

Management of Manufacturing Changes and Comparability of Cellular and Gene Therapy Products

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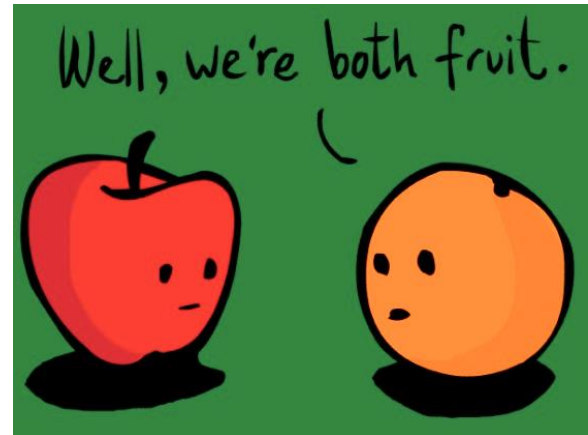
Office of Tissues and Advanced Therapies

CBER, US FDA

What Are Comparable Products?

...does not necessarily mean that the quality attributes of the **pre-change and post-change product** are identical, but that they are **highly similar and that the existing knowledge is sufficiently predictive to ensure** that any differences in quality attributes have **no adverse impact upon safety or efficacy of the drug product.**

Refer to ICH Q5E and FDA Guidance for Industry Q5E
Comparability of Biotechnological/Biological Products
Subject to Changes in Their Manufacturing Process



Demonstrating comparability is essential:

- ❖ Pre-licensure: it allows for a meaningful interpretation and pooling of clinical data that support licensure
- ❖ Post-licensure: it allows for continued marketing of a licensed product post manufacturing changes

Manufacturing Changes

- Manufacturing changes are inevitable but they need to be controlled and managed properly to avoid significant impact on product quality and delays in product development
- Manufacturing changes should be reported to the FDA (21 CFR 601.12 & 312.31).
- The risk of every manufacturing change should be assessed (21 CFR 601.12) and inform any studies that may need to be performed
- Comparability studies may be needed under a BLA as well as under an IND to demonstrate that the quality of product is not negatively affected after a manufacturing change (21 CFR 601.12)
- Manufacturing changes that fundamentally change the design or nature of the product-may require a new IND or BLA

Challenges in Managing Changes in CT and GT Products

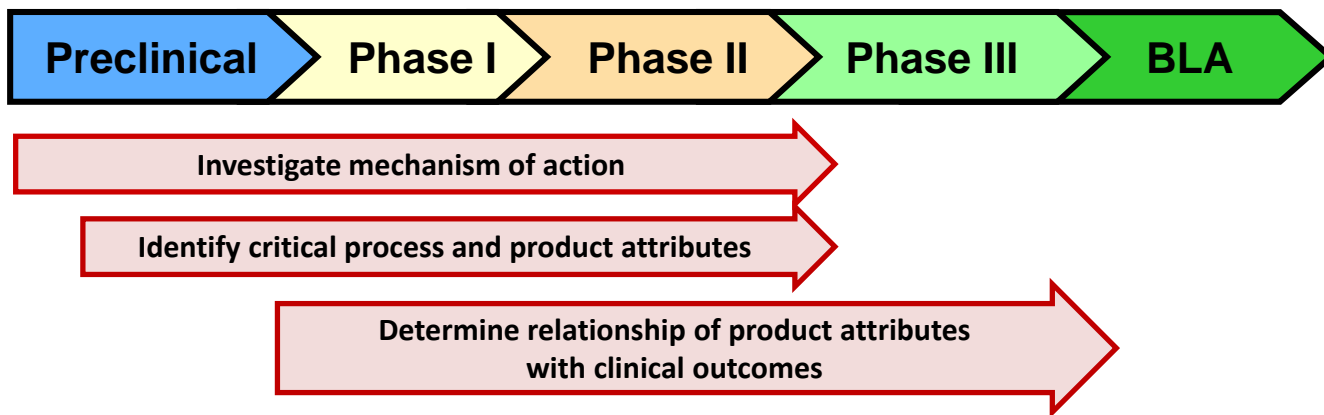
- Limited Number of Lots
- Limited characterization of process and product
- Uncertain mechanism of action and potency
- Variable source material
- Limited source material/small lot size/limited sample volume
- Suitability of analytical methods (e.g., using unqualified or unvalidated assay)

Limited Number of Lots

- Creates a challenge in characterizing CT or GT products and in evaluating manufacturing changes.
- The number of lots needed for a definitive conclusion in the comparability study is often large and not feasible.
- Plan ahead to ensure that a sufficient number of lots will be available to demonstrate analytical comparability using relevant statistical methods.
- If can be justified, using preclinical lots and retained product samples could be considered

Limited Characterization of Process and Product

- Product and process complexity and rapid development make it difficult to
 - i) establish meaningful release specifications and process controls
 - ii) demonstrate that manufacturing changes do not adversely affect product quality.
- Understanding the relations between product attributes and process parameters early on may prevent delays in product and clinical development due to manufacturing changes.

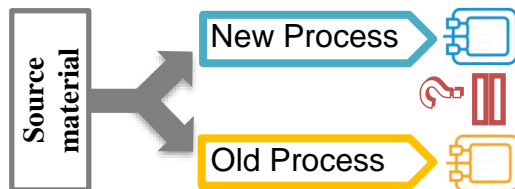


Mechanism of Action and Potency

- A qualified potency assay should be in place before initiating efficacy studies
- Understanding MOA is critical in developing a meaningful potency assay, yet the MOA is often not entirely clear and there might be multiple mechanisms of action
- Potency assays are challenging to develop and could be inherently variable
- It can be difficult to establish meaningful potency specifications if the relationship with safety and efficacy is not well understood
- Biological activity can be highly sensitive to manufacturing changes
- Evaluate several measures of potency early to identify and qualify a suitable assay
- Include a qualified (if not validated) potency test in your comparability study
- Investigate the correlation between potency and safety and efficacy
- Retain samples that could be useful for a retrospective potency analysis, including for comparability

Inherently Variable Source Material

- Donor-derived cells are highly variable
- Results in variable product attributes which can make it difficult to evaluate how manufacturing change affects product quality
- Often requires large number of lots for comparability evaluation
- A split source material comparability study design can eliminate the effect of source material variability if enough source material is available
- Understanding the relationship between product attributes and clinical outcomes can potentially reduce the number of lots needed for comparability if a wider equivalence margin is justified by the clinical data



Limited Source Material

Cellular and tissue source material may only be available in small quantities and from small numbers of donors, which limits:

- Product characterization and identification of CQAs
 - In-process and final product testing
 - Retention of samples
 - Comparability analysis (e.g., insufficient number of lots, inability to split source material, limited test samples)
- In these situations, alternative approaches to demonstrating comparability may be considered

Suitability of Analytical Methods

- Variability/inconsistency of analytical methods may limit the ability to detect a meaningful change in a quality attribute
- Multiple suitable assays may be needed to sufficiently understand the full potential impact of a manufacturing change on a particular product quality attribute
- The same method should be used to assess the pre- and post-change product attributes to minimize assay variability in comparability studies.
- The use of standards, when possible and applicable, can enhance the speed and quality of suitable assay development, qualification, and validation

Risk Management

- Potential impact of each manufacturing change on product safety and quality should be determined via risk assessment
- The risk of making major manufacturing changes to CT/GT products is generally considered high due to the complex nature of the product characteristics and often limited ability to demonstrate comparability
- A systematic approach to risk management enables effective, consistent and predictable risk-based evaluation of manufacturing changes and facilitates the comparability study design and selection of CQAs
- Decrease risk by having a clear understanding of CQA, CPP, and the relationship between CQAs and clinical outcomes

Risk Management

- When product characteristics are not well understood it is critical to have a consistent and well controlled process
- Consider potential impact of manufacturing change on product stability. Adverse impact on stability could result in a significant delay in clinical development
- Define CQAs and CPPs early when a product is developed under an expedited program (e.g., Fast Track, Breakthrough, and RMAT designations)

Management of Manufacturing Changes Through the Product Lifecycle



- In general, the amount of information needed to assure the quality of an investigational product increases as product development proceeds
- Manufacturing changes that have a potential to affect product quality should be submitted in an amendment to the IND for FDA review before administering the post-change product to subjects
- Changes with a moderate or substantial potential to affect product safety or efficacy may require comparability studies; however, the extent of product quality characterization in the comparability study may depend on the stage of development and type of change

Comparability Study

- Comparability of CT and GT products is mainly demonstrated using appropriate analytical and/or nonclinical studies
- The extent of comparability data required depends on the type of change and its risk as well as stage of development.
- Preclinical studies may be needed, if applicable, to support comparability if results from the analytical comparability assessment are inadequate or uncertain



Submission of Comparability Study

Introduction

- Description of change
- Rationale and justification
- Timeline for implementation

Risk Assessment

Provide a detailed risk assessment to support:

- Selection of product attributes and process parameter to be evaluated
- Suitable test methods
- Comparability acceptance criteria

Submission of Comparability Study



Comparability Study Design:

- Full Scale process should be used unless otherwise justified
- Side-by-side testing of pre-change and post-change process is a superior approach.
- Historical data or retained samples from historical lots may be used, but description of suitability should be provided
- Split-source material study design and paired analyses is recommended when the source starting material is variable.
- When manufacturing product specifically for comparability studies, use the same type of source material as used for clinical production unless otherwise justified (e.g., limited source material, ethical concerns, or other justified reasons).
- Sufficient number of lots should be evaluated to reach a statistically meaningful conclusion



Submission of Comparability Study

Statistical Method

- Different statistical methods may be used to analyze different CQAs.
- Describe the statistical method, justify the assumptions of the statistical approach, specify the acceptance criteria selected, and discuss limitations.
- Two-sample t-test is usually not appropriate.
- Define meaningful differences in product quality attributes to establish the equivalence margins.
- If the lots selected for the comparability study are not representative of your typical manufacturing lots, the corresponding results will have no meaningful interpretation; the comparability lots should be selected in an unbiased manner.

Summary

- CT and GT products complex and generally not well characterized.
- Manufacturing changes can affect product quality of CT and GT products in an unpredictable way
- Risk assessment should be performed for all manufacturing changes
- Comparability study is required for changes that have moderate or substantial potential to affect product quality.
- Comparability is exercised pre-licensure and post licensure
- Demonstration of comparability enables 1) pooling of clinical data generated with the pre-change and post-change product to support licensure, or 2) continued marketing the post-change product
- Investing in product characterization early in development allows for better controls over manufacturing changes and product quality.

References

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