Roundtable Session 2 - Table 2 - Industry Feedback on FDA Comparability Guidance

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Abstract:

In July 2023, the FDA released a Guidance for Industry entitle Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Product. In it, they address risk management as a cornerstone for both manufacturing changes and analytical comparability study design. This session will explore industry feedback on the guideline that is currently out for comment. This roundtable will assume that participants have already familiarized themselves with the guideline and will ask and answer questions associated with it. Copies of the guideline will be made available to participants by the roundtable facilitator.

Discussion Questions:

1. How does this guideline address comparability concerns unique to the CGT drug modalities that are different from traditional biotherapeutic comparability guidance?

2. Have you submitted a CGT protocol for preapproval to the FDA and what type of feedback did you receive?

3. What, if any, content in the guidance seems like a difficult barrier to overcome to demonstrate comparability? e.g., requiring a number of 'at scale' batches for low yield processes.

4. In the Analytical section what strategy do you use to address study design and statistical approach when the batch number and size may be extremely small? How do you set appropriate acceptance criteria to establish comparability.

Notes:

- Cell and Gene Therapy Guidance is less specific. It provides more optionality.
- Statistics is deemphasized yet sponsors are seeing regulators ask for statistics.
  - Small patient populations present issues
  - An example was discussed of having a 1:1 lot comparison of pre and post changes. The study statistics was powered by repeat testing of the study test articles. It was noted that this did give confidence to the test results and an understanding of analytical variability but not an understanding of differences in process performance resulting from the changes made.
  - EMA feedback has deemphasized statistics and requesting graphical representation of the data instead.

- When beginning a comparability evaluation, Tier 1 considerations are the criticality of the change after which consideration can be given to whether the clinical data can be pool pre and post change. Be clear about your intention in the purpose of your study when writing your protocol and providing information to an agency.
- Ultra-rare diseases are treated on a case-by-case basis. Understanding that all patients treated, even your first patient in ultra rare diseases may be included in your pivotal study analysis, is important. (This feedback was provided by Eric Levenson from FDA who participated in the panel discussion).
- Can you use pre-clinical data to help support your comparability study in ultra rare diseases?
    - An understanding of how this data relates to your clinical data is important. A comparison of early-stage potency assay data is not always predictive enough to support use of this data.
- Is data from a scaled-down model suitable to help support a comparability study, particularly in helping with setting acceptance criteria for your study?
    - This would require sufficient data to support that the scale-down model is representative of clinical/commercial scale manufacturing.
- Different levels of change require different levels of data to support the change.
    - If the change is only in one-unit operation, then a study across that unit operation can be acceptable if there is sufficient support to show the subsequent unit operations are not affected.
- Would it be acceptable early in development to evaluate a drug substance change with data only from drug substance without needing to take the product all the way to drug product?
    - The answer was yes if there was sufficient support that drug product would not be impacted.
- Where is stability data needed post change? When not? This question was not fully answered during our time allotted.