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 attributed to shipment delays, unanticipated temperature extremes during shipment, or incorrect shipping methods. In addition, the position
of primary containers within the shipping 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 shipping 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 conditions. Properly placed temperature monitoring devices included in shipments 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 and the amount of stability data available may dictate the final disposition of the batch.

Exposure to Dry Ice: Dry ice is widely used for frozen shipments, where temperatures of –70° C must be maintained. 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 shipping container and the method of transport. It is important to account for the maximum percentage of dry ice expected to be lost during shipment.

  For long duration shipments, dry ice may have to be added to the shipping container by the carrier in order to maintain appropriate temperature conditions.

- $C0_2$ 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 $C0_2$ by using additional protective intermediate packaging.

- 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

- Temperature requirements
- Degree of thermal insulation and damage protection required
- Maximum possible duration of shipment
- Material sensitivity

Shipping containers are tested for their ability to withstand and protect the product from rigorous environmental conditions or rough handling damage. The International Safe Transport Association (ISTA) Guidance and the American Society for Testing and Materials (ASTM D 4169-98 and ASTM D3103-92) provides standard test methods for qualification testing of shipping containers. Standard tests for 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.

- Packing instructions
- Diagram outlining placement of temperature monitoring probes / devices
- Name and qualifications of carrier(s)
- Shipment instructions: Specify shipment for the maximum allowable duration OR provide instructions for qualified carrier to recharge container with coolant.
- Fastest possible route
- A plan for unexpected conditions during the ship test
- 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.

