Table 27: Shipping Studies – Analytical Strategies.

Facilitator: Jin Qian, *Merck & Co, Inc.*

Scribe: Srinivas Gunturi, *Janssen Biologics, B.V.*

SCOPE:

Regulatory expectations around shipping validation/qualification studies for biological products are steadily increasing globally. Late stage biologics drug substances and drug products as well as biologic-combination products are in scope of this round table discussion. The focus will be on the current regulatory guidance's, recent health authority feedback and industry benchmarking data.

QUESTIONS FOR DISCUSSION:

1. What are the current regulatory guidances for shipping studies- to assess product quality post shipping; to assess damage to the primary/ secondary packaging or device constituent part after shock and vibration; to assess performance of a thermal protection system; qualified vendors with capacity for temp controlled systems.
2. What type of studies recommended to be conducted in support of overall shipping package for biologics? Are all the release assays included in the studies (e.g. particles and polysorbate testing)? Any Specific requirement for setting the acceptance criteria? Are studies completed in a simulated environment or after real-world shipping?
3. Do the companies generate stability data from product quality shipping lots and provide the data during the submissions? What information from those studies are typically included in filings?
4. How to design the studies to support shipping outside of the labeled storage temperature? Is PDA Technical Report 53, "Guidance For Industry: Stability Testing to support Distribution of New Drug Products" used as a guidance? What info from those studies are typically included in filings (e.g. TOS, freeze/thaw)?
5. How can we leverage ICH Q12 to minimize filing burden for regions needing data/studies in application? How do we manage changes post approval in these regions and what can we do?

DISCUSSION NOTES:

Question 1- What are the current regulatory guidance's for shipping studies to assess product quality post shipping; to assess damage to the primary/secondary packaging or device constituent part after shock and vibration; to assess performance of a thermal protection system; qualified vendors with capacity for temperature-controlled systems?

1. One member talked about Pharma-iQ forum and requirements of Australia and Brazil for temperature control studies.
    a. Where the stability guidance is provided but not shipping guidance. Brazil requires the validation of shipping studies throughout the transport chain.
    b. How to do the study is missing in the guidance. New guidance to do simulated studies and real time field studies. Is that available?

2. Transport – ISTA, ASTM, internationally recognized standards to be applied. And consider how is that representative to the product in question. Justify the simulation studies how representative of the real time conditions or not, throughout the shipping chain.
3. Vendors – None disclosed or discussed.
4. Type of containers used for shipping included active and passive – systems. Example – Active systems employed batteries to deal with excursions or diesel. Passive systems employed - thermal insulation and boxes.

Question 2- What type of studies are recommended to be conducted in support of overall shipping package for biologics? Are all the release assays included in the studies (e.g. particles and polysorbate testing)? Any specific requirement for setting the acceptance criteria? Are studies completed in a simulated environment or after real-world shipping?

1. What type of testing is needed/performed?
    a. The type of testing depends on the risk assessment for the shipping step involved. Container, integrity, storage temperature are key parameters qualified.
    b. Thermal and physical qualification of the product is performed.
    c. Temp Tales are used for temperature monitoring.
    d. Early product development shipping studies are performed under formulation development work.
        i. Quality testing – particles and aggregates testing is performed.
        ii. If it is a liquid product then simulated shaking studies are performed.
2. How is the acceptance criteria set?
        i. If the product is aged and not at release, then stability acceptance criteria is used.
        ii. If it is at PPQ then use the release criteria.
        iii. Assay variability and Spec range are considered to set the shipping studies acceptance range.
        iv. Example: If the release results for charge variants are ok but the shipped samples are not - then analyze the method variability and use stability specification.
3. Simulated shipping conditions or real-world data collection?
        i. Can we use a surrogate? Should this be evaluated?
        ii. Real world is not always the worst case – So simulated conditions are performed first, and the samples are put-on real-time stability. Agency expects that information to be available at the stability sections of the BLA. One lot is used typically.
        iii. (TGA – Australia.) – 3 lots with multiple cycles on stability needed.
4. What happens when they are OOS?
        i. Deviation is initiated and justify the compliance based on the shipping validation.
        ii. Evaluate if meets the end of shelf life, release specs or not?
        iii. The longest excursion seen was for 3 months. The company could not import the product for 3 months due to hold up in customs and the temp tale batteries ran out.
        iv. Time out of storage (TOS) – documented in the quality event.

Question 3- Do the companies generate data from product quality shipping lots and provide the data during the submission? What information from those studies are typically included in the filings?

1. What kind of data companies put into submission?
    a. Manufactured drug product is set at different stability conditions and all stability lots go through shipping.
    b. Product development, validation and stability sections:

        i. Freeze Thaw and Temperature cycling information is included in stability studies sections.
    c. Thermal, packaging integrity and product quality assessment data packages are typically reviewed by the agency.
    d. PQ- not all tests but subsets that are stability indicating should be included (FDA). From the analytical methods validation package, they look for which one is stability indicating and decide which method should be included in the panel for the shipping studies. Will see justification used for the excursion.

Question 4- How to design the studies to support shipping outside of the labeled storage temperature conditions? Is PDA technical report 53, "Guidance for industry: Stability testing to support distribution of new drug products" used as a guidance? What information from those studies are typically included in the filings (e.g.,> TOS, freeze thaw)?

    a. One has to ensure that the intended shipping conditions for the product are simulated in the intended storage conditions.
    b. Long term and short-term stability data can be used to support the shipping outside the labeled storage conditions.
    c. Accelerated conditions may help define the maximum temperature exposure at which the change will not occur at release. 6 months data can also be leveraged while justifying an excursion and its duration. Example - The freezing studies were done on PFS, DPD starts the work and supply chain takes over.
    d. Cane we use development study data be used for GMP excursions? No Answer.

    e. How many lots to be set for DS, and DP?
        i. Typically, one lot is done. Verify if this is same for all countries.

Question 5- How can we leverage ICHQ 12 to minimize filing burden for regions needing data/studies in application? How do we manage changes post approval in theses regions and what can we do?

    1. Explore what is an already established condition for shipping and the gaps for the intended country specific shipping conditions.
    2. Depends on the post approval changes proposed. If active transport system is previously used and is now changing to a passive one, or from road to air shipping etc.,
    3. Study how the change impacts the quality of the product. Example - use horizontal position of vials during shipping to simulate worst case shaking scenarios or for Prefilled syringes.

Questions Asked by the members:

1. Any experience with exposure to X-rays?
    a. Situations include screening of cargo in customs or in case of patients carrying their own medicine.
    b. TGA (Australia) requires the X rays stability testing. Customer asked if they can use the product that has been exposed to X-rays in the airport screening.
        i. Suggestion to include a x ray dosimeter to test the amount of radiation and the stability under such conditions.
2. Orientation of vials/Prefilled syringes for shipping – should be defined in the product configuration.