Table 28: Formulation Development

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SCOPE:

Development of the formulation matrix for clinical trials requires a balance of accelerated and real time stability data to ensure the drug substance and drug product will meet retest dating requirements throughout clinical development. Chemical and physical stability attributes can be tested using high throughput techniques which enable exploration of the formulation space using minimal sample volume and accelerated storage conditions. In general, chemical stability can be modeled based on limited data sets to project shelf-life, whereas physical stability attributes (e.g., particulate matter, solubility behavior) may not be as predictable. In some cases, the instability of polysorbate may require a more complex approach to assess degradation mechanism, stability of the surfactant, stability of the protein and overall physical stability. This roundtable aims to discuss approaches and considerations for high throughput chemical and physical stability as well as considerations for assessing polysorbate stability and impact to other quality attributes.

QUESTIONS FOR DISCUSSION:

1. What analytical properties and methods are suitable for high throughput screening?
2. What storage temperatures and durations are suitable for accelerated conditions to project chemical and physical stability?
3. How much real time stability data is needed to support stability projections based on accelerated conditions?
4. What storage conditions and durations are predictive of solubility behavior (e.g., phase separation, cryoglobulin)?
5. How predictive is oxidative degradation of polysorbate and impact to product quality?
6. How predictive is hydrolytic degradation of polysorbate and impact to product quality?
7. Is there an acceptable level of polysorbate hydrolysis that does not lead to free fatty acid particulate matter formation?

DISCUSSION NOTES:

The roundtable was a grand success with full participation at the table. The attendees discussed a range of contemporary topics in formulation development and stability determination/ prediction methodologies including need for extrapolating stability behavior as it is impractical to wait for years during formulation development to collect real-time stability data.

<u>Stress studies used in development:</u> Thermal stress and pH stress continue to be frequently used approaches to test/predict stability behavior of biologics. Use of high temperature (such as 40°C, 50°C) depends on the molecule type, although limitations of using high temperature are recognized such as strong mismatch of degradation profile/species between high and low temperatures. Issues with high temperature also included ‘false positives’ that may cause unnecessary churns and use of mitigations (e.g. frozen storage or lyophilization) that are actually not needed. Examples were provided to highlight potential benefits of using 35°C as a stress condition, particularly for relatively well-behaved monoclonal

antibodies for which the T_{onset} (a temperature at which protein shows a certain amount of detectable unfolding) is well above 45°C. For such cases, collecting data up to 2-3 months at 35°C along with data at other temperatures may enable Arrhenius projection to estimate stability at 2-8°C. For example, data at 15°C or 20°C or 25°C will be useful. The high temperature condition of 35°C can be used to screen a set of formulations (say, 10-15) that cover a range of conditions such as pH, stabilizer, surfactant (PS80, PS20) etc. It was also noted that poloxamer as a surfactant often does not perform as well. Another attendee noted that some monoclonal antibodies crash out even at 35°C. Discussion on formulation development included use of DoE. Partial DoE instead of full DoE is commonly used.

Testing: Testing of standard attributes (e.g. SEC monomer, HMW, charge, particles) is employed during formulation development/screening. Peptide mapping is used infrequently, as needed, to determine a specific post-translational modification or degradation caused by applied stress. The discussion briefly dabbled into potential use of multi-attribute methods including throughput methods. For antibody aggregation testing by SEC, there might be a need for certain proteins to understand aggregate properties such as reversible, irreversible etc. AUC (analytical ultracentrifuge) is a good orthogonal technique. For wider size ranges, DLS, light obscuration particle counting (e.g. HIAC), and flow imaging based particle counting (e.g. Flowcam, MFI) will be helpful. Such characterization testing used in formulation development can be outsourced. Material need for testing is a major consideration during development.

Real-time stability data: Regarding real-time stability data to be included in IND/IMPD/CTA filing, a diverse set of experiences was shared. While some health authorities accept development data (and minimal GMP stability data) for the first filing enabling First-in-Human trial, some agencies might ask for longer real-time data from GMP stability studies. However, certain countries that traditionally had been conservative appear to be accepting development stability data embracing science-based approaches.

Freeze-Thaw: Should freeze-thaw be included in stress testing? There are no good models to predict freeze-thaw behavior at bulk. Scale down models may help, such as pie-shaped wedge that works relatively well. Although difficult to simulate scale for bulk, fast vs. slow freezing do have impact. One company reported conducting 3 F/T cycles. Testing in F/T screening studies should include physical stability tests such as aggregates by SEC, particulate matter, opalescence etc. Discussion also included selection of freezing temperature. Is -20°C a good temperature for freezing? Although -20°C is used frequently for frozen storage, it is known to have issues. One company noted observing issues in some ~30% cases that require using a different temperature such as -40°C or -70°C. Container choice for frozen storage was discussed. Choices include PETG, Polycarbonate, HDPE etc; no clear consensus if any of them works better. Issues with frozen bag were discussed, especially the integrity of the connectors and tubes and potential microbiological contamination resulting from integrity issues. Handling of bags at low temperatures such as -70°C may pose a problem for potential breakage, especially at the creases. Access to frozen storage at intermediate temperatures such as -40°C or -60°C is still an issue in the supply chain. Leachables also need to be considered from bag films that contain ethyl vinyl acetate.

Clinical In-Use Stability: Attendees shared their experiences regarding recent queries they received from FDA for microbiological safety. Request was to shorten in-use stability to 4 hrs at room temperature. The discussion included need to demonstrate no trend in growth if longer than 4 hrs at room temperature. Is it a general trend that sponsors are getting these questions from FDA? The attendees opined that a consistent guidance will be useful. Has there been any adverse event? Also, refer to the papers by John Metcalf (2009, 2011, 2014 talk) for evaluation of the microbial growth potential of pharmaceutical drug products. One attendee commented that the USP pharmacy compounding guideline does not work well for clinical products. Discussion also included maximum duration of use-time. Is it total 24 hrs? Such as 20hrs at 2-8°C and 4 hrs at room temperature?

Lyo: Use of lyophilized formulation was discussed briefly. Does Lyo provide any advantage in early stage of development (FIH)? It may provide dose flexibility in Ph1 and mitigate any major instability due to protein/polysorbate hydrolysis. However, if stability is not a major issue, lyophilized drug product carries significant disadvantages including higher cost of manufacturing, less convenient dose preparation, specification setting issues, and others.

Emerging modalities: The attendees briefly discussed stability of AAV particles for gene therapy. Physical stability might be a major issue including aggregation, pH sensitivity etc. Protein modification (e.g. oxidation) within AAV particles can be tested by traditional methods such as MS. It is understood that formulation of gene therapy compounds is not well studied; the field is still in infancy.