Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion

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

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

Biopharmaceuticals Background

Biopharmaceuticals, like other drugs, are used for the treatment, prevention or cure of disease in humans. Biopharmaceuticals are of large molecular size and structural complexity and may include proteins, monoclonal antibodies, glycosaminoglycans, hormones, vaccines, oligonucleotides and PEGylated

vial which contains the drug product

- Secondary package – Contains the primary package; e.g., the box which contains a vial of drug product (shelf packs, unit cartons, etc)
- Tertiary package – Contains secondary package(s), often used to provide protection against mechanical impact. Example: shipper carton, case, etc.
- Ancillary packing system or equipment – Used to maintain temperature and/or integrity of shipment. Examples: shipper, pallets, etc.
- Active Transport System – System that utilizes a thermostatically-controlled container (or vehicle) that usually employs fans, a refrigerant, and is designed/engineered to maintain a desired temperature range for as long as the unit is on and will function as intended against all ambient conditions (i.e. Enviro Tainers, etc).
- Passive Transport System – Typically consist of a box with gel-packs, freezer packs or dry ice within an insulated box. These systems are designed/engineered to passively cool for a period of time against specified ambient conditions.

NOTE: the primary package, the secondary package, and the tertiary package are the GMP components that are typically applied to the product during the packaging operation at a manufacturing/packaging facility. The manufacturing facility will probably also utilize ancillary packing equipment (i.e. pallets) to assist with the movement and storage of the product. However, it is typically the warehouse or distribution center that utilizes the (active or passive) transport systems to assist with the shipping /distribution of the products.

Active and passive systems are often sold as pre-qualified stock items by commercial vendors to maintain a specified temperature range against moderate, predefined ambient temperatures for a minimum duration of time. Such systems are routinely and successfully employed, however, it is important to understand the conditions under which the system was qualified. For instance, a passive shipping solution which has been qualified to maintain 2-8^{0}C for 48-hour may satisfactorily perform well in shipments during summer temperatures, but may fail to provide protection from freezing the product when the exterior temperature falls below -10^{0}C. Thermostatically controlled active systems are typically more capable to hold the desired interior temperatures against a wider range of ambient exterior temperatures and may function for a longer duration of time, but are more expensive.

Temperature Controlled Trucks, Trailers and Ocean Containers: Transport vehicles themselves may function as an active system (i.e. temperature controlled trailers). Proper setting of the temperature set point and loading of materials in a container or trailer is required to ensure that the temperature is properly controlled. Unless otherwise qualified, loads should not be placed against the walls of the transport vehicle to allow for proper air circulation within the cargo area and to ensure ambient outside temperature does not transfer directly to the load. Temperature is typically controlled by air circulation; as such air vents must not be blocked by the shipment materials.

Most temperature controlled trucks, trailers ands containers are not intended to meet GMP requirements, with the exception of certain specialty carriers. Temperature mapping is not valid without GMP controls. The requirements to maintain GMPs include written procedures for operation, maintenance, change control, and deviation handling, which are rarely maintained by most commercial carriers. From a Quality perspective, there should not be a reliance on the temperature of the transportation environment. The

Passive transport systems are usually controlled by wet ice (<-15^{0}C), dry ice (<-60^{0}C), or liquid nitrogen in a dry shipper (<-90^{0}C). Among the points to consider during the transit of frozen biopharmaceuticals are:

- Temperature: The temperature of biopharmaceuticals must be maintained below a specified maximum temperature. Cooling too low generally is not a technical concern. The Tg' must be determined for the specific formulation, as it may be well below the visual appearance of being a solid. The provided temperature should be below <Tg' of the formulation. The Freeze/thaw impact on product integrity must also be understood in order to evaluate the effects of multiple freeze/thaw cycles which may occur during material handling.

- $C0_2$ Generation: As noted above, exposure to $C0_2$ may pose a number of consequences for biopharmaceuticals, which should be considered when establishing shipping protocols.

- Container Characteristics: The characteristics of the product container will undoubtedly have an impact on the cold chain transit requirements.

- Plastics: The container integrity of plastics is greatly affected by temperature. Physical changes to the primary packaging on exposure to temperature extremes should be considered. Loss of closure torque on bottle freezing expansion or contraction due to temperature cannot be prevented, but efforts should be made to ensure the integrity of the seal. For example, bulk shipments made in polymer bottles must be properly sealed.

  Typically, the bottle manufacturer will provide technical information regarding recommended torque to be applied to screw cap type closures. A torque wrench should be used to accurately achieve the recommended torque. Prior to shipment of polymer bottles on dry ice, the bulk bottles should be frozen and then "torqued" to the recommended specification. Meeting the torque requirements in the frozen state will help maintain closure integrity. If the bottles are only "torqued" under warm conditions, expansion/contraction of the bottle may cause the cap to become loose and jeopardize the integrity of the seal. Similarly, multi-layer flexible bags incur different temperature effects per layer. For instance, Stedim Flexboy bag layers include Ethylene vinyl acetate (EVA) as the main bag structure along with EVOH, Ethyl Vinyl Alcohol (EVOH) as the main gas barrier, a Tie which bonds outer film layer and Ethylene Vinyl Acetate Mono-material (EVAM®) as the fluid contact layer. Freezing of bags requires custom equipment and bag sizes are limited to the equipment. The bags may also become brittle or crack at variable freezing temperatures depending on the materials.

- Stainless Steel: Stainless steel containers offer the advantage of robust integrity at the expense of high container costs and high transit costs, thus the use of stainless steel is generally limited to storage and transit of bulk drug substances. The impact of freeze/thaw characteristics of tanks must be carefully evaluated with respect to product impact and thermal changes during transportation. At this time there is no current technology available for controlled rate freeze/thaw of tanks below -40^{0}C.

- Glass Bottles and Vials: As with plastics, the container integrity of glass is greatly affected by temperature. Physical changes to the primary packaging on exposure to temperature extremes should be considered. Loss of vial stopper sealing and/or cap closure torque on freezing expansion or contraction due to temperature cannot be prevented, but efforts should be made to ensure the

represented, and the route and expected duration in transport will dictate the best strategy for including reasonable allowances in the study.

Qualification of the Transit Procedure and Route (Performance Qualification): Once the transport container has been identified and laboratory test results or data support the suitability of the container, the transit procedure and route should be qualified. Actual transits are conducted to substantiate the results of laboratory testing. Several transits over the actual planned route are conducted to demonstrate that the transport container provides thermal and physical protection under actual conditions and that the transport and handling procedures are adequate. Note that seasonal differences in temperatures and routes should be accounted for in either the laboratory or actual transit studies.

Concurrent studies may be conducted with transits of actual material if sufficient experience with similar containers, materials, batch sizes and shipments justifies the risk. Where the benefit of experience does not justify the risks of concurrent studies, trial transits or prospective analysis using buffer placebo or water should be considered.

The qualification of the transport procedure and route is a performance qualification (PQ) of the transit system, which establishes that during the transit of materials in the system are maintained within predefined ranges. The PQ testing of the transit system consists of:

- Replicate field transportation tests
- Actual, rather than simulated, temperature variations
- May use both primary and alternate routes
- May use actual product in one or more of the replicate tests

In considering study design for worst case transit conditions, two to four times the amount of time expected for normal transport should be factored into the test plan, as appropriate.

- A test plan for international transits may include transport to the final destination, where the material is unopened, and returned through customs to the origin. This plan allows for twice the amount of time expected in routine transits.

- An approach for domestic or sample transits may involve a triple shipment (manufacturer to test laboratory, return to manufacturer, return to the laboratory) before opening to examine temperature monitoring data and testing of material. Lesser transit times may be qualified, although additional risk to material integrity is taken.

A complete study design in the shipping qualification test plan should include destination, duration and explanation of bracketing strategy. International transport should be considered and described as appropriate. The test plan should include:

- Pre-Shipment sampling and testing requirements (as required)
- Packing instructions
- Diagram outlining placement of temperature monitoring probes / devices
- Name and qualifications of carrier(s)
- Transit instructions: Specify transits for the maximum allowable duration OR provide instructions for qualified carrier to recharge container with coolant.

