Roundtable Session 2 – Table 3 – Non-Traditional Approaches to Comparability

Facilitator: Rajeev Boregowda, *Sanofi*

Scribe: Andy Weiskopf, *Sana Biotechnology*

Abstract:

Managing manufacturing changes in cell and gene therapy (CGT) products presents unique challenges distinct from those encountered with traditional biologics. These challenges stem from factors such as limited understanding of product quality attributes, manufacturing experience, variability in starting materials, small batch sizes, complex production processes, and limited product shelf life. Consequently, conventional comparability exercises designed for well-characterized biologics are often unsuitable for CGT products. To address these challenges, a risk-based, phase-appropriate approach to comparability is essential. This involves integrating analytical assessments with nonclinical and, when necessary, clinical data to evaluate the impact of manufacturing changes on product quality, safety, and efficacy.

This roundtable will focus on exploring various strategies for designing analytical comparability studies tailored to the unique aspects of CGT products.

Discussion Questions:

a) Discussions will encompass risk assessment methodologies.

b) integration of multidisciplinary data, and the application of innovative analytical techniques to ensure robust comparability evaluations in the context of CGT manufacturing changes.

Notes:

- The key challenge: how do we manage a scenario with such complex products and often limited data sets? It seems like a “perfect storm.”
- Often, raw material changes and process changes are introduced in the same new iteration.
- Regulatory agency expectations need to be considered. Participants noted that FDA is gaining a reputation as being very statistics-forward towards comparability, even asking for a statistical approach for single batch pre- vs. post-change assessments.
    - In later stage comparability, EU regulators tend to be comfortable with a 3-standard-deviation approach and recommend this instead of tolerance intervals.
    - Advice: involve a CMC statistician in your planning, not just a biostatistician.
    - Split pCQAs out appropriately, leverage DS and DP analytical data, and leverage whatever representative lots are available
    - Ground the comparability exercise in a risk-based approach; be thoughtful about which pCQAs/CQAs might be impacted by each change being introduced, and be focused about it.

    - Take a tiered approach: be more stringent towards comparability for the most critical attributes, and one can often justify flexibility for less critical ones.
    - For some lower-tier pCQAs/CQAs, comparability criteria equal to specification ranges are often acceptable. But using specification ranges as comparability acceptance criteria for ALL attributes will not be acceptable.
- Keeping lot retains remains the most valuable means for closing comparability gaps.
- Generally wise to default to conducting side-by-side testing of pre- vs. post-change samples, unless one has high confidence about assay performance and comfort using historical data from unchanged methods.
- In an ideal world, one could leverage in-process data when there are limited numbers of batches, but the opportunities for this are rare. Not only would one have to have had the foresight to implement a meaningful in-process assay back in early development, but after the proposed process change, the same assay and sampling point still need to be relevant.
- How does one approach comparability for personalized medicines? Since every batch is manufactured by a common process but each product is going to be different, is achieving process similarity the best we can do?
- Some helpful “don’ts”
    - Don’t use specification ranges for all comparability acceptance criteria
    - Don’t fail to save retains
    - Don’t proceed without discussing with a health authority first
    - Don’t be overconfident about your protocol
    - Don’t rely on methods which you’re not 100% in control of. Method lifecycle management is important so that you aren’t blindsided by unexpected assay variability.
    - Don’t unnecessarily expose your comparability assessment to site-to-site variability between testing labs, especially for highly complex assays.
    - Don’t assume that comparability risk is too great to implement a change. Do the risk assessment and the development experiments first before making a decision to shelve a potential process improvement.
- Broader organization often needs better awareness of what analytical comparability really means. Many confuse comparability with lot release specifications, and that if a single pCQA is out of range for a comparability criterion, the team has “failed.”
    - Need to educate colleagues about the notion of “totality of evidence” and the ability to leverage nonclinical (and, if needed, clinical) data to close comparability gaps.