Planning a Manufacturing Change to your Cell and Gene Therapy Process?

The new FDA draft guidance has answers to your comparability questions.

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The process defines the product, a catch phrase that was common in the early 2000s, is rarely heard these days. The difference between then and now results from our understanding of the links between a biotherapeutic's process parameters and its product quality attributes. The onslaught of biosimilar product development forced the advancement in technology that led to our understanding of the levers that affect a product's quality profile. Over a number of years, this technology advancement enabled the relationship between biological products' critical quality attributes (CQAs) and the critical process parameters (CPPs) that influence CQA levels to be "well characterized". For this reason, a single process no longer defines a product for many biotherapeutics.

In the world of cell and gene therapy (CGT) products, the links between CQAs and CPPs are much more tenuous and less understood (i.e., more difficult to characterize). Within this modality, the old adage rings very true: the process does define the product. How then **does** a company approach making changes to a CGT manufacturing process without altering the product? A new FDA draft guidance, **Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products (July 2023)**, provides a road map.

WHY CHANGE A CELL AND GENE THERAPY MANUFACTURING PROCESS?

There are practical reasons a sponsor may want or need to make changes to an existing manufacturing process. Whether to increase scale, improve process efficiency, introduce a new supplier, or change the manufacturing site, manufacturing process changes are common, particularly for investigational products. However, within the relatively nascent field of CGT, the "manufacturing and control of CGT products can often be affected by unique factors, including limited knowledge of product quality attributes, limited manufacturing experience, limited and variable starting materials, limited amount of product, complex manufacturing processes, and limited product shelf life. These aspects of CGT products may make the management of manufacturing changes more challenging than for other biological products."[1] The key to successfully managing CGT process changes is to ensure that the pre- and the post-change products are comparable.

EVALUATING CELL AND GENE THERAPY COMPARABILITY AFTER A MANUFACTURING CHANGE

The guiding principles for establishing comparability of a CGT product after a manufacturing change mirror those used for any biotherapeutic: the manufacturing change must not impact the product's safety or efficacy. Specifically, the quality attributes (i.e., identity, purity, safety, strength, and potency) of the pre- and post-change products must be comparable. Similar to biotherapeutics, risk assessments are used to identify the potential effects of the manufacturing process change and a comparability study is designed to evaluate the impact of the change on the product quality. As noted in the draft guidance, "defining acceptable ranges for CQAs and establishing operating ranges for CPPs prior to making a manufacturing change facilitates conducting a risk assessment and evaluating the change."[1] Gaps in both product and process knowledge and their relationship should be considered during the risk assessment given that a lack of understanding elevates risk. Other points to consider during the risk assessment are the:

- Potential impacts of the process change on subsequent manufacturing process steps and in-process parameters.
- Impact of process changes on quality attributes not evaluated during routine release testing.
- Need to evaluate certain quality attributes by orthogonal analytical methods.
- Potential impact of the change on product stability and/or product compatibility with the container closure and delivery device.
- Appropriate statistical approach for assessing comparability, keeping in mind that "higher risk attributes typically warrant a more stringent statistical analysis than lower risk attributes."[1]

The outcome of the risk assessment will inform the comparability study design, the first stage of which is an analytical assessment of comparability. The study design should take into account the quality attributes to be evaluated, the development stage of analytical methods, and the acceptance criteria and the statistical methods that will be applied for demonstration of comparability.

Quality Attributes

It is important to consider the potential impact of any manufacturing change on quality attributes that are not routinely evaluated by release and in-process testing and to include characterization studies in the comparability assessment as well. The specific characterization studies to include will depend on the product type and its stage of development, among other factors, and should be identified during the risk assessment.

Analytical Methods

The analytical test methods used to evaluate comparability should be a blend of suitably validated release and fit for purpose characterization methods with sufficient precision to demonstrate the impact of the manufacturing change. In addition to the quantitative potency method used during product release, orthogonal potency methods or animal models may be useful to assess both the potency and the effect that the manufacturing change has on a product's mechanism of action (MoA). In addition, orthogonal methods may be considered for attributes defined as high-risk during the risk assessment. Another important consideration for comparability analyses is the evolving nature of analytical methods. Specifically, analytical methods may be updated, changed, or transferred to a new testing site over the course of a CGT product's development. In such instances, relying on historical data only during a comparability assessment may not allow for a definitive conclusion. It is therefore useful to retain samples from early manufacturing lots to allow side-by-side comparability analyses after a manufacturing or method change.

Acceptance Criteria

The acceptance criteria for the comparability study must be defined prior to study initiation. The draft guidance notes that "for quantitative attributes, a comparability acceptance criterion may be defined as the largest acceptable difference between the pre-change and post-change attribute (an equivalence margin) or as an acceptable range for the post-change attribute (a quality range)." Additionally, all lots used in the comparability study should be representative of the pre- or post-change manufacturing process and should meet all specifications for release and in-process testing.

Statistical Methods

Selection of the appropriate statistical methods is crucial when assessing product comparability. Details including the number of lots to be evaluated, the distribution and representativeness of the data, and the precision of the test method are some of the factors to consider when selecting a statistical method. Given the criticality of the statistical methods in assessing comparability, the draft guidance suggests consulting with a statistician when designing the comparability study.

It is important to note that an analytical assessment of comparability, which should also include an evaluation of product stability, may not be sufficient to determine the impact of a manufacturing change on the product quality, safety and efficacy. In some cases, nonclinical and possibly even pharmacokinetic/pharmacodynamic (PK/PD) studies may be warranted. To ensure alignment with FDA, the draft guidance recommends that a sponsor "submit a detailed study protocol (comparability protocol) and request feedback from the FDA on the study design and statistical approach."[1]

WHEN CGT COMPARABILITY CANNOT BE ESTABLISHED AFTER A MANUFACTURING CHANGE

When considering making changes to a CGT manufacturing process, it is important to recognize that certain changes may result in a new product. In such instances, a new, separate IND is generally required to initiate clinical studies with this product. The draft guidance provides examples of changes that are likely to result in a new product, such as transitioning from an autologous product to an allogeneic product or changing the sequence of a transgene. Additionally, when there are significant differences in safety and efficacy before and after a manufacturing change, and comparability cannot be established, the pre- and post-change products may be considered different products to be evaluated under different INDs.

THE IMPORTANCE OF EVALUATING THE POTENTIAL IMPACT OF A PROPOSED CGT MANUFACTURING CHANGE

The guiding principle for managing manufacturing process changes for CGT products align with other biologicals: the manufacturing change(s) must not impact the product's safety or efficacy. However, the complexity of both the manufacturing processes and the CGT products themselves means that the bar to establish comparability is more difficult. Comparability may result in assessments beyond the analytical study (e.g., nonclinical or PK/PD) or, in certain cases, may give rise to a new product altogether. It is therefore of utmost importance to fully consider the impact of potential manufacturing changes on a CGT product before implementing the change.

1 Draft Guidance for Industry: Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products, July 2023

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