Roundtable Session 1 – Table 7: Non-traditional Approaches to Comparability

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Abstract:

Comparability demonstration following manufacturing changes is a requirement during clinical development and commercial lifecycle. ICH Q5E [1] provide the foundation for this process. The draft FDA guidance "Manufacturing changes and comparability for human cellular and gene therapy products" [2] emphasises the need for a risk-based approach to identify the potential impact of process changes on critical quality attributes (CQAs), which should drive in-depth analytical characterisation of the product before and after changes. It also suggests the use of statistical approaches, orthogonal methods, and the application of success criteria that go beyond routine specifications, while acknowledging that this may represent a challenge due to limited manufacturing experience, limited and variable starting material, limited amount of product, complex manufacturing process and limited product shelf life.

In this context, recent FDA guidance on CMC flexibility for the development of CGT products [3] indicates that, for investigational drugs, when the change is considered minor, the FDA may accept limited comparability data if the CQAs are met and the changes are submitted before administration of the post-change product.

[1] COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS, ICH Harmonised, 18 November 2004

[2] Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products Draft Guidance for Industry, U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research, July 2023

[3] Chemistry, Manufacturing, and Controls Flexibilities for Developing a Human Cellular and Gene Therapy Product for a Biologics License Application, Guidance for Industry, U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research, May 2026

Discussion Questions:

What are the main hurdles commonly encountered during the comparability exercise? How to overcome those?

Are there different approaches being taken depending on the development phases of the product?

Which statistical tools are used for comparability demonstration, beyond equivalence?

RoundTable Key Themes & Discussion Points

Regulatory Framework & Hurdles

- ICH Q5E and FDA's 2023 draft CGT comparability guidance provide the foundation; risk-based approach is emphasized
- CGT products present unique challenges: limited batches, variable starting materials, complex processes, and short shelf life
- Recent FDA CMC flexibility guidance (May 2026) allows limited comparability data for minor changes at investigational stage

Risk Assessment & Tools

- Comparability planning begins with the CQA risk assessment (high/low impact is straightforward; mid-range is complex)
- FMEA is the predominant tool for risk assessment; ICH training materials offer alternative frameworks

Phase-Appropriate Comparability Round

- Early phase (Ph1): focus is primarily on safety; process robustness not required
    - Lack of robustness early is a business risk, not necessarily a regulatory risk
- Later phases (Ph2/3): increased rigor; potency and extended characterization become critical

Statistical Tools & Approaches

- Stats are a tool — use where feasible, but scientific justification can substitute when n is too low (particularly with the FDA)
- Approaches to increase statistical power: non-GMP lots, stability data, multiple replicates, mixed model statistics
- Pre-define comparability criteria in the protocol; avoid cherry-picking data
- Equivalence testing with one batch (multiple replicates) is acceptable in some cases where limited material is available

Common Hurdles & Strategies to Overcome Them

- Low batch numbers make traditional statistical analysis difficult; compensate by evaluating multiple process steps to increase effective "n"

- Non-traditional characterization methods (single-cell RNA-seq, NGS) can support comparability packages
- Bundle process changes together to perform one comparability study; derisk changes early in process development (PD) space
- Make changes as early as possible so comparability burden is reduced at pivotal stage

CQAs & Extended Characterization

- Regulators expect extended characterization beyond known CQAs because product/process understanding is still evolving
- Standard CAR-T potency assays (e.g., IFN-γ, T cell killing) may be insufficient for late stage; deeper cell characterization is critical
- Empty/full capsid ratio is always a CQA for AAV and presents ongoing challenges, especially when purification processes change

Global Regulatory Considerations

- FDA: data-driven, statistics-friendly, pragmatic on feasibility
- EU: prefers biological relevance and scientific discussion over stats alone; more conservative
- Health Canada generally follows FDA; starting with an FDA-approved approach is recommended for global submissions