Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion
The risk of compromising biopharmaceutical materials in shipping 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 packaging, handling, and transport procedures.

This guidance describes the qualification studies required to validate product specific shipping procedures for biopharmaceutical materials derived from biotechnological processes, including:

- Bulk Intermediates
- Bulk Drug Substance
- Drug Product bulk vials
- Fully packaged sample kits in commercial packaging.
- Samples for analytical testing

The quality of biopharmaceutical materials can be protected during shipping through well-considered planning, selection of appropriate protective packaging, and qualification testing conducted at worst case conditions.

This guidance provides strategies and recommendations for designing studies that cover a broad range of conditions. Planning for worst-case environmental conditions and unexpected shipment delays when designing qualification studies can prevent loss of valuable biopharmaceutical materials. The following topics are covered in this document:

- Conditions known to degrade biopharmaceutical materials, and considerations for preserving quality in shipment;
- Planning for handling and transport;
- Selecting the appropriate shipping container;
- Qualifying transport and handling procedures;
- Protocol and report content recommendations;
- Evaluating the degree of shipping validation for analytical test samples.

Preserving Quality During Shipment of Biopharmaceuticals: Points to Consider
Temperature, agitation, and exposure to light are among the conditions known to degrade protein and oligonucleotide based materials. A risk assessment should be conducted that accounts for ways the integrity of biopharmaceutical materials are compromised. Among the points to consider:

Temperature: Temperature excursions can occasionally occur as a result of inadequate thermal protection under unexpected or unusual circumstances in routine shipments. Temperatures outside of the allowable shipping range can often be

compression, shock, vibration, atmospheric conditions, and thermal insulation quality are generally conducted. Contract packaging laboratories can assist in selecting the test methods required to verify the container's suitability for the application.

Many suppliers maintain a set of qualified shipping containers (for example, ISC has such containers and data available). Suitable shipping containers can be selected based on the size and temperature requirements and expected transport from the set of pre-qualified containers, requesting specific additional qualifications, then proceeding with shipping studies.

Once the shipping container has been identified and laboratory test results or data support the suitability of the container, actual shipments are conducted to substantiate the results of laboratory testing. Three shipments over the actual planned route are conducted to demonstrate that the shipping container provides thermal and physical protection under actual shipping conditions, and that the transport and handling procedures are adequate. Note that seasonal differences in temperatures and shipping routes should be accounted for in either the laboratory or actual shipping studies.

Shipments for Qualification of Transport and Handling Procedures
Concurrent studies may be conducted with shipments 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 shipments or prospective analysis using buffer placebo or water should be considered. In considering study design for worst case shipping 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 shipments may include transport to the final destination, where the material is unopened, and returned through customs to the shipping origin. This plan allows for twice the amount of time expected in shipping.
- An approach for domestic or sample shipments could involve a triple shipment (manufacturer to test laboratory, return to manufacturer, return to laboratory) before opening to examine temperature monitoring data and testing of material. Lesser shipping times may be qualified, although additional risk to material integrity is taken.

Calibrated temperature monitoring devices are included in the shipment to measure the degree to which ideal conditions were maintained inside the container during transport. Carriers must be notified of and understand specific requirements for replenishment of dry ice or cold packs, as well as the procedures for restoring the original placement / orientation of materials (containers and monitoring device) after replenishing coolant. Instructions for resealing the containers must also be provided to the carriers. The carrier is responsible for completing the appropriate documentation pertaining to addition of coolant, manipulation of contents, and chain of custody.

- Pre-established temperature range specifications
- Damage assessment criteria for shipper and primary containers
- Date of shipment
- Post Shipment sampling and testing requirements (as required) and criteria for determining material impact when compared with the test results from pre-shipment samples.

Shipping Study Report

Following execution of the protocol, a summary report will document the study. The following information will be included in the report:

- Number of primary containers (or saleable units) shipped
- Date received
- Actual shipping route
- Inspection of shipper and accounting of damage noted
- Amount of coolant remaining at end of shipping
- Duration of shipment
- Temperature data from all probes
- Full primary container inspection and accounting of damage noted
- Exceptional conditions
- Comparison data from analytical evaluation
- Conclusions

Guidelines for Shipment of Samples for Analytical Testing

The degree to which shipping validation is conducted for analytical test sample transport should be evaluated. The investment in full shipping validation should be made where necessary, but risk may not warrant full validation in all cases.

- Samples that must be shipped routinely for release testing or stability testing should undergo comprehensive shipping validation.
- For infrequent or one-time shipments, qualified shipping containers with calibrated temperature monitoring devices may be adequate for protecting sample integrity.

