

## **Roundtable Session 2 – Table 13: Using Accelerated Degradation Studies to Support Comparability Assessments**

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### **Abstract:**

Manufacturing process changes are introduced throughout the lifecycle of a biologic for a variety of reasons such as supply chain considerations, adoption of new technology, and improvement of process consistency. Given the complex nature of biologics, even small changes to a process can impact the structure, post-translational modifications, purity, or biological activity of a given product. Consequently, manufacturers must demonstrate that a product before and after a process change remains comparable, with no adverse impact on product quality, safety, or efficacy. Analytical comparability studies are the primary tool for demonstrating similarity between pre- and post-change materials, but the extent of such studies is often based risk assessments considering the nature and magnitude of process changes alongside the potentially impacted product critical quality attributes (CQAs) and historical process and product knowledge. This roundtable discussion will focus on one aspect of comparability approaches – the use of accelerated degradation (or forced degradation) studies to demonstrate comparability. Such assessments are not always required but may be included depending on the risk level of the manufacturing change and the need to understand how the change affects product stability and degradation pathways.

### **Questions for Discussion:**

Question 1 – When are accelerated degradation studies justified as part of analytical comparability assessments? What product- or process- specific risks trigger their inclusion?

Question 2 – What are specific advantages and challenges of including accelerated degradation studies as part of a comprehensive analytical comparability assessment?

Question 3 – How are meaningful stability differences distinguished from analytical noise, especially under harsh stress conditions? What constitutes sufficient evidence to carry over shelf life from a pre-change material without waiting for long-term data?

Question 4 – How do participants handle differences observed only under accelerated conditions but not in real-time stability (or vice versa)?

Question 5 – What is the regulatory experience with the use of accelerated degradation data as supportive evidence for shelf-life bridging? Are expectations consistent across regions?

**Notes:****Strategies to Use Accelerated/Stressed Stability to Support Comparability**

To utilize accelerated (stressed or forced degradation) stability as part of comparability, degradation in that study should be observed.

If the molecule is stable, the following strategies may be options:

- A forced degradation studies using conditions (e.g. oxidation or light) other than thermal may be required. Although it is recognized that these are harsh conditions and not likely clinically relevant, a comparison between pre and post change material may be used to support comparability
- If the drug substance is stable, an accelerated stability of drug products derived of pre and post change drug substance may be done
- Typically stability studies at 40C are carried out for 1-2 months; however to observe degradation, longer periods of time may be required.

**Accelerated Stability Design and Data Evaluation**

- The assessment of accelerated studies are usually qualitative with no set acceptance criteria.
- Chromatograms for side-by-side testing are also qualitatively evaluated with criteria of no new peaks and similar profiles.
- Ideally, 3 pre and 3 post change lots are used with side-by-side testing as part of comparability. Industry experience has been that more than 1 lot is required.
- If pre-change lots are not available, historical data may be used and the reference standard may be used in methods where applicable. If method changes have occurred over time, bridging of methods using retain samples or reference standard will be required to leverage historical data.
- If the stability results are used as part of the comparability study, the testing is performed in the QC laboratory.
- To reduce variability, it is recommended to perform batch testing within one method run in contrast to providing samples as they become available.

**Strategies to Address Results from the Accelerated Stability Study that are not similar or comparable**

- Site transfer- Observed a higher level of an impurity post-change-identified levels in an earlier version of material that was used during clinical studies. Historical data that were clinically relevant were used to justify the results and post-change product
- May be able to leverage other data such as potency data that were comparable based on knowledge of the attribute and impact to biological activity
- Increased the concentration of drug substance and during stability observed increase aggregation. A study was performed by concentrating the pre-change material and putting on stability to confirm the increased aggregation was not a result of the change itself.