Roundtable Session 1 - Table 8: When Simulation is Not Enough - When and Why Are Real World Studies of Shipping Needed?

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Abstract

The marketing application for a drug substance and product is expected to include information about the transportation (shipping) of the product and to assess the potential impact to product quality from atypical temperature, humidity, pressure, vibration, and shock. Shipping containers are designed to maintain environmental control and with packaging to protect the product. For the qualification of these containers, laboratory based simulations are widely used based on standards (ASTM, ISO). At least 9 post-marketing commitments for shipping were noted in FDA approval letters for biologics in 2022-2023. This round table discussion will explore potential reasons for this and when shipping simulations are not accepted what are the potential outcomes.

Discussion Questions:

1. Simulation tests provide robust, repeatable, and reliable results and are often viewed as representative for most real-world shipments. To what extent have simulations not been accepted? What additional information has been requested during review?

2. From the perspective of regulators, what are the information gaps in the marketing application? Are studies performed and inadequately presented in the submission? Are the standards (ASTM, ISO) viewed as insufficient for worst case conditions?

3. Do other countries require shipping studies? How would this requirement impact Reliance Pathways?

4. To what extent will legacy products previously approved based on simulation, need to perform real time studies to file updates (post approval supplement, variation, etc)?

5. How to be most efficient with limited resources for small companies or niche products? Can an abbreviated list of product quality tests be performed?

6. Has anyone had success with large-scale simulation equipment to validate shipping without the need for real-world shipping studies?

Roundtable Discussion Notes:

A list of PMCs (post marketing commitments) related to shipping or transportation studies sourced from FDA BLA approval letters was circulated at the table. With 8 PMCs on this topic in 2023 this indicates that the information submitted and provided during review is not meeting the FDA expectations. Participants at the table represented many companies; no regulators attended so it was not possible to hear the perspective of reviewers. It was noted that CDRH in FDA is familiar with shipping studies. Given the current level of PMCs issuance of a draft guidance from FDA and/or other regulators would seem to be worthwhile.

Discussion included a need to standardize nomenclature and terminology. For example, Qualification of a Shipper means to verify physical and environmental aspects for the shipping container such as maintaining temperature for a defined period and that the container remains integral after being subject to stresses (drop, crush, etc). Once qualified it is then typical to proceed to the Validation of Transportation which is a product-specific step involving the testing of product quality attributes including the integrity of the product's container closure after shipment (real world or lab based). A Simulation is a defined as a lab-based, controlled evaluation of shipping stresses followed by testing of product quality attributes.

Technologies – there are chambers that can perform very sophisticated studies, varying temperature, humidity, pressure, vibration, shock etc. Questions remain unanswered as to why the current standards, ISO, ASTM, are not accepted by the US FDA or whether they are being inappropriately applied by sponsors. The ASTM standard includes a drop test, vibration and pressure manipulations. There was experience at the table shared by a single company with multiple approved products in which a simulated study was accepted and approved and another in which the simulated study was not accepted and a real world transportation study was required. The reason for the difference was unknown. It was noted that lab based studies can be more stringent than real world. For example, for products shipped by air, there is no guarantee that the ranges of temperature, pressure, and vibration occurring on the actual day(s) of flight and transfers at shipping/receiving warehouses are worst-case.

Simulation, if sufficiently stressful, is representative and consistently controlled compared to real world shipping. A standard stress profile or set of profiles similar to the concept of ICH climatic zones could be developed in a precompetitive space and published for all to consider using. It was noted that such a profile would need to be translated it into what that means in a real word transportation setting because then it would be more readily understood and accepted in the context of global product registrations. In this context, questions during the review were received from Brazil, China, EMA, and FDA. Additionally, there is evidence that changes to an existing approved product can trigger an additional shipping request.