Important Facts
Health Care Professionals Should Know About Biosimilars
Biosimilars: Defining Characteristics

Biosimilars are highly similar versions of reference biologics, with no clinically meaningful differences in terms of safety, purity, and potency.1

Biologics, including biosimilars, are more complex than small molecules.2-5

Development of Biosimilars

Providing a change in thinking from how reference biologics are evaluated, the FDA evaluates biosimilars based on a totality-of-evidence approach.6,7

The goal of biosimilar development is to demonstrate that there are no clinically meaningful differences between the proposed biosimilar and the reference biologic—not to re-establish the clinical benefit of the reference biologic.1

The Totality of Evidence

The FDA approval process evaluates the totality of evidence to ensure biosimilar quality, efficacy, and safety.1

The Totality of Evidence: A Stepwise Approach

Comparative safety and effectiveness data are necessary if residual uncertainties remain.

Comparative human PK/PD studies and at least one clinical study comparing immunogenicity will be expected.

Nonclinical toxicology studies may depend on the extent of known similarities or differences between the biosimilar and reference biologic.

Extensive analytical characterization to demonstrate highly similar structure and function between the biosimilar and reference biologic.

Approval Pathway for Biosimilars

Biosimilars may be approved through an abbreviated licensure pathway if high similarity with a reference product is established.1

Standard and Abbreviated Pathways for Drug Approval in the United States

Small molecules

Biologics

Development of a biosimilar requires substantial time and financial investment.17

A biosimilar may involve a time investment of 5 to 9 years or more and cost more than $100 million to develop (not including regulatory fees).17,18 whereas development of a small-molecule generic may take up to 2 years and cost $1 million to $4 million.19,20

References


3. Biologic license application (BLA).


5. Biologicals license application (BPLA).


7. Nonclinical biologicals tox.


15. US Food and Drug Administration. Biologics license application (BPLA).


Extrapolation: A Scientific and Regulatory Principle

After biosimilarity is determined, extrapolation enables potential licensure of a biosimilar across indications appropriate for the reference biologic.1,2,3

SCIENTIFIC JUSTIFICATION IS REQUIRED IN EACH INDICATION NOT STUDIED CLINICALLY1

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Extrapolation is not automatic—scientific justification in each indication not clinically studied is organized around 4 key aspects that are considered by the FDA.1

KEY FDA CONSIDERATIONS FOR EXTRAPOLATION1

- Differences that may exist in each indication and patient population
- Expected toxicities
- Immunogenicity
- PK and biodistribution

The rationale for extrapolation is to2,4-6

- Avoid unnecessary clinical studies
- Reduce development costs
- Allow for reallocation of resources

An Interchangeability Designation Is Not Required for a Physician to Switch a Patient to a Biosimilar2-5,9,21

According to the FDA, products designated interchangeable may be substituted at the pharmacy level for the reference biologic without the intervention of the prescribing health care provider.15,31

For a biological product administered more than once, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference biologic is not greater than the risk of using the reference biologic, without such alternation or switching.

The interchangeability designation

An interchangeability designation considers the potential for alternation (multiple switches) between a biosimilar and reference biologic without physician intervention.15,31

- Any substituted biosimilar must first be designated as “interchangeable” by the FDA.
- The prescriber would be able to prevent substitution by stating “dispense as written.”
- The prescriber must be notified of any substitution made by the pharmacy.

Potential of Biosimilars

Biologics have been used successfully to treat many life-threatening and chronic diseases.2-4,36 Between 2006 and 2016, biologics have grown from 18% to 41% as a percentage of new FDA approvals.37-39 Biologics in the United States contribute significantly to prescription drug spending38-41:

- In 2016, specialty medicines—including biologics—accounted for 43% or $384 of the $895 per person per year spent on medicines40
- By 2020, specialty drug sales will reach $402 billion—47% or nearly half of prescription drug spending41.

Biosimilars may offer a number of potential benefits to patients, payers, and providers in addition to cost savings to health care systems42-44.
The development of a small-molecule generic may take up to 2 years and cost more than $100 million to develop (not including regulatory fees), whereas a biosimilar may involve a time investment of 5 to 9 years or more and cost.

Development of a biosimilar requires substantial time and financial investment. Clinical studies are necessary to demonstrate highly similar structure and function of the biosimilar and reference biologic. Extensive bioequivalence studies may be expected. Comparative human PK/PD studies and at least one clinical study comparing immunogenicity will be expected. Additional standards to ensure biosimilarity include in-vivo studies. Clinical studies are necessary if residual uncertainties remain.

**Clinical studies**

**Approval Pathway for Biosimilars**

**Benefit/risk profile**

New drug applications (NDAs) or abbreviated new drug applications (ANDAs), demonstrate highly similar structure and function to the biosimilar and reference biologic. Nonclinical toxicology studies may depend on the extent of known similarities or differences between the biosimilar and reference biologic.

The totality of evidence: a stepwise approach

Analytical

Generics

Abbreviated new drug application (ANDA), demonstrate highly similar structure and function to the biosimilar and reference biologic. Nonclinical toxicology studies may depend on the extent of known similarities or differences between the biosimilar and reference biologic.

Additional standards to ensure biosimilarity include in-vivo studies. Clinical studies are necessary if residual uncertainties remain.

Benefits/risk profile

Approved via Public Health Service Act (PHSA) biologics license application (BPCI Act) >100 kDa

Clinical trials are not required for abbreviated new drug applications and generic biosimilars. Clinical trials are necessary if residual uncertainties remain.

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