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EVOLVING COMPARATIVE CLINICAL DATA EXPECTATIONS

GrxBiosims: Streamlining Biosimilar Development Session

October 27, 2025

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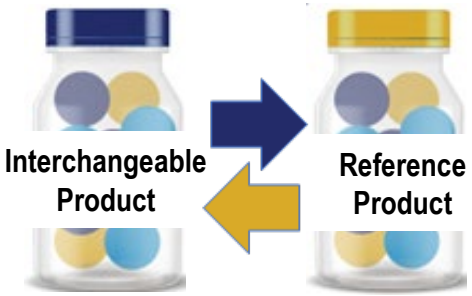
Key Definitions from the BPCI Act

Reference Product

A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared

Biosimilar Product

A biosimilar is a biological product that is **highly similar to and has no clinically meaningful differences from** an existing FDA-approved reference product



Interchangeable Product

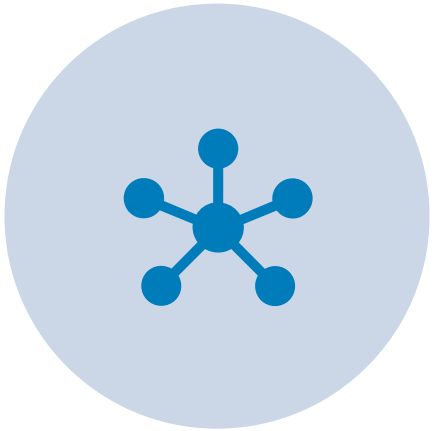
- Is a biosimilar
- Expected to produce the same clinical result as the reference product (RP) in any given patient
- Switching between the proposed product and the RP does not ↑safety risks or ↓effectiveness compared to using the RP without switching

Expectations to Support Biosimilarity

“Abbreviated”: 351(k) BLA
Goal: To demonstrate biosimilarity (or interchangeability) to a reference product based on comparative assessments

- **Comparative clinical studies**
- Pharmacokinetic / pharmacodynamic comparisons
- Immunogenicity assessment

Analogy: Steam Engines to Bullet Trains



SERIES OF PARALLEL EFFORTS CONVERGE TO CATALYZE MAJOR SHIFT

THE LEAP FROM STEAM ENGINES TO BULLET TRAINS WAS AN EFFICIENCY BROUGHT ON BY SCIENTIFIC ADVANCES AND DEEPER EXPERIENCE

REACH THE DESTINATION FASTER, WITHOUT COMPROMISING STANDARDS

Reflecting on Experience with Comparative Efficacy Studies (CES)

- Multiple reviews of comparative clinical study data have shown that CES did not identify true or meaningful differences in efficacy, safety, PK, or immunogenicity between the proposed biosimilar and the reference product.
- Reflection papers also signaling flexibility

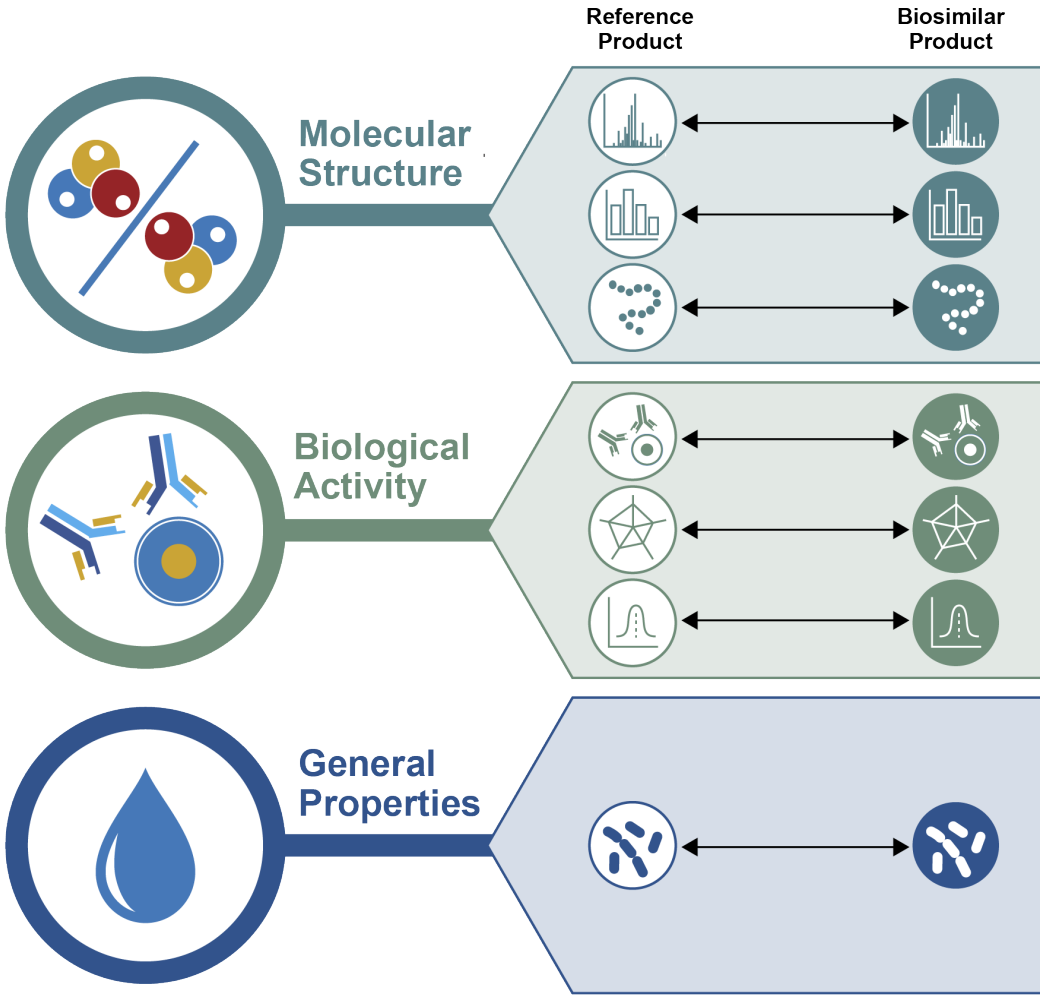
Refining Expectations for Comparative Efficacy Studies (CES)

- IPRP BWG Workshop and Concept paper Refined considerations for a CES

- Updated guidance from multiple health authorities
- ICH M18 Topic: Framework for Determining Utility of Comparative Efficacy Studies in Biosimilar Development

ICH
harmonisation for better health

Analytical Comparisons Inform Clinical Performance



- Methods are state-of-the-art, sensitive, reliable, and capable of detecting differences
- Functional Assays reflect known or potential mechanism(s) of action
- Results strengthened when different (orthogonal) methods used to evaluate same attribute

Breadth of Comparative Analytics

Hypothetical Release (~12 tests)

- Appearance
- pH
- Strength
- Identity
- Potency
- Glycans
- Size Variants
- Charge Variants
- Bioburden/Endotoxin

Additional Attributes

Orthogonal Techniques

Hypothetical CAA (> 40 tests)

- Strength (n=1)
- Primary Structure (n=4)
- Higher Order Structure (n=5)
- Biological/Functional (n=24)
- Post-translational modifications (n=15)
- Product-related variants (n=6)
- Degradation profiles (n=7)

Streamlining Biosimilar Development

Reducing Clinical Study Expectations

Increasing reliance on analytical data

Other Active Discussion Areas

- CES: When would a CES inform a demonstration of biosimilarity?

- Immunogenicity: Are there circumstances when clinical immunogenicity data would not inform a demonstration of biosimilarity? When clinical immunogenicity data are needed, what extent of data is expected?

- What data and information are needed to justify the relevance of comparative PK or other clinical data using a non-US comparator to the assessment of biosimilarity?

References

- Schiestl M et al., The Path Toward a Tailored Clinical Biosimilar Development, BioDrugs (2020) 34:297-306
- Bielsky MC et al., Streamlined Approval of Biosimilars: Moving on from the Confirmatory Efficacy Trial (2020) Drug Discovery Today 9:S1359-6446(20)30343-3. Doi: 10.1016/j.drudis.2020.09.006.
- Guillen E et al. (2023). A Data Driven Approach to Support Tailored Clinical Programs for Biosimilar Monoclonal Antibodies. Clin Pharmacol Ther, 113:108-123. https://doi.org/10.1002/cpt.2785
- Kirsch-Stefan N, et al. (2023) Do the Outcomes of Clinical Efficacy Trials Matter in Regulatory Decision-Making for Biosimilars? BioDrugs 37:855-871. https://doi.org/10.1007/s40259-023-00631-4
- Goto K et al., “Survey on the role of comparative efficacy studies required for biosimilar monoclonal antibodies approval in Japan to justify the quality attributes differences between biosimilars and their reference products based on PMDA assessments” Pharmaceut. Med. 2025. Epub 20250919 http://doi.org/10.1007/s40290-025-00583-w
- European Medicines Agency. Concept paper for the development of a Reflection Paper on a tailored clinical approach in Biosimilar Development. EMA/CHMP/BMWP/35061/2024. Revised 24 November 2023
- European Medicines Agency. Reflection paper on a tailored clinical approach in biosimilar development. Draft. EMA/CHMP/BMWP/60916/2025. Revised 17 March 2025
- FDA guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (April 2015)

Thank You

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