Roundtable Session 1 – Table 3 – Non-Traditional Approaches to Comparability

Facilitator: Chenghong Wei, *AstraZeneca*

Scribe: Melody Gossage, *Eli Lilly and Company*

Abstract:

Comparability for cell and gene therapy (CGT) products presents unique challenges compared to other modalities. Studies are often designed to accommodate small batch sizes and face additional hurdles, such as limited understanding of critical quality attributes (CQAs) in the early phases, underdeveloped potency assays, and the need to control donor variability to ensure product consistency.

This roundtable will focus on conducting comparability assessments when only one lot is used in clinical trials. Guided by the FDA's comparability guidance, we will explore approaches to address challenges like donor variability and the limited number of batches. Our discussion will cover novel study designs and statistical analyses that can help overcome the challenges of assessing CGT product comparability.

Discussion Questions:

1. What are your biggest challenges with CGT product comparability in the early phase?

2. What novel comparability/similarity study designs do you use when batch numbers and sizes are extremely small? How do you set appropriate acceptance criteria to establish comparability?

3. How do you design your comparability study if there is only one lot in your clinical trial? Have you encountered situations where meaningful statistical analyses were impossible due to limited sample sizes? Do you use any innovative statistical analysis tools in your comparability assessments?

4. Have you encountered different expectations or flexibility from health authorities in various regions?

5. Do you have any suggestions for the CGT community to enhance comparability strategy design and knowledge sharing?

Notes:

<u>Summary</u>

Participants in the discussion shared various strategies and challenges related to comparability. It was noted that approaches are specific to the product and vary on a case-by-case basis. Most of the strategies discussed were refinements of traditional methods, with several participants noting that they did not consider these approaches as truly "non-traditional". The most non-traditional methods mentioned involved the use of organ-on-a-chip or human-on-a-chip technology. One participant highlighted that these technologies have demonstrated some success for small molecules and are frequently employed in the Discovery phase. However, no examples of planned or successfully implemented non-traditional approaches were provided.

Key takeaways included the importance of rigorous identification of, or justification for not designating, an attribute as a Critical Quality Attribute (CQA). Alternatives for a true functional potency assay were discussed, as well as the significance of decoupling analytical method changes from material comparability.

Stream of conversation notes

Biggest Challenges in Early Phase:

- Change in Manufacturers: Justifying limited comparability is essential, especially for rare diseases with high unmet needs. Proactively discuss the approach with the agency to gain alignment and identify the most impactful attribute criteria that need to be met or exceeded with the new material. In some cases, use the specification as the comparability criteria.
- Changing Starting Material: Employ a split-source study design to qualify new starting materials (SM) and characterize them with extensive viral testing. Utilize a side-by-side small scale model as long as it can differentiate changes in critical quality attributes (CQAs).
- Considerations Beyond PQ: Safety also needs consideration. One participant noted they were asked for more characterization of the materials.
- Forced Degradation Studies: These are not typically required for this product; however, assess whether changes can impact stability and conduct a risk assessment if necessary.
- Potency Assays: For late-phase products without potency assays, use mRNA expression assays.

Participants observed significant variation in agency expectations and allowances. Approaches are highly product-specific.

mRNA Vaccine Example:

- Every batch is different; demonstrating comparability is challenging.
- The sequence differs for every batch.
- Potency assays should cover the range of sequences.

Challenging Traditional Comparability:

- Using looser tolerances or quality ranges.
- Altering control strategies and challenging tight ranges.
- Extending characterization to justify inconclusive results.
- Traditional statistical ranges may not be appropriate.
- Extensive data packages are usually needed to justify that something is no longer a CQA, particularly post-approval.

When making multiple changes at once, maintain consistent analytics. Use a minimum/maximum approach with solid justification and extended characterization, including testing lots used for approval, to demonstrate that something is not a CQA. Insufficient data in CGTP may limit modeling capabilities.

Cross-functional Collaboration: Work cross-functionally to truly understand the key attributes.

Advancements in Technology:

- Organ-on-a-chip and human-on-a-chip technologies have seen some success with small molecules and are frequently used for discovery purposes.
- Sequencing is being utilized more frequently and earlier in the process.