BIOSIMILARS COUNCIL™
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Understanding the Science Behind Streamlined Biosimilar Development

Why Comparative Efficacy Studies are Generally Unnecessary

At a Glance:

- **Comparative efficacy studies (CES) are generally unnecessary to demonstrate biosimilarity.** FDA's October 2025 draft guidance reflects over a decade of scientific progress and regulatory experience showing that CES rarely provide meaningful, new, or actionable information for regulatory decision-making.
- **Advanced analytical and pharmacokinetic (PK) studies are the best tools for detecting differences, while CES are "blunt instruments" for evaluating biosimilarity.** Small differences captured by modern analytical methods and PK studies are often missed by less sensitive CES. To help illustrate, FDA refused to approve six biosimilars based on differences in their analytical data, and, in only one instance did the CES also detect the difference.
- **Maintaining rigorous safety, effectiveness, and quality standards does not require CES.** Streamlined biosimilar development prioritizes the most scientifically rigorous and accurate evidence, ensuring safety, effectiveness, and quality, while also avoiding exposing patients to unnecessary clinical trials.
- **Streamlining biosimilar development expands access to life-saving medicines.** Eliminating redundant CES could reduce biosimilar development costs by 40%, shorten development timelines by 12-18 months, and help address the growing "biosimilar void."

Background: A More Streamlined, Patient-Friendly Regulatory Paradigm for Biosimilars

For years, developers of biosimilar medicines have been required to conduct human comparative efficacy studies (CES) – large, expensive trials – even when modern analytical tools and comparative pharmacokinetic (PK) studies could already answer the same questions more accurately, faster, and without exposing patients to unnecessary studies. That's why scientists, providers, patients and industry stakeholders applauded when the U.S. Food and Drug Administration announced new draft guidance in October 2025, recognizing that CES are generally unnecessary to demonstrate biosimilarity.

This shift was informed by over a decade of scientific progress and regulatory experience. Through this draft guidance, FDA is formally recognizing that in most cases, the best tools for detecting small differences between the biosimilar and the reference product (should they exist) are advanced analytical and clinical PK studies. Such differences are often not captured by less sensitive CES, leaving CES unable to offer meaningful, new, or actionable information for regulatory decision-making. This fact is supported by multiple studies from regulators and industry, many of which are referenced throughout this document.

Importantly, this evolving approach does not lower FDA's standards for safety, quality, or effectiveness. Instead, it ensures regulatory decisions rely on the most sensitive and scientifically appropriate evidence available, while avoiding unnecessary clinical trials that do not meaningfully inform those decisions.

Crash Course: Not All Studies Are Created Equal When It Comes to Detecting Clinically Meaningful Differences

To get to the bottom of why CES are usually unnecessary, it helps to understand how biosimilars are evaluated and which tools are the most reliable.

Analytical Studies:

Analytical studies, consisting of advanced physiochemical and functional analyses, are **the most sensitive and reliable way to detect differences**, should they exist, between a biosimilar and its reference product. These state-of-the-art methods directly measure a product's structure and function with extraordinary precision.

By confirming that the biosimilar is "highly similar" to its reference product, analytical studies allow developers to demonstrate comparable effectiveness and safety, including immunogenicity, across all reference product indications.

Pharmacokinetic (PK) Studies:

PK studies are conducted in humans (either healthy volunteers or patients) and establish that the biosimilar and reference products are distributed similarly in the body. PK studies are conceptually similar to bioequivalence studies that support generic drug approvals. In addition, PK studies provide supportive data for comparable safety and immunogenicity.

Comparative Efficacy Studies:

CES are conducted in patients and compare the biosimilar and reference product using an efficacy endpoint, which is a measurable outcome intended to reflect whether a treatment is working. Such endpoints can take different forms. Some are pharmacodynamic endpoints, which measure the biological effect of a drug in the body. Others are traditional clinical endpoints, such as symptom improvement or disease progression.

While these studies may seem intuitive, they are the least sensitive tool for detecting clinically meaningful differences between a biosimilar and its reference product. Structural differences between two biological products do not necessarily translate into observable differences in clinical efficacy – and patient variability and confounding factors can obscure meaningful signals.

Data from Analytical and PK Studies Are More Sensitive and Predictive of Safety than CES

For decades, reference biologics have relied on analytical and PK data to support major manufacturing changes. Even substantial changes, like the establishment of a new cell line, rarely require comparative efficacy studies.

When it comes to biosimilars, multiple peer-reviewed articles have reached the same conclusion: CES do not meaningfully contribute to the demonstration of biosimilarity, while physiochemical methods and functional assays are far more sensitive for detecting potential differences (Schiestl et al. 2020, Bielsky et al. 2020, Guillen et al. 2023, Kirsch-Stefan et al. 2023).

Top regulators, including FDA's Dr. Sarah Yim, in the IPRP Summary Report (2024), have recognized CES as "blunt instruments" and the least sensitive tool for detecting differences. FDA has explained that it has refused to approve six biosimilar applications due to deficiencies identified in analytical data. Notably, only in one of those six cases was the difference also flagged by CES. To date, FDA has not identified any biosimilar application in which a clinical study detected a concern that was not already identified through analytical testing (IPRP Biosimilars Working Group 2024).

This experience highlights a critical point: had FDA relied on CES alone, five biosimilars with meaningful analytical deficiencies could have appeared clinically comparable, underscoring that CES often lack the necessary sensitivity to compare a biosimilar and its reference product and the limitations of such studies in supporting robust regulatory decision-making.

Why CES Are Less Sensitive

Why is this the case? CES are limited by patient variability and confounding factors that dilute their ability to detect subtle differences between products. In fact, research has shown that entirely different molecules within the same therapeutic class – molecules with structural differences far exceeding those permitted for biosimilars – can still produce comparable clinical responses (Schmitz 2012).

As a result, observing similar outcomes in patient populations does not reliably confirm biosimilarity. In contrast, analytical and PK studies can robustly demonstrate comparable effectiveness and safety.

How Analytical and PK Studies Demonstrate Effectiveness and Safety

Effectiveness:

Analytical studies compare the structural features of a biosimilar and its reference product — because the same structure dictates same function. These studies also evaluate binding properties (i.e., how the molecule interacts with its intended target), which further supports comparable effectiveness.

In addition, certain tests assess the products in living cells that mimic the condition under which the product works in patients—but without the confounding factors of a CES. PK studies confirm that both products achieve comparable drug absorption and distribution, an essential prerequisite for demonstrating no meaningful differences in effectiveness.

Safety (Including Immunogenicity):

Biologics work highly selectively with molecules in the human body, often described as a lock-and-key mechanism. As a result, they rarely interact with other molecules in the body (i.e., produce off-target effects), with comparable pharmacological activity predictive of comparable safety. In other words, the effectiveness of a biologic determines its safety profile. Moreover, the stringent quality standards, which apply equally to both reference products and their biosimilars, further ensure patient safety. PK studies also provide supportive clinical data for comparable safety.

Biologics can, in some cases, trigger unwanted immune responses. Accordingly, FDA will only approve a biosimilar if it demonstrates comparable or lower immunogenicity than its reference product. Immunogenicity is comprehensively assessed through detailed analytical characterization of critical quality attributes (CQAs) and PK studies measuring anti-drug antibodies (ADA) and neutralizing antibodies (NAb). A single-dose PK study is sensitive enough to detect immunogenicity differences, with CES not providing any additional insight beyond what the PK and analytical data revealed (Schiestl et al. 2025).

Consistent with this conclusion, a meta-analysis authored by FDA scientists found that PK similarity studies provide useful information to evaluate safety (including immunogenicity), while CES do not appear to provide more definitive information (Ji et al. 2025).

The Takeaway

Modern biosimilar development relying on analytical and PK data maintain FDA's stringent safety, effective, and quality standards because they are more sensitive, more predictive, and more scientifically appropriate than CES. FDA's draft guidance reflects this reality and recognizes that streamlined development should be the default approach, with CES reserved only for exceptional cases where a scientific question cannot otherwise be answered. The U.S. should continue to lead instead of risk lagging in this area – the European Medicines Agency, Health Canada, and the UK's Medicines and Healthcare Products Regulatory Agency have revised or are revising biosimilar guidelines to reflect streamlined principles.

Further, streamlining biosimilar development by eliminating redundant and expensive CES could reduce development costs by approximately 40%. These high costs contribute to the "biosimilar void," or the lack of development of biosimilar competition for the 118 biologics that are expected to lose patent protection over the

next decade. It would also shorten biosimilar development timelines by 12–18 months.

To ensure American patients have access to medically necessary, low-cost biologic medicines, policymakers and regulators must ensure that streamlined development is the default regulatory expectation and only require CES in exceptional, justified cases.

Resources:

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