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 high similarity with a reference product is established. Quality, efficacy, and safety are critical considerations. Approval Pathway for Biosimilars:

- New drug application (NDA)
- Biosimilars
- Analytical
- Clinical
- Bioequivalence
- Benefit/risk profile

Nonclinical toxicology studies may depend on the expected results. One clinical study comparing immunogenicity will be expected. Biologicals, including biosimilars, are more complex than small molecules. While small molecule generics are chemically synthesized, biosimilars are created in living cells and require significant consideration due to meaningful differences in terms of safety, purity, and potency. Providing a change in thinking from how reference biologics are evaluated, the regulatory pathway and FDA's guidance for the development and approval of biosimilar products in the US are essential. Important Facts for Health Care Professionals:

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.\(^1,6\)

#### Developmental Pathways\(^7-11\)

- **Standard Biologics**
  - Clinical studies
  - Clinical pharmacology (PK/PD)
  - Nonclinical
  - Analytical
  - Small Molecule Generics

- **Biosimilars**
  - Clinical studies
  - Bioequivalence in healthy volunteers
  - Comparative clinical pharmacology PK/PD
  - Nonclinical
  - Analytical

**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\(^1\)

1. **Clinical studies**
   - Comparative safety and effectiveness data are necessary if residual uncertainties remain.
2. **Clinical pharmacology (PK/PD)**
   - Comparative human PK/PD studies and at least one clinical study comparing immunogenicity will be expected.
3. **Nonclinical**
   - Nonclinical toxicology studies may depend on the extent of known similarities or differences between the biosimilar and reference biologic.
4. **Analytical**
   - 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\(^1,12-16\)

**Small molecules**
- Approved via Food, Drug, and Cosmetic Act (FDCA)
- New drug application (NDA)
- Benefit-risk profile and efficacy must be demonstrated
- Must demonstrate high similarity to reference
- **Additional standards to obtain “interchangeable” designation**

**Biologics**
- Approved via Public Health Service Act (PHSA)
- Biologics license application (BLA)
- Benefit-risk profile and efficacy must be demonstrated
- Must demonstrate high similarity to reference

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 biologics are determined, extrapolation enables potential licensure of a biosimilar across indications approved for the reference biologic.2,3,4

**Extrapolation is not automatic—scientific justification in each indication**

**SCIENTIFIC JUSTIFICATION IS REQUIRED IN EACH INDICATION NOT STUDIED CLINICALLY**

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Reference Biologic</th>
<th>Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology PK/PD</td>
<td>Comparing scientific rationale for differences between indications and available data.1</td>
<td>Extrapolation is required to support regulatory filing.1</td>
</tr>
<tr>
<td>Comparative Nonclinical</td>
<td>Reference biologic and functional moieties in each indication</td>
<td>Biosimilar, when scientifically justified, based on all available data.1,24-26</td>
</tr>
<tr>
<td>Analytical</td>
<td>Comparison of similarity across protein regions.1,24-26</td>
<td>Biosimilar extrapolation occurs from the reference biologic to the approved indication(s).1,24-26</td>
</tr>
<tr>
<td>Clinical</td>
<td>Clinical data that address differences between indications</td>
<td>Biosimilar extrapolation is from the reference biologic to the approved indication(s).1,24-26</td>
</tr>
</tbody>
</table>

**EXPECTED TOXICITIES and IMMUNOGENICITY** are not studied clinically.1,24-26

**Mechanism of Action** and **Preservatives** are not restricted by FDA guidance or the Biologics Price Competition and Innovation Act.1

**MECHANISM OF ACTION**

- Previous experience with the reference biologic helps provide an understanding of the 4 key FDA considerations.1,24-26

**Preservatives**

- Modern therapeutic with the reference biologic helps provide an understanding of the 4 key FDA considerations.1,24-26

**Prescriber Decision**

- Prescribers may prescribe a biosimilar in the same manner 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).1,24-26

**PHYSICIAN-DIRECTED SWITCH**

- Prescribers may choose a biosimilar to patients currently stable on the reference biologic (eg, single transition or switch).1,24-26

**Additional treatment choices at lower cost which may lead to improved health system outcomes**

- Increased access to biologics, which may lead to improved health outcomes overall

- Offer a variety of therapeutic options

**POTENTIAL OF BIOSIMILARS**

- 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:1,24-26
  - Any substituted biosimilar must first be designated as “interchangeable” by the FDA.1
  - The prescriber would be able to prevent substitution by stating “dispense as written.”1
  - The prescriber must be notified of any substitution made by the pharmacy.1
- Biosimilars may offer a number of potential benefits to patients, payers, and providers in addition to cost savings to health care systems.41-43
- Biologics in the United States contribute significantly to prescription drug spending.1
- By 2020, $5 out of every $10 the country spends on prescription drugs will be spent on biologics.1
- Between 2016 and 2025, an average growth of 6.3% in annual prescription drug spending is expected.1
- Between 2006 and 2016, biologics have grown from 18% to 41% as a percentage of new FDA approvals.1
- Overall prescription drug spending was estimated at $325 billion in 2015.1
- Between 2016 and 2025, an average growth of 6.3% in annual prescription drug spending is expected.1
- Between 2006 and 2016, biologics have grown from 18% to 41% as a percentage of new FDA approvals.1

**Physicians**

- 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).1,24-26

**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.1

**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.1

**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 Innovation Act.1**

**EXPERIENCE WITH THE REFERENCE BIOLOGIC**

Building on the high structural similarity between the 2 products, the reference biologic helps provide an understanding of the 4 key FDA considerations.1,24-26

**APPLICATION OF EVIDENCE**

- Structural studies and in vitro models demonstrating functional similarity across protein regions.1,24-26
- Clinical data that address differences between indications.1

**SUPPORT FROM THE TOTALITY OF EVIDENCE**

- Clinical data that may be used to support the similarity of a reference biologic.1

**The rationale for extrapolation is to:**

- 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**

- 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
- A physician-directed switch (eg, from a reference biologic to a biosimilar) is a prescribing decision made by a patient’s physician.1
- 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 Innovation Act.1
- The interchangeability designation considers the potential for alternation or switching between the 2 products, without such alternation or switch.1
- As of August 2017, no biosimilar has been designated interchangeable by the FDA.

**ALTERNATION**

- A biosimilar, when scientifically justified, based on all available data.1,24-26
- Biosimilar extrapolation occurs from the reference biologic to the approved indication(s).1,24-26

**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.1

**Interchangeability designation**

- An interchangeability designation considers the potential for alternation (multiple switches) between a biosimilar and reference biologic without physician intervention.1

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**KEY FDA CONSIDERATIONS FOR EXTRAPOLATION**

**Mechanism of Action**

- Experience with the reference biologic can help define the MSA and functional invariants in each indication.1

**Pharmacodynamics (PD)**

- Differences that may exist in each patient population

**Pharmacokinetics (PK)**

- Differences that may exist in each indication and patient population

**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**

**SCIENTIFIC JUSTIFICATION FOR EXTRAPOLATION**

**EXPERIENCE WITH THE REFERENCE BIOLOGIC**

- Building on the high structural similarity between the 2 products, the reference biologic helps provide an understanding of the 4 key FDA considerations.1,24-26

**SUPPORT FROM THE TOTALITY OF EVIDENCE**

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Visit PfizerBiosimilars.com to learn more about biosimilars.

References