Roundtable Discussions Session 1 and 2 - Table 3: Comparability for Cell and Gene Therapy Products

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Abstract:

Questions on Comparability are frequently posed to regulators. Comparability studies are needed to support manufacturing process changes through the lifecycle of Cell and Gene Therapy Products. Manufacturing process changes may encompass improvements/change in equipment, raw materials and critical starting materials such as the cells or the vector or their suppliers, manufacturing process scale or product stability. The criticality of the changes and the estimation of their impact on the characteristics of the product should determine the amount of comparability data needed. This roundtable will discuss approaches, best practices, and regulatory expectations for evaluating comparability of product quality, safety, and efficacy for manufacturing process changes for Cell and Gene Therapy Products.

Discussion Notes:

Comparability Challenges Faced by CGT Developers

- Sponsors of cell and gene therapies (CGTs) face many challenges when it comes to demonstrating comparability:
- For CGTs, it is often impractical to begin the early phase with the commercial process.
- High COGs and often small patient populations impact that total amount of material that can be economically produced.
- CGT products, especially cell therapies, are highly sensitive and are subjected to numerous open-processing and manual manipulation, introducing significant sources of variability and product quality concerns..
- The lengthy manufacturing timelines of some products (e.g. 4 months) further complicate the implementation of changes.
- By evaluating process changes only from batch-to-batch, this can lead to drift and introduce new risks.
- Allogeneic products, with factors like donor and patient variability, present additional complexities.
- Creating an appropriate scale-down model can be challenging, and identifying the specific drivers of observed changes can be difficult. A reasonable approach for change identification is the use of a partial factorial approach in Design of Experiments (DoE), but justifying the scale-down model can be demanding.
- Establishing appropriate standards and reference banks require justifications and may be limited by product characteristics, along with the implementation of qualification protocols.
- Additionally, the stability and regeneration of retained samples pose challenges that need to be addressed. In some cases, retains of early process runs may have been completely exhausted.

General Comparability Considerations

- With these challenges in mind, it is crucial to establish a Quality Target Product Profile (QTPP) from the outset, and to treat it as a living document. Prior to implementing any modifications, it is important to define the Critical Quality Attributes (CQAs) for CGTs via a comprehensive risk assessment. Furthermore, it is noteworthy that the patients themselves are often the most suitable method for evaluating these products, so early identification of attributes related to toxicity is essential for success. ICH Q5E principles have stood the test of time, however new approaches may be warranted for this new class of products. An updated definition of comparability may be the ability to leverage data across different processes.

Specific Comparability Discussion Points

- Starting from Day 1, it is recommended to retain as many samples as possible, particularly for viral vectors, as that will aid in comparability exercises later in development.
- Collecting extensive data is crucial, and to consider the potential impact of different patient phenotypes on results.
- When dealing with donors, splitting material at scale before and after a change is recommended, with the number of batches depending on variance and acceptance criteria, potentially involving multiple pairs and lots.
- When addressing site or process differences for autologous cell therapy, “pseudo comparability” is utilized via the split stream comparability approach, where the manufacturing process is split at the step of the change, with pre- and post-change results compared. While some argue that running the full product may not be necessary, it is essential to understand the attributes at each stopping point. During early stages of development, there may be more need to run through to the drug product.
- When introducing supplier changes, understanding what level of supplier (n-x; supplier’s supplier, etc.) is relevant, and how much information is expected to be provided becomes important, particularly when entering multiple countries and considering different global regulatory requirements.
- Substituting open processing and manual manipulation with fully closed and automated systems is advised to enhance consistency and eliminate manual/operator-induced inconsistencies, as parallel runs have demonstrated their equivalency or superiority. However, barriers such as cost, engineering constraints, and evaluating a machine’s ability to assess characteristics such as cell readiness to passage must be considered.
- Understanding process and product variability inputs is vital, especially given the complexity of cell therapies with numerous interactions that cannot be fully controlled.
- Although comparability protocols may be established for CGTs, true comparability is only confirmed when clinical results are observed.
- Leveraging platform analytics and utilizing platform assays for amendments can be advantageous.
- Establishing the design space early on is helpful for establishing comparability, and providing a framework for process optimization.

Regulatory Interactions Discussion Points

- Effective regulatory interactions in the context of demonstrating CGT comparability require careful consideration and proactive approaches.
- Bundling changes can effectively reduce regulatory timelines, but there are risks associated with implementing multiple major changes concurrently.

- When defining CQAs, it is crucial to transparently communicate the rationale to regulators, recognizing that the literature may not fully align with the practical aspects of the process or product. Scoring each attribute can aid in this process.
- Communicating the purpose behind process changes, whether for product optimization or addressing supplier changes, to regulators can be helpful. While agencies encourage continuous improvement, they can be strict when it comes to process changes that agencies might consider to be optional.
- Listing assumptions and providing a comprehensive understanding of the product and process development history is important.
- Depending on the circumstances, opting for a Type C submission rather than an amendment, though potentially slower than an IND amendment, can be more appropriate. Presenting the relevant information in a briefing document can be beneficial.
- It is important to recognize that different regulatory agencies may have varying expectations for big pharma versus small biotech companies.
- Different reviewers may hold differing opinions on the impact of a change, emphasizing the need to maintain open communication.
- There is a perception that obtaining regulatory approval outside of the US is easier and more accepting, with more focus on Good Manufacturing Practice (GMP) compliance. Peculiarities in review team expectations can pose challenges for filing an approval in the US even with robust comparability throughout late-stage development. The US regulatory authorities are particularly insistent on post-change patient data.
- In certain cases, for process changes between Good Laboratory Practice (GLP)/toxicology studies and Phase 1/First-in-Human trials, the FDA may not require formal comparability, so a table comparing release data and listing key process differences may be acceptable.
- Obtaining advanced designations such as PRIME and RMAT can significantly impact the relationship with the regulatory reviewers and potentially provide more opportunities for agency interactions. However, currently companies are experiencing delays in timelines for agency interactions due to ongoing agency resource limitations.