The Science Behind Biologics and Biosimilars
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Biologics and Biosimilars

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Financial Disclosure

Ms. Mayden has served as a member of the speakers’ bureau for Takeda Pharmaceutical Company Limited.
Learning Objectives

1. Define key differences between chemical and biological drugs and biosimilar agents
2. Discuss the current history of the first approved biopharmaceuticals and similar biologic medicinal products
3. Recognize the key components of the Biologics Price Competition and Innovation Act of 2009
4. Describe the role of the advanced practitioner in the treatment of patients receiving biosimilar agents
In regard to drug approval pathways, which of the following statements is true?

A. Generic small-molecule drug approval and biologic drug approval are granted under the Hatch-Waxman Act

B. Generic small-molecule pathway approval eliminates the requirements for phase III clinical trials

C. The biosimilar approval pathway eliminates the testing requirements that define an agent’s pharmacokinetic/pharmacodynamic properties

D. The biosimilar approval pathway ensures that an agent is interchangeable with the innovator brand name product
Drug Development

1. Investigational New Drug Application
2. Animal pharmacology and toxicology studies
3. Manufacturing information
4. Clinical protocols
5. Phase I-III clinical trials
6. New drug application
7. Phase IV clinical trials
Generic Approval Process

- Abbreviated New Drug Application
- Preclinical (animal) and clinical (human) data to establish safety and effectiveness usually not required
- Product must be bioequivalent
- Approved Drug Products With Therapeutic Equivalence Evaluations (Orange Book)

Small Molecules: Generic Drugs

- Chemically identical and bioequivalent to a brand name drug
- Active ingredients same as the reference product
- Identical in strength, dosage form, and route of administration
- Same-use indications
- Same batch requirements for identity, strength, purity, and quality
- Manufactured under the same FDA standards for innovator products

Image retrieved from http://www.en.wikipedia.org
Biopharmaceuticals: Biologics

- Genetically engineered proteins derived from human systems
- More structurally/molecularly complex
- Identity variance
- Affected by external conditions
- Immunogenic

- Blood/plasma products
- Vaccines
- Non-recombinant / recombinant proteins
- Cultured cellular and tissue products
- Monoclonal antibodies
Size and Complexity: Small-Molecule Drugs and Proteins

Image retrieved from http://www.azbio.org
### Top-Selling Biologics 2013

<table>
<thead>
<tr>
<th>Drug</th>
<th>Global sales in US billions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>10.7</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>7.0</td>
</tr>
<tr>
<td>Etanercept</td>
<td>8.3</td>
</tr>
<tr>
<td>Infliximab</td>
<td>8.9</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>7.8</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>4.4</td>
</tr>
<tr>
<td>Rituximab</td>
<td>8.6</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>6.8</td>
</tr>
</tbody>
</table>

### Clinical Drug Expenditures 2013 ($ Thousands)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>1,563,678</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>369,257</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>1,921,208</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>288,838</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>1,947,738</td>
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<tr>
<td>Pertuzumab</td>
<td>96,152</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1,718,862</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>1,145,344</td>
</tr>
</tbody>
</table>

Biologic Patents Expiring Before 2020

- Bevacizumab  July 4, 2019
- Cetuximab    February 13, 2016
- Epoetin alfa September 20, 2013
- Filgrastim    December 3, 2013
- Infliximab   September 4, 2018
- Pegfilgrastim October 20, 2015
- Rituximab    September 22, 2016
- Trastuzumab  June 18, 2019

Audience Response Question

Which of the following statements best describes biosimilars?

A. Biosimilars exhibit molecular complexity and can be sensitive to changes in the manufacturing process JL49
B. Biosimilars are approved following the completion of phase I, II, and III clinical trials JL50
C. Biosimilars all exhibit unusual adverse effects as compared with reference products JL51
D. Biosimilars are expected to increase national health care cost JL52
Biosimilars

- Biosimilars highly similar to an already FDA-approved biological product (reference product)
- Shown to have no clinically meaningful differences from the reference product
- Minor differences in clinically inactive components are allowed
- No clinically meaningful differences between the biosimilar and the reference product it was compared with in terms of the safety, purity, and potency of the product
- New version of an existing biologic whose patent has expired

BIOSIMILARs ARE NOT GENERICs

Biosimilar History

- Introduced in Europe 2006
- 400 million patient-days of clinical experience
- No unusual or unexpected effects compared with originator biologics
- Marketed in Australia, Mexico, India, China, Chile, Peru, Colombia, South Korea
- Strict approval process in Europe; Australia has similar process
- Health-care costs estimated to have decreased by 20%–30%

Biosimilars regulation enacted
No formal biosimilars regulation yet in force (but may be pending)

Dates represent year when guidelines or guidance adopted or guidelines issued, unless noted below.

*Regulatory pathway established in the USA; draft guidance issued in 2012.
Based on EMA guidance.
Adopted EMA guidance.
Audience Response Question

All of the following are true about biosimilars except:

A. A biosimilar is highly similar to an already FDA-approved biological product (reference product)  

B. A biosimilar is a generic equivalent of the reference product

C. Biosimilars are similar to reference products in terms of safety

D. Biosimilars are a new version of an existing biologic whose patent has expired
The term “biosimilar” or “biosimilarity,” in reference to a biological product that is the subject of an application under subsection (k), means:

a. The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components

b. There are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product

Audience Response Question

Which of the following statements is NOT true regarding biosimilar products?

A. They are produced through recombinant technology and biosynthesis JL57
B. The manufacturing process has been standardized among manufacturers JL58
C. Biosimilar production involves cell expansion and purification JL59
D. Changes in the production process can have an effect on the biologic and clinical activity of the final product JL60
Biosimilar Development

Final Product Variability

Expression system
Purification process
Growth conditions
Product storage and transport

Glycosylation
Phosphorylation
Deamidation
Methylation
Acetylation
Lipidation
Sulphation
Hydroxylation
Disulphide bond formation

Establishing Biosimilarity

- Process governed by the FDA
- Requires a stepwise approach
- FDA considers the totality of the evidence
Analytic Studies: Structural Characterization

- Amino acid sequence
- Higher-order structures (secondary, tertiary, and quaternary structure)
- Enzymatic posttranslational modification (glycosylation/phosphorylation)
- Protein deamidation
- Oxidation
- Pegylation

Analytic Studies: Functional Characterization

- Enzyme kinetics
- Binding assays
- Biological assays
- In vitro
- In vivo
- Animal studies
Animal Data

- Animal pathology
- Histopathology
- Pharmacodynamics
- Pharmacokinetics
- Immunogenicity assessments
Human Studies

- Human pharmacokinetics
- Human pharmacodynamics
- Clinical immunogenicity
- Comparative clinical studies
Audience Response Question

Which of the following best describes extrapolation?

A. Substitution of a reference product in place of a biosimilar by a pharmacist  JL61
B. Use of a biosimilar for an “off-label” indication with third-party payment approval  JL62
C. Licensure of the proposed product for one or more additional conditions of use for which the reference product is licensed  JL63
D. Adverse event reporting based on the extrapolation of symptoms from a drug recipient  JL64
Extrapolation

“If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure of the proposed product for one or more additional conditions of use for which the reference product is licensed.”

Interchangeability

- Biosimilar to an FDA-approved reference product
- Meets additional standards for interchangeability
- May be substituted for the reference product by a pharmacist without the intervention of the prescribing health-care provider

US Launch…

- Approved March 6, 2015
- First US approval
### Biosimilar Nomenclature

<table>
<thead>
<tr>
<th>CDER: The Purple Book</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of licensed biological products</td>
<td>Filgrastim-sndz</td>
</tr>
<tr>
<td>Product name</td>
<td>Zarxio</td>
</tr>
<tr>
<td>Proprietary name</td>
<td>3/6/15</td>
</tr>
<tr>
<td>DOL</td>
<td>B</td>
</tr>
<tr>
<td>Biosimilarity</td>
<td></td>
</tr>
<tr>
<td>Interchangeability</td>
<td></td>
</tr>
</tbody>
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Advanced Practice Implications


Advanced Practice Implications: Education/Collaboration

- Informed decision-making
- Peer education
- Patient education
- Collaboration
Advanced Practice Implications: Pharmacovigilance

- “Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.” (World Health Organization)
- All scientific and data-gathering activities relating to the detection, assessment, and understanding of adverse events. (FDA)

Pharmacovigilance
FDA Adverse Event Reporting System

- All health-care workers
- Non-health-care workers
- Spontaneous
- Voluntary
- Dual responsibility for prescribers

Advanced Practice Implications: Legislative Compliance

Legislation on Biologics and Biosimilar Substitution, 2013-2015

LEGEND
- Enacted law, 2013-15
- Passed legislature; not law
- Filed; failed/adjourned 2013-15
- Bill filed; pending or carryover, 2015

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“The wilderness holds answers to more questions than we have yet learned to ask.”

–Nancy Wynne Newhall
Reference List


Reference List (cont)
