Pfizer Biosimilars

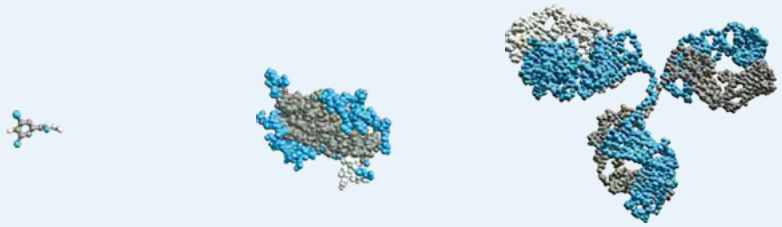
Important Facts

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]

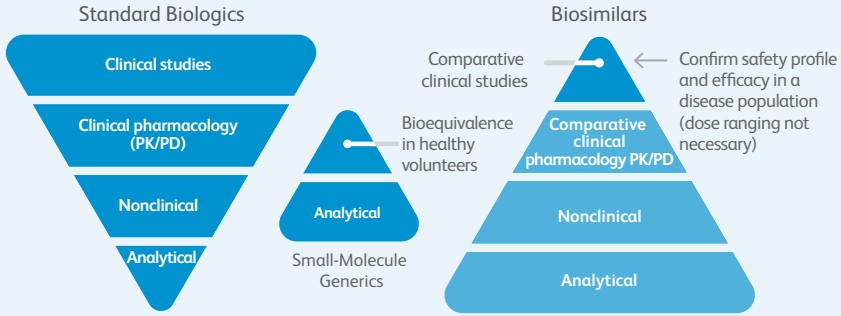


While small-molecule generics are chemically synthesized, biosimilars (and reference biologics) are created in living cells and require significant expertise and state-of-the-art technology to manufacture and produce.[3,6]

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.[1,7,8]

DEVELOPMENTAL PATHWAYS[1,7-11]



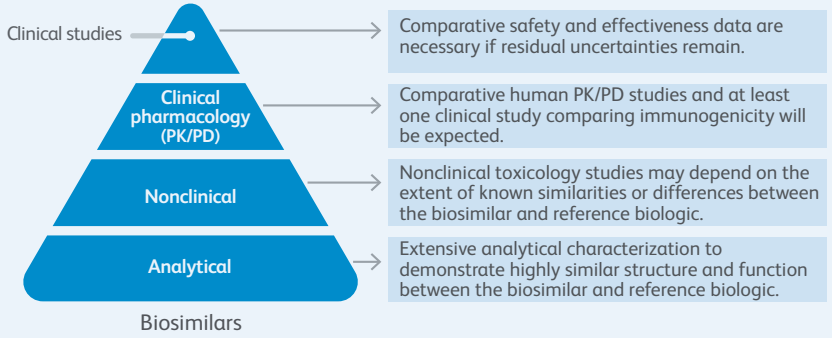
PK, pharmacokinetic; PD, pharmacodynamic.

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]

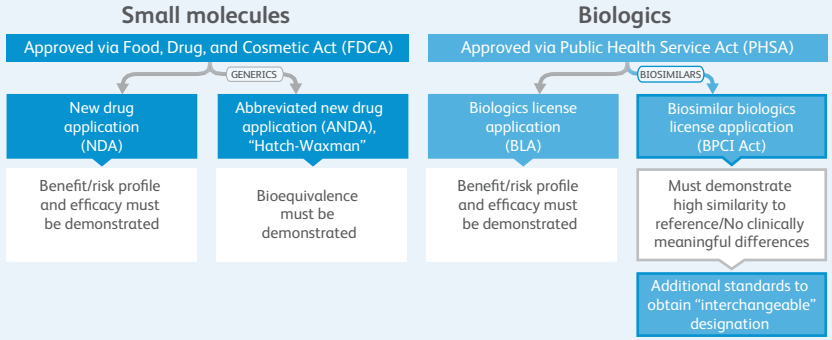
THE TOTALITY OF EVIDENCE: A STEPWISE APPROACH[1]



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[1,12-16]



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]

Extrapolation: A Scientific and Regulatory Principle

After biosimilarity is determined, extrapolation enables potential licensure of a biosimilar across indications approved for the reference biologic.[1,21-23]

SCIENTIFIC JUSTIFICATION IS REQUIRED IN EACH INDICATION NOT STUDIED CLINICALLY [1,24-26]

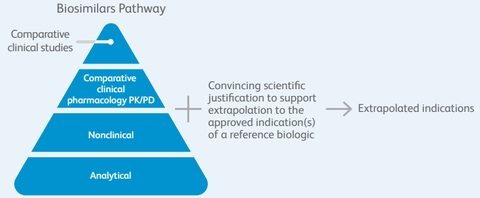


Image adapted from Sherman RE. Biosimilar biological products [biosimilar guidance webinar]. February 12, 2012.[26]

Biosimilar extrapolation occurs from the reference biologic to the biosimilar, when scientifically justified, based on all available data—not from the indication(s) studied with the biosimilar to other indications[25]

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 EXTRAPOLATION[1]

MECHANISM OF ACTION
- Experience with the reference biologic can help define the MOA and functional moieties in each indication

PK AND BIODISTRIBUTION
- PD measures may provide important MOA information

IMMUNOGENICITY
- Differences that may exist in each patient population

EXPECTED TOXICITIES
- Differences that may exist in each indication and patient population

Scientific justification combines experience with the reference biologic and the totality of evidence.[1,27-29]

SCIENTIFIC JUSTIFICATION FOR EXTRAPOLATION[1,27-29]

EXPERIENCE WITH THE REFERENCE BIOLOGIC

Building on the high structural similarity between the 2 products, **experience with the reference biologic** helps provide an understanding of the 4 key FDA considerations

SUPPORT FROM THE TOTALITY OF EVIDENCE

- **Structural studies and in vitro models** demonstrating **functional similarity across potential MOAs**
- Clinical data that **address differences between indications**
- Clinical data that may be compared to **existing evidence with the reference biologic**

The rationale for extrapolation is to[21,24,30]

- 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 Biosimilar[28,29,31]

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]

To be designated interchangeable, the biologic product[15,31]

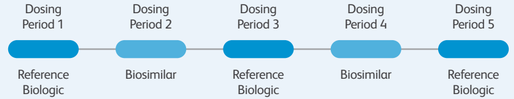
- Must be biosimilar to the reference biologic
- Must be expected to produce the same clinical result as the reference biologic in any given patient

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 switch.

The interchangeability designation

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

ALTERNATION



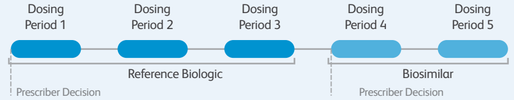
As of January 2018, no biosimilar has been designated interchangeable by the FDA.

Physician-directed switch

A physician-directed switch (eg, from a reference biologic to a biosimilar) is a prescribing decision made by a patient's physician.[32]

Decisions to prescribe a biosimilar to patients currently stable on the reference biologic are not restricted by FDA guidance or the Biologics Price Competition and Innovations Act.[14,31,32]

PHYSICIAN-DIRECTED SWITCH



Physicians may prescribe a biosimilar in the same manner that they would prescribe other medications—this physician-directed decision may include prescribing a biosimilar for patients currently stable on the reference biologic (eg, single transition or switch).[32]

Substitution of Biosimilars

Many states have considered legislation establishing standards for substitution of a biosimilar product to replace the reference biologic. Such legislation may include the following features[33-35]:

- 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
- Product-specific safety monitoring to ensure traceability

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]

Biologics in the United States contribute significantly to prescription drug spending[38-41]:

- In 2016, specialty medicines—including biologics—accounted for 43% or $384 of the $895 per person per year spent on medicines[40]
- By 2020, specialty drug sales will reach $402 billion—47% or nearly half of prescription drug spending[41]

Biosimilars may offer a number of potential benefits to patients, payers, and providers in addition to cost savings to health care systems.[42-44]

POTENTIAL OF BIOSIMILARS[42-44]

Additional treatment choices at lower cost to the health care system	Increased access to biologics, which may lead to improved health outcomes overall
Possible savings and efficiencies to the health care system	Offer a variety of therapeutic options

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