Biosimilars in the US Health Care Landscape
Agenda

- Introduction to Biologics and Biosimilars
- FDA Guidelines for Establishing Biosimilarity
- An Overview of Extrapolation and the US FDA Interchangeability Designation
- How Biosimilars May Help Bring Value to Patients
Introduction to Biologics and Biosimilars
Biologics and Biosimilars Defined\textsuperscript{1,2}

**Biologic**

Wide range of products (eg, vaccines, blood and blood components, somatic cells, gene therapy, tissues, therapeutic proteins) derived from genetically engineered living cells or organisms and intended to prevent, treat, or cure a variety of medical conditions\textsuperscript{1}

**Reference biologic**

Originally licensed biologic product used for comparison\textsuperscript{2}

**Biosimilar**

Biologic that is **highly similar** to the reference product with **no clinically meaningful differences** in terms of the **safety, purity, and potency**\textsuperscript{2}

---

Biologics Have Had a Meaningful Impact on Patient Care\textsuperscript{1,2}

Successfully used to treat many different life-threatening and chronic diseases\textsuperscript{1-5}

Today, Biologics Comprise 5 of the 10 Top-Selling Medications in the United States and Drive Disproportionate Costs\textsuperscript{1,2}

“Biologic medicines are costly. While only \textbf{2\% of the U.S. population} uses them, biologics account for \textbf{40\% of prescription drug spending} in the United States.”\textsuperscript{2}—The Biosimilars Council

\textbf{Biologics Comprise 5 of the 10 Top-Selling Medications in the United States}\textsuperscript{1}

In 2017, biologics accounted for approximately \textbf{$40\text{ billion of $65\text{ billion}}$ in sales for the 10 top-selling drugs}\textsuperscript{1}

---

The Number of Biologic Therapies Is Expected to Grow, Increasing Pressure on the US Health Care System\textsuperscript{1,2}

By 2020, \textdollar{5} out of every \textdollar{10} that the country spends on prescription drugs will be spent on biologics\textsuperscript{2}

\textsuperscript{1}Includes biosimilars.

The Potential Cost Savings From Biosimilars to Health Care Systems May Be Substantial\(^1\)

Estimated Reduction in Direct Spending on Biologic Drugs Between 2017 and 2026 (RAND Corporation)\(^1, a\):

Up to $150 billion

Savings realized by patients may depend on various factors, including changes in copays, coinsurance, etc, which may be more apparent in the future.\(^2\)

\(^a\)Based on an assumption of constant reference biologic prices, a biosimilar market share of 50%, and biosimilar prices that are 50% of the reference biologic.

Biosimilars May Provide Multiple Benefits to the US Health Care System

Potential of biosimilars for patients, payers, and providers

- Additional treatment choices at potentially lower cost
- May increase access to biologics, which may lead to better health outcomes overall
- Possible savings and efficiencies
- Offer a variety of therapeutic options

Key Points

- A biosimilar is a biologic that is highly similar to a reference product, with no clinically meaningful differences in terms of the safety, purity, and potency.

- As the demand and spending for biologics continue to grow, the introduction and successful adoption of biosimilars have the potential to provide additional treatment choices at lower cost.
FDA Guidelines for Establishing Biosimilarity
Standard and Abbreviated Pathways for Drug Approval in the United States

<table>
<thead>
<tr>
<th>Small molecules</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved via Food, Drug, and Cosmetic Act (FDCA)</td>
<td>Approved via Public Health Service Act (PHSA)</td>
</tr>
<tr>
<td>Generics</td>
<td>Biosimilars</td>
</tr>
<tr>
<td>New drug application (NDA)</td>
<td>Biologics license application (BLA)</td>
</tr>
<tr>
<td>Abbreviated new drug application (ANDA), “Hatch-Waxman”</td>
<td>Biosimilar biologics license application (BPCI Act)</td>
</tr>
</tbody>
</table>

**Small molecules**
- Benefit/risk profile and efficacy must be demonstrated
- Bioequivalence must be demonstrated

**Biologics**
- Benefit/risk profile and efficacy must be demonstrated
- Must demonstrate high similarity to reference
- No clinically meaningful differences
- Additional standards to obtain “Interchangeable” designation

BPCI, Biologics Price Competition and Innovation.
## Developing a Biosimilar Requires Substantial Investment Compared With a Small Molecule Generic\(^1-4\)

- Despite being rigorous, the development timeline for biosimilars may be shorter than for a new medicine.

<table>
<thead>
<tr>
<th>New medicine(^1) (including cost of failures)</th>
<th>Development time: &gt;10 years</th>
<th>Cost: ~$2.6 billion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>Development</td>
<td>Nonclinical</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biosimilar(^2) (cost of failures not available)</th>
<th>Development time: ~5 to 9 years</th>
<th>Cost: &gt;$100 million(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical</td>
<td>Nonclinical</td>
<td>Clinical pharmacology/PK/PD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Small molecule generic(^3,4)</th>
<th>Development time: ~2 years</th>
<th>Cost: ~$1 to $4 million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical</td>
<td>Bioequivalence in healthy volunteers</td>
<td></td>
</tr>
</tbody>
</table>

---

**PD**, pharmacodynamic; **PK**, pharmacokinetic.

\(^a\)Not including regulatory fees.

Biosimilar Development Is More Complex Than Establishing Comparability\textsuperscript{1-3}

- Demonstrating biosimilarity to a reference product requires more data and information than establishing comparability between a post- and premanufacturing change\textsuperscript{1}
- Although biosimilars are developed against a reference product, they have their own specifications, dependent on\textsuperscript{2}:
  - Manufacturing process
  - Industry standards
  - Regulatory expectations
  - Data from comparisons with the reference product
- Rigorous control strategies are necessary to maintain consistency and help ensure biosimilars conform to specifications\textsuperscript{3}

The Goal of Biosimilar Development Is to Demonstrate That There Are No Clinically Meaningful Differences Based Upon the Totality of Evidence, Not to Reestablish Benefit\(^1-^4\)


- It is not scientifically necessary to repeat the entire development program of the reference product\(^5,^6\)
- A robust analytical characterization and preclinical foundation reduces the need for extensive animal and clinical testing\(^7\)

---

Development Pathways

**Standard Biologics\(^1,^2\)**
- Clinical studies
- Clinical pharmacology
  - PK/PD
- Nonclinical
- Analytical

**Biosimilars\(^1-^3\)**
- Clinical studies
- Clinical pharmacology
  - PK/PD
- Nonclinical
- Analytical

**Small Molecule Generics\(^1,^4\)**
- Analytical
- Bio-equivalence in healthy volunteers

Confirm safety profile and efficacy in a disease population (dose ranging not necessary)
Robust Analytical Testing Is Used to Establish High Similarity to the Reference Product

- Analytical testing is a major focus throughout biosimilar development

- New techniques and advancements in analytics are available
- More than 1 test method may be used to measure a single quality attribute

Analytical tests maximize the potential for detecting differences between the proposed biosimilar and the reference product

Comparative safety and effectiveness data are necessary if there are residual uncertainties about the biosimilarity of the 2 products.

The need for additional studies may be influenced by many factors:

- Mechanism of action
- Complexity and heterogeneity
- Structure/function relationship to clinical outcomes
- Relevance of clinical pharmacology to predicting outcomes
- Clinical experience in therapeutic class
FDA Biosimilar Guidelines and Resources for Health Care Providers, Patients, and the Industry

“As more biosimilars are approved by FDA, we want health care providers to understand what these drugs are, and how they can help patients.”

—Scott Gottlieb, MD, Commissioner of the US Food and Drug Administration

<table>
<thead>
<tr>
<th>The FDA has developed educational materials to help health care providers better understand biosimilars and their approval process²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosimilar and Interchangeable Products</td>
</tr>
<tr>
<td>Biosimilar Development, Review, and Approval</td>
</tr>
<tr>
<td>Prescribing Biosimilar and Interchangeable Products</td>
</tr>
<tr>
<td>Patient and Prescriber Outreach Materials</td>
</tr>
<tr>
<td>Biosimilar Product Information</td>
</tr>
<tr>
<td>Industry Information and Guidance</td>
</tr>
<tr>
<td>Online Courses, Webinars, and Presentations</td>
</tr>
</tbody>
</table>

Key Points

- The BPCI Act established an abbreviated pathway for biosimilar approval, focusing on high similarity to a reference product.

- Demonstrating biosimilarity requires substantial investment and goes beyond establishing comparability between a post- and premanufacturing change.

- Biosimilars undergo a rigorous development process and are evaluated by the FDA based on a “totality of evidence” approach.
  - A major focus of biosimilar development is thorough analytical testing used to establish high similarity to the reference product.
  - Decisions about the approach to comparative clinical analyses are made on a case-by-case basis and are based on the determination of residual uncertainty.
An Overview of Extrapolation and the US FDA Interchangeability Designation
Scientific Justification Is Required to Support Extrapolation to Indications Not Clinically Studied\textsuperscript{1-3}

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\textsuperscript{4}

**Biosimilar Pathway\textsuperscript{1,2}**

- Clinical studies
- Clinical pharmacology PK/PD
- Nonclinical
- Analytical

Convincing scientific justification to support extrapolation to a reference biologic’s approved indications\textsuperscript{3}

\begin{enumerate}
\item McCamish M. Presented at EMA Workshop on Biosimilars; London; October 2013.
\end{enumerate}
Interchangeability Designation Is an Additional Standard, and Is Not Required for a Physician to Change Therapy to a Biosimilar

To be designated interchangeable\textsuperscript{1,2}:

The biological product:
- 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 to a patient:
- The risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference biologic is not greater than the risk of using the reference biologic without such alternating or switching

Alternation:

Dosing Period 1
Reference Biologic

Dosing Period 2
Biosimilar

Dosing Period 3
Reference Biologic

Dosing Period 4
Biosimilar

Dosing Period 5
Reference Biologic

Dosing Period 6
Biosimilar

The FDA issued draft guidance related to interchangeability designation in January 2017\textsuperscript{2}

Physicians may prescribe a biosimilar in the same manner as they would prescribe other medications—including prescribing a biosimilar for patients currently stable on the reference biologic\(^1\)

**Physician-Directed Switching:**

- Dosing Period 1
- Dosing Period 2
- Dosing Period 3
- Dosing Period 4
- Dosing Period 5
- Dosing Period 6

Reference Biologic

Biosimilar

Prescriber Decision

Prescriber Decision

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\(^1-3\)

---

Substitution of Biosimilars With an Interchangeability Designation May Be Addressed by State Law¹-³

**Substitution at the Pharmacy¹-⁴**

- 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 provider¹

- Many states have considered legislation establishing standards for substitution of a biosimilar product to replace the reference biologic².ᵃ

- Such legislation may include the following features²-⁴:
  - Any substituted biosimilar must first be designated “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
  - Requirements for pharmacy record keeping when a biosimilar is substituted for a reference product

---


The FDA Purple Book provides a list of all biological products licensed by the FDA, including biosimilars and interchangeable biologics.

The list provides information on:

- **Date of product licensure** under the 351(a) of the PHS Act and whether the biological product was evaluated for reference product exclusivity under section 351(k)(7)

- Whether the biological product has been determined by FDA to be biosimilar to or interchangeable with a reference biological product (an already-licensed FDA biological product)

- Biosimilars may still be designated interchangeable by the FDA while final guidance is underway

Key Points

- The FDA has stated that a biosimilar may be licensed for one or more indications of the reference product not studied clinically with the biosimilar
  - 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
  - Extrapolation is not automatic and will be determined based on the “totality of evidence” and scientific justification

- Interchangeability designation is an additional standard, and is not required for a physician to switch a patient to a biosimilar
  - Physicians may prescribe a biosimilar in the same manner as they would prescribe other medications—including prescribing a biosimilar for patients currently stable on the reference biologic
  - 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
  - State law will govern substitution of biosimilars that have an interchangeability designation
How Biosimilars May Help Bring Value to Patients
Many Commercially Insured Patients Have High Coinsurance Requirements for Medical Specialty Drugs

>50% of commercial payers **required coinsurance** for specialty drugs covered under the medical benefit in 2016\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Physician Office</th>
<th>Home Infusion</th>
<th>Outpatient Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coinsurance % (mean)</td>
<td>21%</td>
<td>21%</td>
<td>22%</td>
</tr>
</tbody>
</table>

In many cases—especially for economically vulnerable patients—**out-of-pocket (OOP) costs reduce or prevent access to prescribed medications**, and this negatively impacts both quality of life and the course of disease\(^3\)

---

For Medicare Patients, Annual OOP Costs Associated With Biologic Therapy May Be Substantial¹

Medicare beneficiaries
- Pay 20% coinsurance for most outpatient therapies, after deductibles are met²
- 14% do not have supplemental coverage³

Depending on the therapy, the top 10 Medicare Part B-covered biologics with the highest OOP expenses may¹,a:

Impact nearly **300,000** patients annually

Incur annual OOP costs of **~$2,500-$15,000** for 14% of beneficiaries

Annual OOP costs may reach up to **~58%** of the median income of Medicare beneficiaries¹,4,b

---

¹Based on average annual OOP costs per patient; excludes small molecules, hormones, and human immunoglobulin G therapies.
²Percentage based on the annual OOP cost for a biologic costing $15,119 and a median per capita income of $26,200 reported for Medicare population in 2016.⁴
How Biosimilars May Help to Bring Value to Patients

Biosimilars may...

Improve access to biologics

- Biosimilars have the potential of offering additional treatment choices to patients, physicians, and payers at a lower cost to the health care system\(^1\)-\(^3\)
  - These savings to the health care system may enable more patients to have access to biologics, which could result in improved health outcomes for patients

Help reduce the OOP costs of biologic medicines

- It is expected that health care providers, such as clinics or hospitals, will be able to acquire biosimilars at a lower wholesale cost than their reference products\(^2\),\(^3\)
  - Because of this, biosimilars may have the potential to lower OOP costs for patients with cost-sharing requirements, such as coinsurance and copayments

Patients who may pay less in the form of coinsurance:

- Patients with Medicare Part B without supplemental coverage\(^4\),\(^5\)
- Patients with private insurance required to pay coinsurance for specialty drugs, including biologics\(^2\),\(^6\)

---

Key Points

- Patients treated with specialty drugs, including biosimilars, may have high cost-sharing requirements, such as coinsurance and copayments.

- Biosimilars have the potential of offering additional treatment choices at lower cost to the health care system.
  - Savings to the health care system may enable more patients to have access to biologics, which could result in improved health outcomes overall.

- It is expected that health care providers, such as clinics or hospitals, will be able to acquire biosimilars at a lower wholesale cost than their reference products.
  - Hence, biosimilars may have the potential to lower OOP costs for patients with cost-sharing requirements.
Extrapolation and interchangeability designation

- Extrapolation is not automatic and requires scientific justification in each indication not studied clinically
  - 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
- Draft guidance on interchangeability designation was issued by the FDA in January of 2017
  - An interchangeability designation is not required for a physician to switch a patient to a biosimilar

Potential value to patients and the health care system

- Biosimilars may have the potential to lower OOP costs for patients with cost-sharing requirements
- Savings to the health care system may enable more patients to have access to biologics, which could result in improved health outcomes overall
- As the demand and spending for biologics continue to grow, the introduction and successful adoption of biosimilars have the potential to provide additional treatment choices at a lower cost to the health care system
For More Information

- To provide clinicians with an in-depth look into the science of biosimilars, Pfizer Biosimilars has established a peer-to-peer professional speakers’ bureau.

- Available speaker programs include:
  - Biosimilars: An Overview for Health Care Professionals
  - A Practical Approach to Biosimilar Implementation
  - Beyond Being Biosimilar: A Closer Look at the US FDA Interchangeability Designation, Substitution, and Extrapolation of Biosimilarity

- For more information or to arrange a speaker program, contact your Pfizer Biosimilars Representative.

- For more information on biosimilars, also visit PfizerBiosimilars.com
Thank You!

For more information on biosimilars, visit PfizerBiosimilars.com