticals Background
- Regulatory Expectations
- Cold Chain Basics
- Cold Chain Management (CCM) Considerations for Biopharmaceuticals
- Recommendations for CCM of Biopharmaceuticals

Definitions:

Shipping:	Transit of materials from one site location (including contract organizations) to another site location (i.e. from a manufacturing site to a distribution center)
Distribution:	Delivery of materials (usually finished product from a distribution center) to a first paying customer external to Site
Packaging:	The GMP activity at the packaging site. Typically include components such as primary, secondary and tertiary containers
Packing:	The process of preparing and protecting the material for transit usually conducted at a warehouse or distribution center. Packing components include but are not limited to bubble wrap, paper dunnage, Expanded Polystyrene containers, temperature monitoring/temperature indicating devices, etc.
Production materials:	All APIs, drug substances, work in process materials, bulk materials, finished products, etc

refrigerated materials, should be avoided due to potential light exposure in walk-in cold rooms.

Regulatory Expectations

Cold chain management of biopharmaceuticals is regulated by cGMPs and GDPs, which require that the storage and transportation of materials shall be conducted in a manner that prevents alterations to the safety, identity, potency, purity and quality and physical properties of any product. Storage and transportation procedures for products requiring special conditions should be based on local GMP/GDP regulations; regulations in the markets where the product may be sold, the product's labeled storage conditions, allowances made in product filings, and relevant product stability data. In addition, numerous industry organizations provide guidance on maintaining the quality of temperature sensitive products through the transportation environment.

There is a continuum of expectations for clinical supplies to commercial supplies. For clinical materials, a generic qualification of the shipping process/container is often sufficient. However, if there is a unique or known issue with the product, then additional qualification may be required beyond the generic qualification to ensure the integrity of the material. For commercial materials, qualification of the transport process/containers with actual data from the product is required. Additionally, there is a need to consider data that may be required to meet this requirement for older/existing products.

The shipping and distribution processes for drug substances and drug products should be qualified for commercial products, a summary of which is required for regulatory marketing applications of biopharmaceuticals. It should be noted that transport temperature ranges may be wider than the labeled storage temperature range for any given product, however, data to cover the anticipated transport process (mode, duration, container) and qualification testing of the product after transport is expected.

How to meet this requirement should be evaluated on case-by-case basis, utilizing stability data. There is no need to temperature monitor every transport if there is sound qualification data including lane characterization information, pack out qualification, thermal mapping, etc. The decision for inclusion of temperature loggers should be based on an assessment of the product value, criticality of the shipment and chance of excursions versus the qualification data.

Basics of Cold Chain Management

Temperature: Temperature excursions can occasionally occur as a result of inadequate thermal protection under unexpected or unusual circumstances in routine transits. Temperatures outside of the allowable shipping range can often be attributed to shipment delays, unanticipated ambient temperature extremes during transit, or incorrect shipping methods. In addition, the position of primary containers within the transport container should be carefully considered to prevent unintended warming or freezing as a result of proximity to external conditions or cooling source. These factors are typically considered in transport container selection and designing the qualification study.

Even with careful planning and rigorous qualification testing, excursions may occur from time to time under extreme and unanticipated ambient conditions. Properly placed temperature monitoring devices included in transits record the severity and the duration of excursions, and set the foundation for investigating the root cause and product impact evaluation. The severity and duration of the excursion

The focus of the cold chain management approach for the commercial supply chain is on the entire cold chain process and compliance with regulatory expectations and product filings. At the commercial stage there should be an established understanding of product attributes and verification of planned commercial transport supports. The product temperature stability profile should be well established, including storage temperature, allowable excursions, and the effects of freeze/thaw. There should also be available data on the physical restrictions such as limitations for CO₂ exposure (pH) and vibration effects.

Exposure to CO₂: Dry ice is widely used to maintain the temperature for frozen shipments of biopharmaceuticals. Exposure to dry ice may pose a number of consequences for biopharmaceuticals, which should be considered when establishing shipping protocols.

- **Sublimation rate:** The rate of dry ice sublimation is dependent on the transit container and the method of transport. It is important to account for the maximum percentage of dry ice expected to be lost during transit. For long duration transits, dry ice may have to be added to the transport container by the carrier in order to maintain appropriate temperature conditions.
 - **CO₂ Generation:** Carbon dioxide gas generated from dry ice sublimation may alter the pH of protein based material if the shipping container does not allow venting and / or the primary packaging does not adequately protect the material. When using dry ice, the integrity and impermeability of the primary container should be established. It may be necessary to increase protection from CO₂ by using additional protective intermediate packaging/packing.
 - **Thermal Expansion/Contraction:** Physical changes to the primary packaging on exposure to temperature extremes should be considered. Expansion or contraction due to temperature cannot be prevented, but efforts should be made to ensure the integrity of the seal.
- Liquid Biopharmaceuticals. Liquid biopharmaceuticals are typically stored at refrigeration temperature (2° - 8°C), whereas the transport of liquid biopharmaceuticals is often carried out at either 2° to 8°C, With excursions allowed down to 0°C and up to 15°C during storage, internal shipping and external distribution, as long as the Mean Kinetic Temperature [MKT] does not exceed 8°C, or are carried out at 0°-15°C (depending on the availability of supporting stability data). There is a need to understand the allowable excursions and transit temperature ranges for the particular biopharmaceutical formulation. In some cases shipping at 2-30°C may be acceptable, whereas in other cases the MKT must be maintained at or below 8°C.

Liquid biopharmaceuticals are often transported in containers typically from <0.3mL to 200L, with containers ranging from pre-filled syringes and vials to flexible bags and stainless steel tanks. It is relatively easy to maintain 2° to 8°C with active thermostatically controlled transit systems, but typically harder to control the same temperature range with passive transit systems, thus the weight and cost of the passively temperature controlled transports may be of concern with larger volumes of liquid biopharmaceuticals.

Frozen biopharmaceuticals are typically stored below -30°C, as the T_{gq}(Glass Transition Temperature) for many formulations of biopharmaceuticals is near -30°C. Frozen biopharmaceuticals are often transported in containers typically ranging in size from 10mL to 500L, with container types varying from vials to flexible bags and stainless steel tanks. It is relatively easy to maintain frozen temperatures with passive transport

Qualification of the transport container system requires an operational qualification (OQ) to establish that the system will consistently maintain the established temperature range under defined conditions. OQ testing of the transit system is performed under a pre-approved protocol or procedure using temperature controlled rooms and/or laboratory controlled temperature, such as a Heat/Summer simulation and a Cold/Winter simulation or combination profile. OQ testing is performed for durations and temperatures beyond what is expected for typical transits in order to provide assurance that the system will provide controlled temperatures during atypical transport events. Calibrated temperature data loggers are used during qualification, in direct contact with simulated product at representative positions.

The OQ protocol for a transit container system includes:

- **Description of Transport Containers** - The primary, intermediate packaging, and outside transit container should be described in sufficient detail, including supplier, and technical features applicable to the study (physical and thermal protection capability). A description or drawing of the packing configuration for securing the primary or intermediate containers and preventing movement. Procedures for opening and repacking during transport should be provided. Coolant addition, customs inspection, or other issues may necessitate accessing the inside of the shipping container.
- **Coolant Required for Maintaining Temperature** - If dry ice or liquid nitrogen is used for international transit, the amount used must comply with International Law. National or local transit regulations should apply. The carrier can provide specific information.
- **Batch size** - Maximum and minimum batch sizes are represented among the packaging configurations. Where batch sizes or conditions are expected to vary, extremes should be represented using a bracketing approach in the design of the study. Worst-case conditions should be carefully considered, and rationale should be provided in the study protocol. For example, in frozen shipments, minimum batch sizes provide less thermal mass and are often considered worst case; however, in refrigerated shipment, the opposite may be true. The worst-case condition may be represented twice in the study.
- **Transit container interior temperature** - The acceptable temperature range (supported by stability data) is defined. This temperature range is often wider than the recommended labeled storage temperature under normal conditions, but the range specified must be supported by stability data (including expiry considerations). A description of the calibrated monitoring device that will log interior temperatures during temperature and transport should be included.
- **Transit container exterior temperature** - The acceptable temperature range within a transport container is a function of the exterior temperature surrounding the container. Transits that are subject to a number of transfers between carriers, or material sent via ground transportation could be exposed to extreme seasonal temperatures. Laboratory testing of temperature extremes conducted during container selection will demonstrate the minimum time that the shipping container will maintain the specified temperature, such as a Heat/Summer simulation, a Cold/Winter simulation, and/or a combination profile (i.e. thermal profile of the route)

The purpose of testing actual shipments of product is to test for product sensitivity to transit conditions. The test is of the product, and is not a test of the qualified transit procedure or a duplication of stability data. Multiple product lots should be considered. While OQ, PQ and stability testing addresses the expected variations in temperature and handling, biopharmaceuticals may be susceptible to unanticipated variations encountered during transport. For instance, USP guidance allows use of MKT when evaluating temperature excursions; however, the USP mean kinetic temperature (MKT) may adversely affect biopharmaceuticals if temperature excursions limits exceed the thermal denaturation limit of the protein

Similarly, proteins may be susceptible to oxidation, shear or formation of aggregate caused by shaking or rough handling. Vibration may cause foaming and turbidity of liquid solutions shipped under refrigerated conditions. While motion in shipment is obviously inevitable, the packing configuration should be designed so that the primary containers are secured and cannot move in the container interior.

Additionally, proteins may be exposed to magnetic fields, X-rays (radiation), ingress (CO₂, microbial), leakage (liquid, gas overlay, sublimation), and physical inspection. Testing of samples is generally performed using stability indicated assays

Summary of Recommendations for Shipment of Clinical Stage Biopharmaceuticals

The focus of the cold chain management approach for the clinical supply chain is on maintaining temperature. Operational qualification of the transit container is recommended. Often the OQ is commercially available from the vendor or for transit of other products. Temperature should be monitored as necessary within the assurance limits provided by the qualification of the shipping and storage units.

As such, platform technologies are generally employed for the storage of clinical stage biopharmaceuticals while stability data is generated.

Performance qualification of the transport procedure and route is not required, but should be conducted during the progression from clinical to commercial stages, or if special known product consideration. Stability data should be used to determine transit temperature range and allowable excursions. If the biopharmaceutical material is frozen, knowledge of the T_g and the impact of freeze/thaw on the product, and knowledge of the temperature effect on the product container is required prior to shipment.

The use of different transit temperature ranges versus storage temperature may be acceptable if supporting data is available. The use of temperature data loggers is recommended for all transports of bulk drug substance and bulk drug product due to the high value of the material. The use of temperature data loggers is also recommended for transits critical for the market or clinical trial and transits via shipping lanes where the delays are not uncommon. The use of temperature data loggers may not be necessary for routine low-value shipments when a qualified transit container is used.

Summary of Recommendations for Shipment of Commercial Stage Biopharmaceuticals

The focus of the cold chain management approach for the commercial supply chain is on the entire cold chain process and compliance with regulatory filings. At the commercial stage there should be an established understanding of product attributes and verification of planned commercial transport supports.