Biosimilars in the US Health Care Landscape
Agenda

- Introduction to Biologics and Biosimilars
- Development of FDA Guidance for Establishing Biosimilarity
- An Overview of Extrapolation and the US FDA Interchangeability Designation
- How Biosimilars May Reshape the US Health Care Landscape
Introduction to Biologics and Biosimilars
## Biologics and Biosimilars Defined\(^1,^2\)

### Biologic

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>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(^1)</td>
</tr>
</tbody>
</table>

### Reference biologic

- Originally licensed biologic product used for comparison\(^2\)

### Biosimilar

- Biologic that is highly similar to the reference product with no clinically meaningful differences in terms of the safety, purity, and potency\(^2\)
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}

Biologics in the United States Contribute Significantly to Prescription Drug Spending

Overall prescription drug spending was estimated at $325 billion in 2015

**Spending on the Top 25 Prescription Drugs**

- Biologics accounted for $60.9 billion (nearly half) of approximately $126 billion spent on the top 25 drugs in 2015
- By 2020, biologics spending is expected to exceed $250 billion, when nearly $5 out of every $10 the country spends on prescription drugs will be on biologics

*Based on 2015 sales estimates, inclusive of brand and generic spending, and various dose forms.

There Is a Strong Desire to Drive Increased Savings and Efficiencies Within the US Health Care System\textsuperscript{1-3}

Over the past two decades, the United States has experienced a \textbf{dramatic and unsustainable rise in health care costs}…As the protective patents on new biologic therapies reach expiration, the race to \textbf{develop similar agents (biosimilars)} has begun, hopefully \textbf{increasing competition and reducing costs}\textsuperscript{4} – Gary Lyman

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Annual Growth in Health Care and Prescription Drug Spending Is Predicted to Exceed GDP Growth}
\end{figure}

\begin{itemize}
\item \textbf{Gross Domestic Product (GDP) 2015-2025}\textsuperscript{1} \hspace{1cm} 2.1\%
\item \textbf{Health Care Spending 2015-2025}\textsuperscript{2} \hspace{1cm} 5.8\%
\item \textbf{Prescription Drug Spending 2015-2025}\textsuperscript{3} \hspace{1cm} 6.5\%
\end{itemize}

\begin{footnotesize}
\end{footnotesize}
The Number of Biologic Therapies Is Expected to Grow, Increasing Pressure on the US Health Care System

*Biologics More Than Doubled as a Percentage of New FDA Approvals Over 10 Years*

*Includes biosimilars.
Cost Savings From Biosimilars to Health Care Systems May Be Substantial¹

Estimated Biosimilar Savings to the Health Care System (Express Scripts):

$250 billion savings possible during 2014-2024, if 11 likeliest biosimilars enter the market¹

Savings realized by patients may depend on various factors, including changes in co-pays, coinsurance, etc., which may be more apparent in the future.²

Standard and Abbreviated Pathways for Drug Approval in the United States\textsuperscript{1-6}

**Small molecules**
- Approved via Food, Drug, and Cosmetic Act (FDCA)
  - New drug application (NDA)
    - Generics
      - Benefit/risk profile and efficacy must be demonstrated
  - Abbreviated new drug application (ANDA), “Hatch-Waxman”
    - Bioequivalence must be demonstrated

**Biologics**
- Approved via Public Health Service Act (PHSA)
  - Biologics license application (BLA)
  - Biosimilar biologics license application (BPCI Act)
    - Must demonstrate high similarity to reference
      - No clinically meaningful differences
    - Additional standards to obtain “Interchangeable” designation

---

Developing a Biosimilar Requires Substantial Investment Compared With a Small Molecule Generic\textsuperscript{1-4}

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

### New medicine\textsuperscript{1} (including cost of failures)
- Development time: >10 years
- Cost: ~$2.6 billion

### Biosimilar\textsuperscript{2} (cost of failures not available)
- Development time: ~5 to 9 years
- Cost: >$100 million\textsuperscript{a}

### Small molecule generic\textsuperscript{3,4}
- Development time: ~2 years
- Cost: ~$1 to $4 million

---

PD, pharmacodynamic; PK, pharmacokinetic.

\textsuperscript{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}

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.

- There is a strong desire to drive increased savings and efficiencies within the US health care system.

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

- Cost savings from biosimilars may be significant but savings realized by patients may depend on various factors like co-pay changes, which will become more apparent in the future.

- Demonstrating biosimilarity requires substantial investment and goes beyond establishing comparability between a post- and premanufacturing change.
Development of FDA Guidance for Establishing Biosimilarity
FDA Biosimilar Guidelines Developed From Preexisting Guidance, Knowledge, and Experience1-4

Some examples of preexisting sources of information

1. FDA

Assessments of reference products undergoing manufacturing changes1,2

2. FDA

Experience evaluating biologics citing previously approved reference products3

3. EMA

Biosimilar regulation and postapproval experience4

EMA, European Medicines Agency.

EMA Guidelines Provide Detailed Requirements for the Approval of Biosimilars\(^1,2\)

- **FDA considered the EMA guidelines as a key source of information in developing US guidelines\(^1\)**

<table>
<thead>
<tr>
<th>Defining principles(^2)</th>
<th>Guideline on Similar Biological Medicinal Products(^a) (Adopted October 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General comparability guidelines(^2)</td>
<td>Immunogenicity Assessment (Adopted May 2017)</td>
</tr>
<tr>
<td></td>
<td>Quality Issues (Adopted May 2014)</td>
</tr>
<tr>
<td></td>
<td>Nonclinical and Clinical Issues (Adopted December 2014)</td>
</tr>
<tr>
<td>Product-specific comparability guidelines(^2)</td>
<td>FSH Non-clinical Clinical</td>
</tr>
<tr>
<td></td>
<td>IFN-β Non-clinical Clinical</td>
</tr>
<tr>
<td></td>
<td>IFN-α Non-clinical Clinical</td>
</tr>
<tr>
<td></td>
<td>mAbs Non-clinical Clinical</td>
</tr>
<tr>
<td></td>
<td>Insulin Non-clinical Clinical</td>
</tr>
<tr>
<td></td>
<td>EPO Non-clinical Clinical</td>
</tr>
<tr>
<td></td>
<td>LMWH Non-clinical Clinical</td>
</tr>
<tr>
<td></td>
<td>GH Non-clinical Clinical</td>
</tr>
<tr>
<td></td>
<td>GCSF Non-clinical Clinical</td>
</tr>
</tbody>
</table>

EPO, erythropoietin; FSH, follicle-stimulating hormone; GCSF, granulocyte colony-stimulating factor; GH, growth hormone (somatropin); IFN, interferon; LMWH, low-molecular weight heparin; mAbs, monoclonal antibodies.

\(^a\)Original guidelines adopted in 2005.

FDA Has Developed Guidance for the Regulatory Approval of Biosimilars

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Reference/Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mar 2010</td>
<td>Biologics Price Competition and Innovation (BPCI) Act passed as part of the Affordable Care Act¹</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>Draft guidance on biosimilars² Additional questions and answers May 2015</td>
<td>Draft guidance on labeling of biosimilar products and “Deemed to be a License”¹⁰,¹¹ Mar 2016</td>
</tr>
<tr>
<td>2013</td>
<td>First biosimilar approved³ Mar 2015</td>
<td>Final guidance on biosimilar naming⁸ Mar 2016</td>
</tr>
<tr>
<td>2015</td>
<td>Draft guidance on biosimilar naming⁸ Aug 2015</td>
<td>Draft guidance on statistical approaches to evaluate similarity¹⁴ Sep 2017</td>
</tr>
<tr>
<td>Apr 2015</td>
<td>Final guidance on biosimilars 1. Scientific considerations⁴</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Quality considerations⁵</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Questions and answers⁶</td>
<td></td>
</tr>
<tr>
<td>Sep 2014</td>
<td>First biosimilar approved³ Mar 2015</td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>Final guidance on biosimilar naming⁸ Mar 2016</td>
<td></td>
</tr>
</tbody>
</table>

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


- It is not scientifically necessary to repeat the entire development program of the reference product
- A robust analytical characterization and preclinical foundation reduces the need for extensive animal and clinical testing
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.**
Any Comparative Clinical Evaluation Is Designed on a Case-by-Case Basis

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

- Degree of analytical and functional similarity

- 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

Reference

Key Points

- The FDA has adopted biosimilar guidance based on previous US experience with biologics and EMA experience with biosimilars

- Biosimilars undergo a rigorous but abbreviated 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
Scientific Justification Is Required to Support Extrapolation to Indications Not Clinically Studied\textsuperscript{1,2}

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{3}

\textbf{Biosimilar Pathway}\textsuperscript{1}

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

Convincing scientific justification to support extrapolation to a reference biologic’s approved indications\textsuperscript{2}


Interchangeability for Biosimilars

- A biological product designated interchangeable must demonstrate that it can be expected to produce the same clinical result as the reference biologic in any given patient.

The designation of “interchangeability” requires additional standards after biosimilarity is established.

- In addition, if the biologic product is administered more than once to an individual, the risk in terms of safety profile or diminished efficacy of alternating or switching between the use of the biologic product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

The FDA issued draft guidance related to interchangeability designation in January 2017.
The FDA Purple Book is 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

Substitution of Biosimilars With an Interchangeability Designation May Be Addressed by State Law

- 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.
- 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:
  - 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.

Many states have enacted laws concerning biosimilars and biosimilar substitution—specific legislation may vary by jurisdiction.

---

The FDA has stated that a biosimilar may be licensed for one or more additional conditions of use for which the reference product is licensed.

- This may occur if the biosimilar has not been directly studied in a comparative clinical trial for that condition.

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 rationale.
- Scientific justification is required to support extrapolation to a reference biologic’s approved indications.

A biosimilar may also be designated as “interchangeable.”

- This means that it can be expected to produce the same clinical effect as the reference product in any given patient.
- In January 2017, the FDA issued draft guidance for demonstrating interchangeability of a biosimilar and reference biologic.
- As of September 2017, no biosimilar has been designated interchangeable by the FDA.
How Biosimilars May Reshape the US Health Care Landscape
Biosimilars May Provide Multiple Benefits to the US Health Care System


Potential of biosimilars for patients, payers, and providers

- Additional treatment choices at lower cost to the health care system
- Increase access to biologics, which may lead to better health outcomes overall
- Possible savings and efficiencies to the health care system
- Offer a variety of therapeutic options
The Future of Biosimilars in the United States Will Require Thoughtful Consideration in Clinical Practice

- Will future biosimilar approvals face any unique challenges in the United States?
- How will reimbursement be managed?
- How will payers and PBMs drive value for patients?
- How will states regulate substitution?
- How will the appropriate decision-making groups be educated about biosimilars?
- What information will patients look for when transitioning to a biosimilar?
- When will final guidance on an interchangeability designation be released?

Pfizer Biosimilars
Program Summary

- There is increasing demand for biologics.
- The introduction of high-quality biosimilars may provide additional treatment choices at lower cost to the health care system and increase access to biologics, leading to better health outcomes overall.
- The goal of biosimilar development is to avoid unnecessary clinical studies.
  - The FDA evaluates biosimilars based on the totality of evidence.
- 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.
- **For more information on biosimilars, visit PfizerBiosimilars.com**
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