Roundtable Session 2 – Table 7 - Early Phase vs. Late Phase Comparability Analysis After CMC Changes

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Abstract:

Chemistry, Manufacturing, and Controls (CMC) evolution is inevitable in the development of cell and gene therapies, driven by process optimization, scale-up, analytical improvements, and supply chain considerations. However, the expectations for demonstrating product comparability differ significantly between early- and late-phase development, creating both scientific and regulatory challenges.

In early phases, greater flexibility is typically afforded, with limited clinical data and evolving analytical characterization strategies. In contrast, late-phase development requires a higher degree of assurance that manufacturing changes do not impact product quality, safety, or efficacy, often necessitating robust analytical comparability assessments and, in some cases, clinical bridging data. For complex and heterogeneous products such as cell and gene therapies, establishing meaningful comparability frameworks can be particularly difficult due to limited assay sensitivity, evolving potency assays, and incomplete understanding of critical quality attributes.

This roundtable will explore how organizations navigate the continuum from early- to late-phase development when implementing CMC changes, including risk-based strategies, regulatory expectations, and emerging best practices.

Questions:

1. What are the key differences in the objectives of comparability exercises in early-phase vs. late-phase development?
2. How should the *extent of comparability data* scale with product knowledge, process maturity, and clinical stage?
3. How should acceptance criteria and statistical approaches evolve across phases in comparability exercises?

4. How should sponsors assess and justify residual uncertainty differently in early vs. late phase following a manufacturing change: what level of uncertainty is acceptable in early IND stages vs. near BLA submission?
5. What are some challenges you have had particularly in late-phase comparability, where the burden is higher?

Notes:

This roundtable discussion focused on different aspects of (i) comparability exercise and (ii) early phase vs late phase comparability analysis after CMC changes. For any of comparability exercise, risk assessment for CMC changes is important step to figure out how extensive comparability testing is required. As suggested in regulatory guidance, appropriate statistical method should be used to justify number of lots used for comparability exercise as well as to set comparability acceptance criteria.

For comparability exercise, not only release testing but also extended characterization testing and in-process testing need to be performed based on comparability risk assessment and tiering of CQAs

For early phase comparability, i.e. before Phase I or IND, normally comparative analytical assessment needs to perform if process change is done between Toxicity GLP lot and Phase I clinical lot. For late-stage process changes, comparability testing can be extensive based on risk assessment and how big the process changes are.

Comparability exercise can be performed (i) between historical batches and post change batches OR (ii) using split runs. For autologous products, comparability exercise should be performed on split product run to mitigate starting material variability.

The robust justification is required for selection of appropriate comparability testing design. As per team, most difficult comparability exercise is when there can be multiple changes at a time – i.e., process change, manufacturing site change as well as analytical method change. Sample retention (i.e, reserved samples) is one of the important aspects of comparability exercise.