Final Concept Paper

M18: Framework for Determining the Utility of Comparative Efficacy Studies in Biosimilar Development Programs
November 2025

Endorsed by the MC on 19 November 2025

Type of Harmonisation Action Proposed

This proposed new multidisciplinary guideline will outline the factors to consider when determining the utility of comparative efficacy studies (CES) in biosimilar development programs intended to support regulatory approval. It will also describe the conditions under which similar efficacy and safety and an acceptable immunogenicity profile can be ensured should such trials be deemed unnecessary. The guideline will describe how these factors may be applied in determining the utility of CES and provide guidance for tailored biosimilar development programs (without CES), to facilitate consistent global expectations early in biosimilar development when planning for CES typically occur.

Background to the proposal and Statement of the Perceived Problem

Historically, CES have been a default expectation as part of a biosimilarity assessment to support regulatory approval of biosimilars. As experience with the development and approval of biosimilars has grown, there has been increasing recognition that CES lack the sensitivity required to differentiate between products with differences in quality attributes, including physicochemical, structural and functional attributes. Additionally, modern analytical technologies have the sensitivity to discriminate differences between biosimilars and their reference products, providing assurance about their clinical performance thereby leaving little residual uncertainty. Therefore, CES may not provide useful information, yet require substantial time and resources in biosimilar development programs.

Over time, this has led to increasing calls from industry, academia, and regulators in support of streamlining biosimilar development by eliminating the default expectation for CES. For example, multiple publications of accrued clinical study data have shown that CES results were consistent with analytical similarity data, did not inform approvability, and required extensive resources to conduct. [Refs 1, 2, 5, 6, 8, 9]. Additionally, an increasing number of regulatory health authorities have issued updated guidelines to reflect the position that CES are not generally necessary [Refs 3, 4, 5, 11, 14, 15, 17, 18, 19].

The performance of CES that are not scientifically warranted involves the use of valuable resources, including clinical trial participants for studies that do not provide additional information, and potentially discourages biosimilar development.

Because biosimilar development often occurs simultaneously across multiple regions, a lack of harmonization may result in regions having different expectations, which may result in the continued default use of CES even if not scientifically warranted. The intent of this guideline is to promote a consistent and scientific-based approach to the regulatory considerations by outlining the key factors to consider and providing a framework for their consistent application.

ICH Q5E, Comparability of Biotechnological / Biological Products Subject to Changes in their Manufacturing Process [Ref 12], contains a list of high-level factors to consider when deciding if nonclinical and clinical studies should be considered to establish comparability of biotechnological/biological products subject to changes in their manufacturing process.

Because the types of analytical differences between proposed biosimilars and their reference products are often analogous to the types of differences that may occur with manufacturing process changes, the EWG will use the Q5E factors as a starting point in developing a framework for determining the utility of comparative efficacy studies for biosimilars. However, important contextual differences between the post-approval manufacturing change setting and the biosimilar development setting may affect the relevance of some factors and influence how they are applied.

Issues to be Resolved and Expected deliverable(s)

1. **Issues to be Resolved**

- Factors that are relevant to consider for the context of determining the utility of CES, or other clinical studies, in biosimilar development programs.
- In a framework where there is no CES in a biosimilar development program, how efficacy, safety, and an acceptable immunogenicity profile are assured.

2. **Expected Deliverables**

The expected deliverable of this work is a multidisciplinary guideline that describes a risk-based framework that can help to determine the utility of CES in biosimilar development programs. The framework will be developed by using the "factors to consider" described in ICH Q5E as a starting point for developing consistent scientific principles to apply to the biosimilar context and including other considerations relevant to biosimilar development. The framework will draw upon the considerable experience of industry in the development of biosimilars and regulatory authorities in the review and authorization of biosimilars. Ultimately, the guideline will help identify the specific situations in which a CES would or would not be scientifically warranted to inform a conclusion of biosimilarity. This will foster greater regulatory consistency and predictability for all stakeholders across jurisdictions.

Type of Expert Working Group and Resources

*The harmonisation project is proposed to be performed by a standard ICH Expert Working Group, to be populated **primarily** by experts in Quality of biological medicines with expertise in analytical comparability and biosimilar program design/review and clinical/clinical pharmacology.*

Once established, the expert working group would assess whether it would benefit from onboarding experts from other disciplines with expertise in the proposed scope of the guideline.

Timing

We do not anticipate competition with resources allocated to other ongoing ICH projects. Much of the conceptual work and considerations have been identified and discussed publicly already, as evidenced in the references below. The draft (*Step 1 and 2a/b*) deliverable could be developed well within 18 months and completed (*Step 3 and 4*) within 3 years, if not sooner.

References

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