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\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 profile, purity, and potency**\textsuperscript{2}

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Biologics Have Had a Meaningful Impact on Patient Care\textsuperscript{1-3}

Successfully used to treat many different life-threatening and chronic diseases

Global Sales of Innovative Biologics Continue to Grow$^{1,2}$

- Biologic sales have increased in recent years$^{1,2}$
- Globally, there is a strong demand for patient access to innovative biologic therapies$^2$

**Global Biologic Sales, 2014**

- Biologic sales have increased in recent years$^{1,2}$
- Globally, there is a strong demand for patient access to innovative biologic therapies$^2$

**LCU, local currency unit.**

### Standard and Abbreviated Pathways for Drug Approval in the United States

#### Small molecules

<table>
<thead>
<tr>
<th>Approved via Food, Drug, and Cosmetic Act (FDCA)</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>New drug application (NDA)</td>
<td>Approved via Public Health Service Act (PHSA)</td>
</tr>
<tr>
<td>Generics</td>
<td>Biosimilars</td>
</tr>
<tr>
<td>Benefit/risk profile and efficacy must be demonstrated</td>
<td>Must demonstrate high similarity to reference</td>
</tr>
<tr>
<td>Abbreviated new drug application (ANDA), &quot;Hatch-Waxman&quot;</td>
<td>No clinically meaningful differences</td>
</tr>
<tr>
<td>Bioequivalence must be demonstrated</td>
<td>Higher standards to obtain “Interchangeable” designation</td>
</tr>
</tbody>
</table>

#### Biologics

<table>
<thead>
<tr>
<th>Biologics license application (BLA)</th>
<th>Biosimilar biologics license application (BPCI Act)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit/risk profile and efficacy must be demonstrated</td>
<td>Must demonstrate high similarity to reference</td>
</tr>
</tbody>
</table>

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BPCI, Biologics Price Competition and Innovation.


Developing a Biosimilar Requires Investment Compared With a Small Molecule Generic\textsuperscript{1-3}

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

**New Medicine** (Including Cost of Failures)


- **Development Time:** >10 Years\textsuperscript{1}  
  - Cost: ~$2.6 Billion

- **Biosimilar**  
  - (Cost of Failures Not Available)  
  - Development Time: ~5 to 9 Years\textsuperscript{2}  
  - Cost: ~$135 Million

- **Small Molecule Generic**  
  - Development Time: ~2 Years\textsuperscript{3}  
  - Cost: ~$1-$2 Million

PD, pharmacodynamic; PK, pharmacokinetic.

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 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\textsuperscript{1-4}

Some examples of preexisting sources of information

1. FDA
   - Assessments of reference products undergoing manufacturing changes\textsuperscript{1,2}

2. FDA
   - Experience evaluating biologics citing previously approved reference products\textsuperscript{3}

3. EMA
   - Biosimilar regulation and postapproval experience\textsuperscript{4}

EMA, European Medicines Agency.
EMA Guidelines Provide Detailed Requirements for the Approval of Biosimilars\textsuperscript{1,2}

**FDA considered the EMA guidelines as a key source of information in developing US guidelines**\textsuperscript{1}

### Defining Principles\textsuperscript{2}
- Guideline on Similar Biological Medicinal Products\textsuperscript{a} (Adopted October 2014)

### General Comparability Guidelines\textsuperscript{2}
- Immunogenicity Assessment (Revision March 2014)
- Quality Issues ( Adopted June 2014)
- Nonclinical and Clinical Issues (Adopted December 2014)

### Product-Specific Comparability Guidelines\textsuperscript{2}

<table>
<thead>
<tr>
<th>Product</th>
<th>FSH</th>
<th>IFN-(\beta)</th>
<th>IFN-(\alpha)</th>
<th>mAbs</th>
<th>Insulin</th>
<th>EPO</th>
<th>LMWH</th>
<th>GH</th>
<th>GCSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non clinical</td>
<td>Clinical</td>
<td>Non clinical</td>
<td>Clinical</td>
<td>Non clinical</td>
<td>Clinical</td>
<td>Non clinical</td>
<td>Clinical</td>
<td>Non clinical</td>
<td>Non 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.

\textsuperscript{a}Original guidelines adopted in 2005.

As Experience Grows in Europe, So Has Uptake of Biosimilar Use

Biosimilars constitute
- 53% of the daily GCSF sales
- 69% of the filgrastim sales

GCSF, granulocyte colony-stimulating factor.
Uptake of Biosimilar GCSFs in Europe Has Coincided With Increased Utilization and Decreased Costs

GCSFs in EU5: Market Volume Versus Spending (2010-2013)

Market volume has increased by 13%...

...at the same time, spending has decreased by 5%

EU5, France, Germany, Italy, Spain, United Kingdom.

Cost Savings From Biosimilars to Health Care Systems May Be Significant (Although Estimates Vary)\(^1\)-\(^5\)

<table>
<thead>
<tr>
<th>Source</th>
<th>Examples of Estimated Biosimilar Savings</th>
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<tbody>
<tr>
<td><strong>Express Scripts</strong>(^1)</td>
<td>$250 billion savings during 2014-2024, if 11 likeliest biosimilars enter the market</td>
</tr>
<tr>
<td><strong>PCMA</strong>(^2)</td>
<td>Medicare Part B could save $14 billion over 10 years</td>
</tr>
<tr>
<td><strong>EGA</strong>(^3)</td>
<td>Savings of €1.6 billion assuming a 20% discount for 5 biologic drugs across Europe</td>
</tr>
<tr>
<td><strong>IGES</strong>(^4)</td>
<td>€11.8 billion and €33.4 billion in 8 EU countries from 2007 to 2020</td>
</tr>
<tr>
<td><strong>IMS</strong>(^5)</td>
<td>€50 billion to €100 billion in cumulative savings in the EU5 and United States combined over the next 5 years</td>
</tr>
</tbody>
</table>

EGA, European Generic Medicines Association; IGES, IGES Institut GmbH; IMS, Intercontinental Marketing Services; PCMA, Pharmaceutical Care Management Association.

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

- The uptake of biosimilars in Europe indicates a possible increase in access to medication
Summary of FDA Guidance on Establishing Biosimilarity
FDA Has Developed Guidance for the Regulatory Approval of Biosimilars\(^1\)-\(^9\)

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mar 2010</td>
<td>First Biosimilar Approved(^3)</td>
</tr>
<tr>
<td>2011</td>
<td>Draft Guidance on Biosimilars(^7) Additional Questions and Answers</td>
</tr>
<tr>
<td>2013</td>
<td>Draft Guidance on Biosimilar naming(^8)</td>
</tr>
<tr>
<td>2015</td>
<td>Draft Guidance on “Deemed to be a License”(^10)</td>
</tr>
<tr>
<td>2015</td>
<td>Final guidance on formal meetings between FDA and biosimilar sponsors</td>
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<tr>
<td>2016</td>
<td>Draft Guidance on labeling of biosimilar products</td>
</tr>
<tr>
<td>2015</td>
<td>Final Guidance on Biosimilars</td>
</tr>
<tr>
<td>2015</td>
<td>1. Scientific Considerations(^4)</td>
</tr>
<tr>
<td>2015</td>
<td>2. Quality Considerations(^5)</td>
</tr>
<tr>
<td>2015</td>
<td>3. Questions and Answers(^6)</td>
</tr>
<tr>
<td>2011</td>
<td>FDA Purple Book(^2)</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\(^1-^4\)

**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

- **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\(^5,^6\)
- A robust analytical characterization and preclinical foundation reduces the need for extensive animal and clinical testing\(^7\)

PD, pharmacodynamics; PK, pharmacokinetics.

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 profile and effectiveness data are necessary if there are residual uncertainties about the biosimilarity of the two 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}


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 that bridges all data
  - 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
  - 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\textsuperscript{1-3}

According to the Centers for Medicare & Medicaid Services, prescription drug spending growth is projected to average 6.3% annual growth from 2015 through 2024\textsuperscript{1}.

\begin{itemize}
  \item 2014-2024 health care spending projected to grow\textsuperscript{1} 1.1% faster than the GDP → 5.8% on average
  \item 24\% of pharmaceutical products approved in 2015 were biologics\textsuperscript{2}
  \item 67\% 3-year compound increase in US specialty drug spending forecast by the end of 2015\textsuperscript{3}
\end{itemize}

Biosimilars May Provide Multiple Benefits to the US Health Care System$^{1-3}$

Potential of biosimilars for patients, payers, and providers$^{1-3}$

- Foster innovation
- Expand the use of biologics, which may lead to better overall health outcomes
- Additional treatment choices at lower cost
- Increase access to biologics
- Savings and efficiencies to the health care system

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, safe, and effective biosimilars may
  - Expand the use of biologics, which may lead to better overall health outcomes
  - Provide savings and efficiencies to health care systems
  - Increase access to biologics
  - Provide additional 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