Comparability Studies
Unique Challenges and Key Considerations for Cell and Gene Therapy Products (CGTPs)

Zenobia Taraporewala
FDA/CBER
Office of Tissues and Advanced Therapies

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Overview
Comparability studies of CGTPs

- **Introduction**
- **Key considerations**
- **Challenges**
- **Summary**

Introduction

For most programs, it is anticipated that manufacturing changes will be made throughout development; commonly to support product needs for late phase trials and/or commercialization

For e.g.,

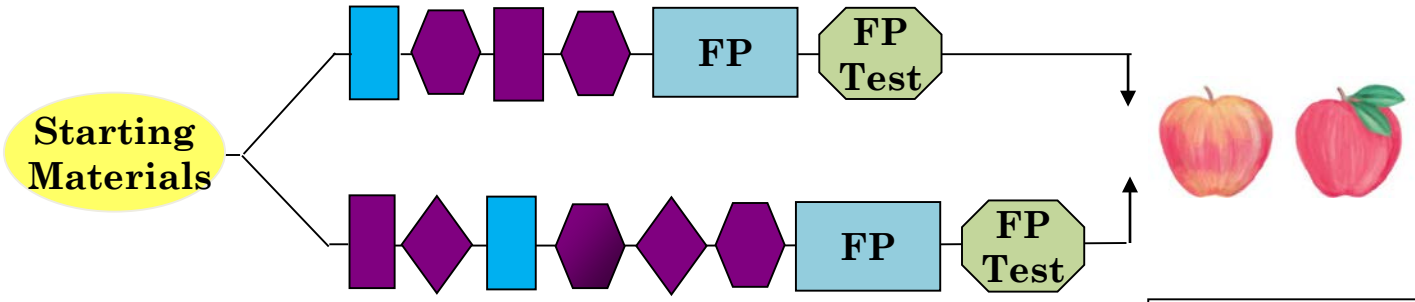
- *Manufacturing site (adding new sites)*
- *Scale/platform: upstream/downstream processing*
- *Formulation, storage conditions*
- *Automation to expand market and fulfill business needs*
- *Changes made to improve product stability*
- *Complying with changes in regulatory requirements*
- *Change in suppliers/source of reagents/critical starting material (cell banks)*

Guidance

FDA (ICH) Guidance: Q5E Comparability of Biotechnological or Biological Products Subject to Changes in Their Manufacturing Process (2005):

> *When changes are made to the manufacturing process,* ***the sponsor generally evaluates the relevant quality attributes of the product to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the drug product.***
>
> *Determinations of product comparability can be based solely on quality considerations* ***if the manufacturer can provide assurance of comparability through analytical studies.*** *Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish comparability.*

What are Comparable Products?



- **Highly similar quality attributes before and after change**
- **No adverse impact on the quality, safety or efficacy**

Establishing Product Comparability
What are the Expectations?

Expectations

- Statistically robust and comprehensive data
  - Side-by-side analysis of multiple lots (pre and post change): Developmental, engineering, clinical
  - Comparison to historical data (manufacturing clinical lots) may be acceptable during early development, if justified
  - Acceptance criteria with predefined variability: Consider criticality of the product attribute, sensitivity of the analytical assay, past manufacturing experience/data, sources of variability
- Well-developed (and validated, when possible) assays should be used
  - Assays that measure CQAs (Critical Quality Attribute)
- Comparability protocol should be developed and discussed with FDA prior to comparability demonstration

ICH Q5E Guidance on Comparability Protocols

Key Considerations for Comparability Studies

1. Risk assessment and mitigation plan

What impact does the manufacturing change have on product quality and any mitigation strategy?

Is it a minor or major change?
- *Major changes will likely require comprehensive comparability studies.*

Consider the stage of product development: early vs late vs post-approval.

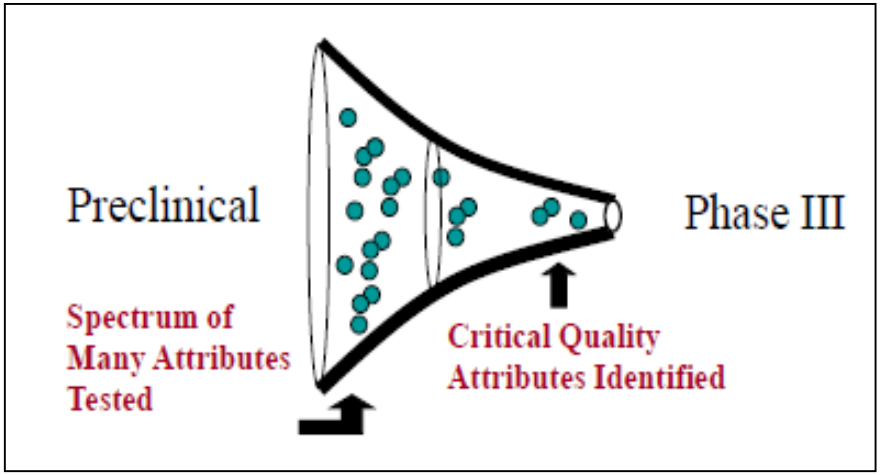
- If manufacturing changes are introduced in late stages of development with no additional clinical studies planned to support the BLA, the expected level of comparability demonstration will be significantly higher.
- If analytical comparability study data are not sufficient to establish comparability, additional pre-clinical and/or clinical studies may be required to demonstrate comparability of product safety and efficacy.

Key Considerations for Comparability Studies

2. Knowledge of CQAs of the product under study is critical to establishing comparability

A Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Evaluate many attributes early during development and prune during lifecycle to those that can discern process-related changes in product safety, quality and efficacy.



Key Considerations for Comparability Studies

3. Adequacy of the analytical tool box

Well-controlled, sensitive and quantitative assays are crucial when product comparability has to be demonstrated using analytical methods (*particularly for complex biologics*).

<u>Assays used in comparability study of CGTPs should:</u>

- Be qualified and controlled.
- Orthogonal (different assays should be used to measure a CQA)
- Include a biological potency assay
- Include product characterization assays [can be valuable in identifying changes in product attributes (purity, identity, quality) not otherwise monitored for release testing]
- Include assays that use current technology to allow greater understanding of the product characteristics and reduce the risk of the "unknown" change.

Key Considerations for Comparability Studies

4. Adequacy of manufacturing data

- Depends on the stage of clinical development
- Comparability plan should have preset acceptance criteria for testing product attributes
  - Not necessarily lot release criteria
  - Justification/rationale
- Manufacturing history should be leveraged
  - Consider in-process testing data, product characterization data and lot release data
  - Development lots, engineering lots, pharm-tox lots, **clinical lots**
- Appropriate and robust statistical analysis with rationale for approach, *when possible*.

Common Challenges for Comparability of CGTPs

- **Limited lots** (manufacturing history):
  - Comparability studies are not statistically powered
  - Not enough retention/test samples available
- **Limited assay development** (potency, purity); assays not qualified; reference standards not established or adequately characterized.
- **Limited product characterization**; CQAs not known
- **Limited knowledge of product- and process-related impurities**
- **Limited in-process testing**; process variables and critical process parameters (CPP) not known
- **Limited product stability data collected**; limited product attributes tested in stability plan.

Common Challenges for Comparability of CGTPs

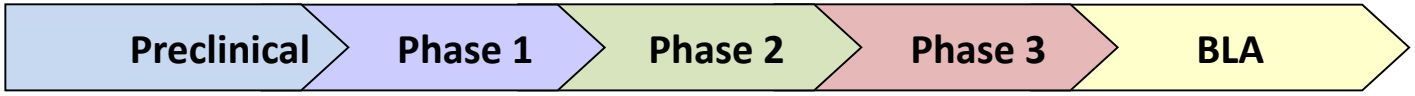
Expedited programs:

- Breakthrough (BT)
- Regenerative Medicine Advanced Therapy (RMAT)
- Fast Track
- Accelerated Approval
- Priority Review

Expedited programs often have faster, and therefore compressed timelines for clinical development…….but commonly, the CMC development is lagging.

Comparability Studies
Expedited Programs

When a clinical program advances rapidly the timelines from early to late development may be compressed



<u>Planning</u> for commercial scale manufacturing including comparability studies (when needed) should be conducted early (Phase I/II).

Challenges for CGTPs on Expedited Pathways

- Limited manufacturing experience
- Limited process knowledge and variables
- Inadequate analytical development and
- Lack of comprehensive product characterization.

In this scenario, there are challenges in:

- Assessing the risk to product quality and safety due to the manufacturing change(s)
- Designing robust and statistically sound comparability studies
- Meeting the product needs of a late phase trial and/or licensure due to manufacturing programs that are slowed.

Summary

Key Considerations:

- Understand critical process parameters and critical quality attributes early in development.
- Understand the risk (safety and efficacy) and develop a risk assessment and mitigation plan; develop a comparability strategy accordingly.
- Build a robust analytical tool box for product characterization and testing early.

Gain alignment from the agency on comparability plans for seamless early to late phase transition (even more so for products in expedited programs!).

Seek OTAT advice early !

Contact Information

Zenobia Taraporewala

Zenobia.Taraporewala@fda.hhs.gov

FDA Headquarters

Regulatory Questions:

OTAT Main Line – 240 402 8190

Email: OTATRPMS@fda.hhs.gov and

Lori.Tull@fda.hhs.gov

OTAT Learn Webinar Series:

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Consumer Affairs Branch: ocod@fda.hhs.gov

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