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Points to Consider: Comparability Assessments for Cellular and Gene Therapy Products When Changes are Made in their Manufacturing Processes

Comparability assessments are crucial for life cycle management of all biological products, including cell and gene therapy (CGT) products, and are utilized to ensure that manufacturing changes will not have an adverse effect on product quality, safety, and efficacy. ICH Q5E provides sound principles for assessing comparability and should be applied to CGT products using a risk-based approach, along with the appropriate flexibility to take into account the extenuating circumstances often posed by these innovative therapeutics. Flexibility is needed in order to maintain high standards of quality while applying fit-for-purpose comparability approaches for CGT modalities, depending on the particular product and the level of product and process understanding.

Because CGT products encompass a wide array of modalities, including but not limited to plasmid DNA- and mRNA- and viral vector-based gene therapies, cell-based gene therapies (also known as ex vivo gene therapies), and somatic cell therapies, as well as tissue engineered products, it is difficult to derive broadly applicable principles. There is no “one size fits all” approach and instead, fit-for-purpose approaches focused on relevant quality attributes that could potentially be impacted by the process change should be developed and applied for the particular product. For some innovative CGT products, new concepts will be needed.

At this time, CGT products generally cannot be considered “well characterized”, though product and process understanding are evolving rapidly in this field. While certain CGT modalities should eventually become well characterized, others are composed of living cells and may not be fully characterized at a molecular level. Given the current limitations in characterizing these products, and the complexity of many CGT modalities, evaluating the impact of manufacturing changes is often a complicated endeavor and may involve more uncertainty than for conventional biologics. The sponsor sometimes cannot rely solely on analytical data to demonstrate comparability. The evidence that a manufacturing process change has not adversely affected the quality, safety or efficacy of a CGT product is often multidisciplinary.

Manufacturing changes are inevitable, and are necessary to ensure continuity of supply, e.g., dual sourcing of raw materials, and other best practices for biopharmaceuticals. For example, scaling up or scaling out or introducing new manufacturing facilities is often required to produce sufficient amounts of product to treat all patients. Manufacturing processes for CGT products are complex, and improvements and innovation should be encouraged. Manufacturing capacity is a recognized limitation in the CGT field, and contract manufacturing organizations are often involved. Regulatory requirements are also evolving rapidly for CGT products and manufacturing changes may be needed to keep pace with these evolving expectations.

While there is a need for regulatory flexibility, this should not imply that quality standards can be lower for CGT products but rather that new approaches may be needed to ensure high standards. While CGT products pose many new challenges, they also bring new concepts and opportunities. The bulleted list below highlights some considerations when assessing the comparability of pre- and post-change CGT products:

1. The CGT product needs to be defined early, and the use of a quality target product profile (QTPP) is encouraged so that sponsors set and maintain boundaries as they develop the manufacturing processes along with the analytical methodologies for characterization, release and stability testing. Having a QTPP in place early in development will help raise awareness of when the boundaries of the defined product have been exceeded and the developer actually has a new product. The comparability assessment should be done in a phase-appropriate manner, as indicated in ICH Q5E.

2. Analytical methodologies evolve in parallel with product and manufacturing process development. With the development of new analytical methodologies, product quality attributes that can be detected and quantified often change during development. The comparability assessment should be focused on the relevant quality attributes of the product and not simply on what attributes can be measured. Understanding of the relevant product quality attributes and maturity of analytical methods should increase throughout the product development lifecycle, so advance planning to reserve appropriate amounts of product for later evaluations is recommended (while sample stability over time needs to be kept in mind).

3. Analytical methods supporting CGT products are often product-specific, non-compendial, and complex. Early implementation of reference materials and/or assay controls is recommended to enable bridging to new and improved analytical assays.

4. CGT products are often produced in small amounts and may even be manufactured at laboratory scale, therefore, the analytical methodology approach taken must accommodate the product and patient needs. There are often only small amounts of material available for development of analytical techniques, routine analyses, and characterization studies, as well as comparison of pre- and post-change products. In some cases, side-by-side comparability exercises are not feasible. The use of established assays with understanding of intermediate precision may be used as a means of analytical comparability instead of side-by-side testing.

5. Comparability exercises should always involve an assessment of the risk that the proposed manufacturing changes may impact the product, as well as other parts of the process downstream from the change. With this in mind, for highly complex CGT

products, it may be appropriate to focus the comparability assessments more on the process itself. Examples include but are not limited to complex cellular and tissue-based products, which have numerous product quality attributes that may be relevant to safety and efficacy but may not ever be fully defined. Furthermore, cellular product quality attributes may be dynamic and change upon administration to the patient. This requires working with more inherent uncertainty about the product quality.

6. Individualized (i.e., make-to-order) CGT products are custom made for a specific patient, and they are intended to vary from batch to batch in order to be tailored to each patient (e.g., autologous CAR-T cell product). It's necessary to account for this intended variability during comparability assessments of individualized products. The patient-specific product quality attributes vary intentionally and should not be the focus of a comparability assessment. Instead, the product-specific attributes should be comparable after manufacturing changes.

7. Product improvements should be enabled, particularly when safety improvements can result from manufacturing changes. Examples include improved purity profiles, such as a reduction in process residuals or product-related impurities. The ICH Q5E and FDA guidelines on comparability leave room for improvement of the product, and this should be encouraged.

8. Incoming materials (e.g., raw materials, starting materials, etc.) can have a significant effect upon the final CGT product and should have consistent quality. Introduction of new raw material batches from the same vendor, or raw materials from new vendors, should be evaluated carefully and in a controlled manner

9. Split manufacturing can be an effective approach for assessing comparability of pre- and post-change products. For example, this approach can be used effectively for individualized products when new manufacturing sites are introduced, or process changes are made, or new input materials are introduced. When applied, the manufacturing stream is split at the point of the change and run in parallel down to the drug product. Head-to-head comparisons can then be conducted (e.g., on the resulting pairs of drug product or drug substance batches). While split manufacturing can be highly effective, it is not always feasible due to limitations in the availability of material, and patient derived materials are particularly limited in their availability.) Alternative approaches to split manufacturing may also be preferable when a risk assessment is supportive, for example in the transfer of fully closed, automated manufacturing processes to new sites of manufacture.

10. While non-clinical data may be desirable to assess the potential impact of manufacturing changes on product quality, safety or efficacy, there may not be good animal models for CGT products, especially for cell- and tissue-based products. If animal studies are conducted, their relevance to patients should be considered. There may also be limitations in the sensitivity of in vivo assessments to changes in product quality.

11. While the CGT field poses many challenges, it also poses opportunities. Because CGT products tend to be manufactured in small batches for few patients (or even one batch for a specific patient for individualized products), clinical outcomes are more readily available on a per batch basis than for conventional biological products. When CMC and clinical data can be correlated in appropriate data and analytics ecosystems, then safety and efficacy (including durability) can be more readily monitored with the corresponding product quality information. It is recommended to archive appropriate manufacturing and product quality data as well as clinical data (e.g., long-term follow up (LTFU), durability of benefit, and other information) in a searchable and retrievable manner. This can be valuable for comparability assessments as well as the establishment of patient centric product specifications.

12. CGT products generally require LTFU to monitor for delayed adverse events and may involve patient registries to monitor efficacy longer term. Some CGT products are commercialized with limited clinical data packages, particularly in the case of rare diseases, so collection of additional clinical information post-approval is valuable for these products. In case comparability of quality attributes related to safety and efficacy cannot be fully demonstrated by in vitro technical studies, additional clinical data may be needed. Under circumstances where the sponsor proposes to rely on patient outcome as the final verification that the post-change product has not been adversely impacted for quality, safety and efficacy, a rigorous assessment of the patient benefit:risk profile should be conducted, and the post-approval path forward justified.