Biosimilars in the US Health Care Landscape
Agenda

- Introduction to Biologics and Biosimilars
- Considering the European Biosimilar Experience
- Summary of FDA Guidance on Establishing Biosimilarity
- Overview of Extrapolation and Interchangeability
- How Biosimilars May Reshape the US Health Care Landscape
Introduction to Biologics and Biosimilars
Biologics and Biosimilars Defined\(^1,2\)

**Biologic**

Wide range of products (e.g., 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\(^1\)

**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 profile, 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

- Biologics accounted for nearly half of approximately $85 billion spent on the top 15 drugs in 2015

- 7 of the 15 highest expenditure drugs were biologics, accounting for $39.5 billion in spending in 2015

- Nearly $220 billion in sales for 8 key biologics could potentially be impacted by biosimilars between 2016 and 2020

*By non-discounted spending.

Global Sales of Biologics Continue to Grow

- Biologic sales have grown as a proportion of total pharmaceutical sales.
- Globally, there is a strong demand for patient access to innovative biologic therapies.

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<table>
<thead>
<tr>
<th>Year</th>
<th>Conventional Therapies</th>
<th>Biologic Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>86%</td>
<td>14%</td>
</tr>
<tr>
<td>2008</td>
<td>84%</td>
<td>16%</td>
</tr>
<tr>
<td>2010</td>
<td>82%</td>
<td>18%</td>
</tr>
<tr>
<td>2012</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>2014</td>
<td>77%</td>
<td>23%</td>
</tr>
<tr>
<td>2016</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>2018</td>
<td>74%</td>
<td>26%</td>
</tr>
<tr>
<td>2020</td>
<td>74%</td>
<td>27%</td>
</tr>
</tbody>
</table>

\(1^a\) Includes over-the-counter sales.

### Standard and Abbreviated Pathways for Drug Approval in the United States\(^1-^6\)

<table>
<thead>
<tr>
<th>Small molecules</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved via Food, Drug, and Cosmetic Act (FDCA)</strong></td>
<td><strong>Approved via Public Health Service Act (PHSA)</strong></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>

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

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

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BPCI, Biologics Price Competition and Innovation.

Developing a Biosimilar Requires 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.

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

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Development</th>
<th>Nonclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Biosimilar\textsuperscript{2}</th>
<th>Development time: ~5 to 9 years</th>
<th>Cost: Up to $135 million\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>(cost of failures not available)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analytical</th>
<th>Nonclinical</th>
<th>Clinical pharmacology/PK/PD</th>
<th>Clinical studies</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Small molecule generic\textsuperscript{3,4}</th>
<th>Development time: ~2 years</th>
<th>Cost: ~$1 to $4 million</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Analytical</th>
<th>Bioequivalence in healthy volunteers</th>
</tr>
</thead>
</table>

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

- Global sales of innovative biologics continue to grow and have outpaced total pharmaceutical sales.

- 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.

- BPCI Act established an abbreviated pathway for biosimilar approval focusing on similarity to a reference product.
Considering the European Biosimilar Experience
FDA Biosimilar Guidelines Developed From Preexisting Guidance, Knowledge, and Experience\(^1-4\)

Some examples of preexisting sources of information

1. FDA
   Assessments of reference products undergoing manufacturing changes\(^1,2\)

2. FDA
   Experience evaluating biologics citing previously approved reference products\(^3\)

3. EMA
   Biosimilar regulation and postapproval experience\(^4\)

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EMA, European Medicines Agency.


EMA Guidelines Provide Detailed Requirements for the Approval of Biosimilars

- FDA considered the EMA guidelines as a key source of information in developing US guidelines

### Defining principles

<table>
<thead>
<tr>
<th>Guideline on Similar Biological Medicinal Products</th>
<th>Adopted October 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogenicity Assessment</td>
<td>Revision March 2014</td>
</tr>
<tr>
<td>Quality Issues</td>
<td>Adopted June 2014</td>
</tr>
<tr>
<td>Nonclinical and Clinical Issues</td>
<td>Adopted December 2014</td>
</tr>
</tbody>
</table>

### General comparability guidelines

<table>
<thead>
<tr>
<th>Product-specific comparability guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
</tr>
<tr>
<td>Non clinical</td>
</tr>
</tbody>
</table>

**Notes:**
- 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.

Cost Savings From Biosimilars to Health Care Systems May Be Significant (Although Estimates Vary)\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Source</th>
<th>Examples of Estimated Biosimilar Savings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Express Scripts\textsuperscript{1}</strong></td>
<td>$250 billion savings possible during 2014-2024, if 11 likeliest biosimilars enter the market</td>
</tr>
<tr>
<td><strong>IMS\textsuperscript{2}</strong></td>
<td>$54 billion to $108 billion in cumulative savings in the EU5 and United States combined over the next 5 years</td>
</tr>
</tbody>
</table>


Key Points

- Biosimilars undergo a rigorous but abbreviated development process
  - This abbreviated development process, based on European experience, allows for potentially lower costs compared with reference biologics

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

- Cost savings from biosimilars may be significant, although estimates vary
Summary of FDA Guidance on Establishing Biosimilarity
FDA Has Developed Guidance for the Regulatory Approval of Biosimilars¹⁻⁹

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mar 2010</td>
<td>US House of Representatives, HR 3590 Patient Protection and Affordable Care Act¹</td>
</tr>
<tr>
<td>2011</td>
<td>Purple Book²</td>
</tr>
<tr>
<td>2013</td>
<td>Draft guidance on biosimilars⁷</td>
</tr>
<tr>
<td>2015</td>
<td>First biosimilar approved³</td>
</tr>
<tr>
<td>Mar 2015</td>
<td>Final guidance on biosimilars</td>
</tr>
<tr>
<td>Apr 2015</td>
<td>1. Scientific considerations⁴</td>
</tr>
<tr>
<td></td>
<td>2. Quality considerations⁵</td>
</tr>
<tr>
<td></td>
<td>3. Questions and answers⁶</td>
</tr>
<tr>
<td>May 2015</td>
<td>Draft guidance on biosimilar naming⁸</td>
</tr>
<tr>
<td>Aug 2015</td>
<td>No specific guidance on interchangeability yet</td>
</tr>
<tr>
<td>Nov 2015</td>
<td>Final guidance on formal meetings between FDA and biosimilar sponsors⁹</td>
</tr>
<tr>
<td>Mar 2016</td>
<td>Draft guidance on “Deemed to be a License”¹⁰</td>
</tr>
<tr>
<td>Mar 2016</td>
<td>Draft guidance on labeling of biosimilar products¹¹</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\textsuperscript{1-4}

### Development Pathways

**Standard Biologics\textsuperscript{1,2}**
- Clinical studies
- Clinical pharmacology PK/PD
- Nonclinical
- Analytical

**Biosimilars\textsuperscript{1-3}**
- Clinical studies
- Clinical pharmacology PK/PD
- Nonclinical
- Analytical

**Small Molecule Generics\textsuperscript{1,4}**
- Analytical

- Bio-equivalence in healthy volunteers

- Confirm safety profile and efficacy in a disease population (dose ranging not necessary)

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

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.
Key Points

- The FDA will evaluate biosimilars 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 Interchangeability
Scientific Justification Is Required to Support Extrapolation to Indications Not Clinically Studied\textsuperscript{1,2}

Extrapolation: Extending conclusions from studies in one patient population to make inferences in another population\textsuperscript{1}

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


Interchangeability of Biosimilars

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

The designation of “interchangeability” requires higher standards than “biosimilarity” alone.

- 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.
Key Points

- 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

- Extrapolation refers to extending conclusions from studies in one patient population to make inferences in another population
  - Extrapolation will be determined based on “totality of evidence” and is a scientific rationale
  - In order for this determination to be made, there must be convincing evidence 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
  - It is important that the policy regarding interchangeability be established based on both science and physician supervision
  - To date, the FDA has not issued final guidance regarding interchangeability
How Biosimilars May Reshape the US Health Care Landscape
There Is a Strong Demand for Increased Savings and Efficiencies for Health Care Systems\(^1,2\)

- According to the Centers for Medicare & Medicaid Services, prescription drug spending growth is projected to average 6.3% annual growth from 2015 through 2024\(^1\)

\[\text{2014-2024 health care spending projected to grow}^{1} 1.1\% \text{ faster than the GDP} \rightarrow 5.8\% \text{ on average}\]

\[27\% \text{ of pharmaceutical products approved in 2015 were biologics}^{2}\]

GDP, gross domestic product.

Biosimilars May Provide Multiple Benefits to the US Health Care System¹⁻³

The Future of Biosimilars in the United States Will Require Thoughtful Consideration in Clinical Practice

- Will biosimilar approvals face any unique challenges in the United States?
- How will the appropriate decision-making groups be educated about biosimilars?
- What will the FDA guidance be on interchangeability?
- Will extrapolation be sufficient to approve all indications of the reference product?
- How will states regulate automatic substitution?
- How will reimbursement be managed?
Program Summary

- There is increasing demand for biologics
- The introduction of high-quality biosimilars may
  - Increase access to biologics, which may lead to better health outcomes overall
  - Provide savings and efficiencies to health care systems
  - Provide additional treatment choices at lower cost to the health care system
  - Provide a variety of treatment choices
- The FDA has issued guidance for biosimilars
  - Totality of evidence will be evaluated for each biosimilar on a case-by-case basis
  - Focus is on similarity to a reference biologic
  - Intent is to minimize unnecessary duplication of large clinical studies
  - Scientific justification is required to support extrapolation to indications not clinically studied
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

- Topics covered in the program include more information on
  - Establishing and regulating biosimilarity
  - Extrapolation
  - Interchangeability and automatic substitution

- Ask about this opportunity today

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

For more information on biosimilars, visit PfizerBiosimilars.com