Table 1 and Table 19: Comparability for Cell & Gene Therapy Products and Other Complex Modalities

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Scope:

Change is inevitable and occurs throughout the lifecycle of most biotherapeutic products. Challenges and approaches in demonstrating comparability of complex products after CMC changes can be as complex as the products themselves. Some examples of changes include manufacturing process changes, new manufacturing sites, the use of alternate raw materials to improve process economics and production yields, advances in test methods, improvements in process controls, and overall drug product capacity increases (scale up or scale out). This roundtable will discuss approaches, best practices, and regulatory expectations for evaluating comparability of product quality, safety, and efficacy before and after manufacturing changes for cell & gene therapy and complex products.

Questions for Discussion:

1. How are risk assessments used to assess the potential impact of changes on product quality as it relates to safety and efficacy? How is a risk-based approach applied to risk mitigation strategies?
2. What are some best practices for demonstration of analytical comparability for C & GT programs?
3. What's a good approach for demonstration of method bridging following analytical development? How many samples should be tested?
4. What statistical assessments are performed to justify pre- and post-change differences in product purity and potency and for method equivalency?
5. What strategies are used to overcome limited amounts of material available for analytical comparability testing?
6. What strategies are used for stability studies supporting comparability of C & GT products and other complex products?
7. How are stability studies for comparability different from typical studies in the stability program?
8. How and when should comparability protocols be used? How are comparability acceptance criteria established? When are acceptance criteria or non-quantitative acceptance criteria not required/expected?
9. What factors should be considered to demonstrate comparability at different phases of development and in post approval scenarios
10. What are best practices to address patient-specific variability? What items are considered utilizing as risk based approach?

Discussion Notes:

- Most companies are using risk assessments to assess the potential impact of changes on product quality.
- Pre- and post-changes should be evaluated using the same or equivalent (pre- and post-change) analytical methods. Most CDMOs have their own methods which may not be the same as another CDMO. Details on CDMO methods may not be shared with clients. Methods should be qualified and validated for Ph3.

- Most companies are keeping pre-change retains and doing side by side testing of 3 pre- vs 3 post-change samples. Expiration of retains is not typically considered since most are stored frozen in ultracold conditions.
- One RT attendee described a case where only 1 old process DP was available, and FDA requested production of more old process material for the comparability study.
- DP comparability evaluations are required by the health authorities even if a change occurs in only the DS manufacturing process with no change in the DP process.
- Pre- and post-change stability studies are always required for comparability assessment. Testing of at least 3 timepoints (even 0, 1, 2M) is recommended. Stressed storage conditions should be used where possible. Forced degradation is typically not used in comparability assessments, but may be useful for input to the risk assessment
- Some companies are doing modular (or unit operational unit) comparisons and using platform knowledge, if available, to justify comparability acceptance criteria and conclusions.
- Most companies are using data from historical lot testing (HLT) and mean ± 3SD to establish comparability acceptance criteria.
- Some RT attendees described situations where bioequivalence/clinical data was requested by regulators for a new process since HLT data was lacking.
- All RT attendees are using comparability protocols with pre-set comparability criteria for Ph1 to commercial studies. Both lot release tests and characterization assays should be used. Comparability protocols are not needed for comparisons of pre-/non-clinical to clinical phase materials.
- Comparability decisions and conclusions should be made for each product quality attribute based on the comparability risk assessment and sound science.
- When results exceed Comparability Acceptance Criteria, sponsors should provide scientific rationale for comparability conclusions and justify any potential clinical impact. Structure activity relationship (SAR) data using a matrix of potency assays will be very useful. Results from characterization testing using orthogonal methods is very valuable for justification of comparability conclusions, especially when method variability is observed.
- FDA, EMA, and the major health authorities are aligned on comparability assessment approaches. See ICH Q5E. Also see the Zolgensma EMA EPAR for good examples of where there were issues with comparability evaluations.
- Pro-active discussions with relevant health authorities on strategies and expectations for developing a clinical to commercial comparability protocol is strongly suggested.
- Since C&GT methods and processes are variable, FDA is asking to see comparisons of in-process data for an early manufacturing process (Ph1) to a late stage manufacturing process.
- Potency evaluations are a weak area for C&GT comparability studies since potency assays may be difficult to develop and sufficient correlation between clinical efficacy and potency assays may be lacking. A matrix of potency assays is best practice.
- Most companies are not establishing reference standards (RS) until the final commercial process is developed therefore RS are typically not used for comparability assessments.
- No RT attendees are using ICHQ12 concepts for comparability of C&GT products.
- For an ultra-rare disease (Luxturna), less analytical data was available and acceptable for demonstration of comparability.
- See the McKinsey & Co. article, “Viral-vector Therapies at Scale: Today’s Challenges and Future Opportunities”. The authors describe comparability as one of the challenges for C&GT programs.