Biosimilars: Current Challenges and Opportunities for Pharmacists

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2016 TSHP Winter Meeting – Nashville, TN – February 28
2015 SDSHP Annual Conference – Rapid City, SD – April 8-9
NYSCHP Annual Assembly – Saratoga, NY – April 30

Planned by ASHP Advantage and supported independent educational grants from Boehringer Ingelheim Pharmaceuticals, Inc. and Sandoz, a Novartis company.
Activity Overview

With biosimilars now available in the United States, pharmacists must address the operational challenges and opportunities related to introducing biosimilars into the medication-use process. In this activity, the faculty will explain how FDA guidance documents and long-term experience with biosimilars in the European Union can be useful in guiding the implementation of these agents in U.S. health systems. Key formulary, legal, and operational factors to consider when integrating biosimilars into the medication-use process will be reviewed, including practical issues related to pharmacovigilance.

Learning Objectives

After the conclusion of this application-based educational activity, participants should be able to

- Use FDA guidance documents and the European Union’s experience to guide formulary committee discussion on strategies for promoting the safe and effective use of biosimilars
- Consider the factors that need to be taken into account when integrating biosimilars into the medication use process, including regulatory and pharmacovigilance concerns.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit (ACPE activity # 0204-0000-16-412-L03-P).

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Faculty

Edward C. Li, Pharm.D., M.P.H., BCOP
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Edward C. Li, Pharm.D., M.P.H., BCOP, is Associate Professor in the Department of Pharmacy Practice at the University of New England College of Pharmacy in Portland, Maine.

Dr. Li earned his Doctor of Pharmacy degree from Philadelphia College of Pharmacy and his Master of Public Health degree from University of New England (UNE). He completed a pharmacy practice residency at University of Wisconsin Hospital and Clinics and an oncology pharmacy practice residency at University of Maryland School of Pharmacy, both accredited by ASHP.

Dr. Li is a board-certified oncology pharmacist who maintains a practice with New England Cancer Specialists, the region’s largest oncology group located in Scarborough, Maine. He also works with New Century Health, a leading innovator of quality and cost management programs, to develop cancer treatment pathways. Before joining UNE, he was Oncology Pharmacy Manager at National Comprehensive Cancer Network, a not-for-profit organization whose clinical practice guidelines in oncology are the standard of care in the United States.

Dr. Li’s research focuses on cancer pharmacoepidemiology, pharmacoeconomics, and evaluations of health policy issues as they relate to oncology practice.
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Professor, Department of Clinical Pharmacy
University of Michigan College of Pharmacy
President, Hospital and Health System Services
Visante, Inc.
Ann Arbor, Michigan

James G. Stevenson, Pharm.D., FASHP, is Professor in the Department of Clinical Pharmacy at University of Michigan College of Pharmacy in Ann Arbor and President of Hospital and Health System Services for Visante, Inc.

Dr. Stevenson received his Bachelor of Science in Pharmacy and Doctor of Pharmacy degrees from Wayne State University in Detroit, Michigan. From 1999-2014 he served as Chief Pharmacy Officer in the University of Michigan Health System. During that same time period he was Associate Dean for Clinical Sciences at the College of Pharmacy, assuming the additional responsibilities of Chair of the Department of Clinical, Social, and Administrative Sciences from 2011-2014. In 2014 he assumed his current position for Visante, a medicines management consulting company. Before joining the University of Michigan Health System, Dr. Stevenson served as Director of Pharmacy Services at West Virginia University Hospitals and Detroit Receiving Hospital and University Health Center and as Executive Director of Pharmacy Services for the eight-hospital Detroit Medical Center. Previous academic appointments were at West Virginia University and Wayne State University.

Dr. Stevenson is a fellow of ASHP, and he is widely recognized as a leader in pharmacy. He was named Pharmacist of the Year by both the Michigan Society of Health-System Pharmacists and the Michigan Pharmacists Association for a state-wide patient safety initiative. In addition, he was honored with the Distinguished Alumnus Award by Wayne State University College of Pharmacy and the Joseph Oddis Leadership Award by Michigan Society of Health-System Pharmacists. Dr. Stevenson served on the ASHP Board of Directors and is currently Treasurer of the Hospital Pharmacy Section of International Pharmaceutical Federation. He received the 2010 John W. Webb Lecture Award for extraordinary dedication to fostering excellence in pharmacy management, as well as the 2013 ASHP Award for Distinguished Leadership in Health-System Pharmacy Practice.

Dr. Stevenson’s specific areas of expertise include pharmacy practice management, pharmacy informatics, and medication safety.
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- James G. Stevenson, Pharm.D., FASHP, declares that he has served as a consultant for Amgen Inc.

- All other planners report no financial relationships relevant to this activity.

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Learning Objectives
At the conclusion of this educational activity, participants should be able to

• Use FDA guidance documents and the European Union’s experience to guide formulary committee discussion on strategies for promoting the safe and effective use of biosimilars.
• Consider the factors that need to be taken into account when integrating biosimilars into the medication-use process, including regulatory and pharmacovigilance concerns.

Background on Biosimilars
• The Biologics Price Competition and Innovation Act was enacted to increase competition with biological medications
• Competition will lead to
  – Decreased prices (or overall expenditures)
  – Increased innovation

European Union Biosimilar Experience
• Biosimilars are high-quality products with strict regulations in manufacturing and scientific development
• Similar vs. identical debate is not unique to biosimilars (applies to each biologic for lot-to-lot comparability)
• Safety data is required pre-approval (including immunogenicity)
• Postmarketing surveillance (mandatory) seeks to identify residual concerns; not unique to biosimilars
• Efficacy comparison trials will use the most clinically sensitive endpoint
• Be aware of differences in indications for use and extrapolate if appropriate
• Interchange practices highly variable

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Biosimilars Market Uptake in Europe:
Erythropoiesis Stimulating Agents (ESAs)


European Experience:
Biosimilar Myeloid Growth Factors (MGFs)
- European Union G5 countries — Germany, France, Italy, Spain, UK
- Compared prices of filgrastim (brand) to biosimilar filgrastim and pegfilgrastim

<table>
<thead>
<tr>
<th>Product</th>
<th>Day 1 price (Euros)</th>
<th>Total price after 14 days (Euros)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim (originator)</td>
<td>128.16</td>
<td>1794.30</td>
</tr>
<tr>
<td>Biosimilar filgrastim</td>
<td>95.46</td>
<td>1336.46</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>1414.96</td>
<td>1414.96</td>
</tr>
</tbody>
</table>


Change in Price (%)

Change in Access to 2nd Gen ESAs (%)

European Experience:
Biosimilar Myeloid Growth Factors (MGFs)

Cost of Outpatient GCSF Products in Germany
- Analysis of prescriptions for MGFs between Jan 2008 to July 2010
- Data from IMS LRx database

<table>
<thead>
<tr>
<th>Product</th>
<th>Average cost per cycle (Euros)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosimilar filgrastim</td>
<td>1,875.69 (SD: 1,562.40)</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>1,915.20 (SD: 1,817.59)</td>
</tr>
<tr>
<td>Filgrastim (originator)</td>
<td>2,336.66 (SD: 2090.66)</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>5,710.36 (SD: 3,574.72)</td>
</tr>
</tbody>
</table>

EPO = human erythropoietin

Biologics: More Complex than Traditional Small Molecule Drugs

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Produced by</th>
<th>High molecular weight</th>
<th>Complex &amp; heterogeneous structure</th>
<th>Impossible to fully characterize</th>
<th>Sensitive to external conditions &amp; manufacturing changes</th>
<th>Relatively high immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human EPO</td>
<td>Produced by living systems</td>
<td>High molecular weight</td>
<td>Complex &amp; heterogeneous structure</td>
<td>Impossible to fully characterize</td>
<td>Sensitive to external conditions &amp; manufacturing changes</td>
<td>Relatively high immunogenicity</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Produced by chemical reactions</td>
<td>Relatively low molecular weight</td>
<td>Final structure independent of process</td>
<td>Able to be characterized fully</td>
<td>Mostly non-immunogenic</td>
<td></td>
</tr>
</tbody>
</table>

| Small-molecule drugs | Produced by chemical reactions | Relatively low molecular weight | Final structure independent of process | Able to be characterized fully | Mostly non-immunogenic |

Immunogenicity Concerns
- All biologics confer a risk of immunogenicity
  - Related to patient, disease, and product factors
  - Consequences include neutralizing antibody formation and cytokine release
  - Scientific tools for detecting immunogenicity exist, but they are not precise
- Changes to the structure of the protein increase variation in immunogenicity
  - Lot-to-lot and between manufacturers
  - Variations in manufacturing must be minimized
- Clinical consequences
  - Loss or diminished efficacy or safety
  - Case reports of rare but serious adverse reactions have been received

Originator Manufacturing Process Changes

- Small modifications may result in gradual changes
  - Darbepoetin alfa
  - Rituximab
  - Etanercept

- Despite these differences, when the products are within a prespecified acceptable range, the products are marketed with no change in label
- If large alterations occur, analytical studies (and possibly additional clinical studies) are required to compare post-change product with existing pre-change product

Biologic Manufacturing Changes – Demonstration of Comparability

Guidance for Industry

“...The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.”


Regulatory Definitions of a Biosimilar

- Food and Drug Administration (U.S.)
  - A biological product that is highly similar to a U.S.-licensed reference biological product notwithstanding minor differences in inactive components and for which there are no clinically meaningful differences in safety, purity, or potency of the product
- European Medicines Agency – Europe
  - ...structurally highly similar versions of an already authorized biological medicinal product (the reference product) with demonstrated similarity in physicochemical characteristics, efficacy, and safety based on a comprehensive comparability exercise


General Principles for Demonstrating Biosimilarity

- Biosimilars approved via an abbreviated pathway
- Demonstration of biosimilarity is a comparability exercise and not a therapeutic equivalence study
- Goal of the biosimilarity exercise is to establish that the candidate biosimilar is not significantly different from the reference product and is unlikely to have any clinically significant differences
  - Smaller-scale direct comparisons and extrapolation are used


FDA Specifications for Biosimilars

<table>
<thead>
<tr>
<th>Biosimilar Product Specification</th>
<th>Comparison with Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>May be different</td>
</tr>
<tr>
<td>Delivery device/container</td>
<td>May be different</td>
</tr>
<tr>
<td>Routes of administration</td>
<td>May obtain licensure for fewer than all routes of administration for which reference product is licensed</td>
</tr>
<tr>
<td>Indications for use</td>
<td>May obtain licensure for fewer than all conditions of use for which reference product is licensed</td>
</tr>
<tr>
<td>Strength</td>
<td>Must be the same</td>
</tr>
</tbody>
</table>

Demonstrating Biosimilarity: A Stepwise Approach

- Compare proposed biosimilar to reference in terms of
  1. Structure
  2. Function
  3. Animal Toxicity Studies
  4. Human Pharmacokinetics (PK) and Pharmacodynamics (PD)
  5. Clinical Immunogenicity
  6. Clinical Safety and Effectiveness
- FDA intends to use a “totality of the evidence” approach

Biosimilar and Biologic Development

Totality of the Evidence

- 351(a)
- 351(k)
- Highly Similar

No “one size fits all” assessment:
- FDA will evaluate the integration of various types of information to provide advice on size and extent of labeling plan.
- Ultimately, an overall assessment that a biologic product is or is not biosimilar to an approved reference product.

See enlargement, p. 18

Structure and Function

- Serve as the “foundation” of biosimilar development
- Useful in determining what future studies are necessary
- Structure
  - Amino acid sequence, higher-order structures, glycosylation, pegylation, etc.
  - Analyze lot-to-lot variability
- Function
  - Evaluate pharmacologic activity via in vitro or in vivo experiments
  - Functional evaluation that compares candidate to reference

See enlargement, p. 18

Analytical Characterization: Fingerprinting

- Sequence & Modifications
- Higher Order Structures
- Bioactivity

See enlargement, p. 18

Human Pharmacokinetics and Pharmacodynamics

- “Fundamental” for demonstrating biosimilarity
- Both PK and PD will be necessary
  - PK: patient population considerations
  - PD should study measures that
    - Are relevant to clinical outcomes
    - Can be quickly assessed with precision
    - Have the sensitivity to detect clinically meaningful differences
- Ideally correlate exposure to clinical outcomes
- Use crossover and parallel designs

See enlargement, p. 18

Comparative Clinical Studies

- Clinical immunogenicity
  - Goal is to evaluate potential differences in incidence and severity of immune responses using endpoints such as antibody formation (binding, neutralizing), cytokine levels, etc.
  - FDA recommends a comparative parallel study
- Efficacy and safety: specific clinical trial design will depend on what residual questions remain
  - Clinical studies should be designed to demonstrate neither decreased nor increased activity
  - Use clinically relevant and sensitive endpoints in the right population
  - Biosimilar sponsor to justify comparability delta


See enlargement, p. 18

Clinical Trial Design: Equivalence

- Establish the equivalence margin (δ) via the 95-95 method
- 95% CI should fall between -δ and +δ for equivalence

- However, non-inferiority studies may be appropriate if it is well-established that the biologic saturates the receptors at the clinical dose


See enlargement, p. 18
**Indication Extrapolation Framework**

**Patient Factors**
- Similarity of biologic disposition: PK/PD
- Organ function
- Age, ethnicity, etc.

**Disease Factors**
- Clear MOA?
- Similarity of disease (e.g., histology, stage, pathophysiology, etc.)
- Single vs. combo therapy
- Clinical manifestation

**Endpoint Factors**
- Efficacy and toxicity
- Short-term vs. long-term
- Sensitivity of surrogate outcome

**Quantitative Evidence of Biosimilarity**
- In vitro, preclinical, epidemiological studies, diagnostic studies, clinical trials, and observational studies

**Indication Extrapolation Determination**
- No extrapolation; extrapolation to some indications; extrapolation to all indications

See enlargement, p. 19

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**European Experience: Infliximab**

- Indications: rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis, inflammatory bowel disease
- Two large clinical trials in AS and RA
- European Medicines Agency used these data to extrapolate to other agency-approved indications
- Residual questions about switching, real-world immunogenicity, and pharmacovigilance

(Isaacs JD et al J Intern Med. 2015 Sep 25. [Epub ahead of print])

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**Biosimilar Pharmacovigilance**

**Risk Identification and Characterization**

- Pharmacovigilance
  - Practical to encourage healthcare provider reporting
  - Real-time data
  - Ensure traceability

- Healthcare Provider Responsibility for Reporting
  - Correct attribution of safety event
  - Maintenance of electronic medical record
  - Bar code administration
  - Medication reconciliation
  - Consideration of transitions of care

See enlargement, p. 19

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**There Will Be Many Types of Biologic Products**

<table>
<thead>
<tr>
<th>Description</th>
<th>351(a) Originator</th>
<th>351(k) Biosimilar</th>
<th>351(h) Interchangeable Biosimilar</th>
<th>351(a) Non-originator biosimilar</th>
<th>351(a) Real-generation &quot;Bio-better&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data package</td>
<td>Demonstrates safety &amp; efficacy</td>
<td>Demonstrates safety &amp; efficacy</td>
<td>Demonstrates safety &amp; efficacy</td>
<td>Demonstrates safety &amp; efficacy</td>
<td>Demonstrates safety &amp; efficacy</td>
</tr>
<tr>
<td>Practice Implications</td>
<td>Biologic reimbursement equivalent (same margins as reference)</td>
<td>Biologic reimbursement equivalent (same margins as reference)</td>
<td>Biologic reimbursement equivalent (same margins as reference)</td>
<td>Biologic reimbursement equivalent (same margins as reference)</td>
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See enlargement, p. 20

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**Biological Prescription Cost Implications in U.S.**

- Biologicals and specialty pharmaceuticals are the fastest growing pharmaceutical expense in the U.S.
- The Economist estimates that biologics could make up 32% of total big pharma sales by 2023
- 7 of top 10 drugs by sales in 2014 were biologics
- Significant interest on the part of payers/employer groups in managing the specialty cost trend
- Estimate savings of approximately 20%-30%

See enlargement, p. 20

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**Why are Biologics Important?**

<table>
<thead>
<tr>
<th>Top 15 Drugs by Expenditures in Clinics in 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug/Biologic Name</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
</tr>
<tr>
<td>Humira (adalimumab)</td>
</tr>
<tr>
<td>Enbrel (etanercept)</td>
</tr>
<tr>
<td>Remicade (infliximab)</td>
</tr>
<tr>
<td>Xeloda (capecitabine)</td>
</tr>
<tr>
<td>Taxotere (docetaxel)</td>
</tr>
<tr>
<td>Vialine (vaccines)</td>
</tr>
<tr>
<td>Z-pack (zinc)</td>
</tr>
<tr>
<td>Protonix (omeprazole)</td>
</tr>
<tr>
<td>Zopiclone (zopiclone)</td>
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<tr>
<td>Lipitor (atorvastatin)</td>
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<td>Lipitor (atorvastatin)</td>
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</tbody>
</table>

See enlargement, p. 20

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Significant Impact of Biosimilars on Pharmaceutical Expense Trend

- Estimate of $250 billion savings in U.S. over next 10 years from just 11 biosimilar products (Express Scripts)
- 2008 Congressional Budget Office (CBO) estimated a $25 billion reduction in U.S. expenditures on biologics by 2018
- Rand Corporation (2014) predicts that biosimilars will lead to a $44.2 billion reduction (range $13B-$66B) in direct spending on biologic drugs from 2014 to 2024

There will be significant pressure from payers to use biosimilars to control healthcare costs


Formulary Selection Considerations: Efficacy and Safety

- Clinical data and populations studied in FDA approval
- Range of indications
- Presence of biomarker to assess efficacy and safety
- Experienced vs. de novo patients
  - Immunogenicity concerns due to switching


Extrapolation of Indications

- Extrapolation of data from a clinical trial in one disease to support approval for additional indications
- Factors to be considered
  - Clinical experience with the reference product
  - Mechanism(s) of action in each indication
  - Target receptors
  - Product structure and target/receptor interactions
  - Pharmacokinetics in different patient populations
  - Differences in the safety/immunogenicity profile between indications


Formulary Selection Considerations: Manufacturer Considerations

- Expertise manufacturing biologics
- Supply reliability
- Supply security and anti-counterfeit measures
- Patient assistance programs
- Reimbursement support programs


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Formulary Selection Considerations: Payer, Provider, and Patient Factors

- Economic considerations
  - Payer
  - Provider
  - Patient out-of-pocket cost – impact on adherence
- Management of transitions of care
  - How many products in “preferred” status
  - Consistency of product provided

Will you review a biosimilar through the routine P&T process or handle like a “generic”?

a. Full P&T review
b. Abbreviated review
c. Manage like a generic

Operational Challenges: Financial Analysis

- Pricing information comparison (provider, payer)
  - Portfolio pricing
- Reimbursement implications for healthcare provider
- Patient assistance and out-of-pocket expenses
- Determine financial impact from various perspectives


On the formulary, will you have only one biologic in a therapeutic category, or will you have both the reference product and biosimilar(s)?

a. Only the reference product
b. Only a biosimilar
c. Both

On the formulary, will you have only one biologic in a therapeutic category, or will you have both the reference product and biosimilar(s)?

a. Only the reference product
b. Only a biosimilar
c. Both

If you have the biosimilar on formulary, will you consider a therapeutic interchange for patients who are admitted on the reference product?

a. Yes
b. No
c. Unsure

• If more than one, under what circumstances will you use each?
If you have the biosimilar on formulary, will you consider a therapeutic interchange for patients who are admitted on the reference product?

a. Yes  
b. No  
c. Unsure

• If you execute an interchange, how will you educate patients?  
• How will you notify physicians?

Operational Challenges: Information Systems

• Differentiate between similar biologics in electronic systems  
  – Pharmacy information systems  
  – CPOE and ePrescribing systems  
  – Dispensing systems and automation  
  – eMAR

• Order sets, protocols  
• Medication reconciliation  
• Patient’s own home medicine


Operational Challenges: Inventory Management

• Purchaser needs adequate information (NDC, etc.)  
• Will multiple products be stocked?  
  – Reference and biosimilar  
  – Multiple biosimilars  
• Product storage, placement on shelf, etc.  
• Inventory costs  
• Wrong product dispensing errors


Interchangeability

• Will be “difficult” in the initial 351(k) application due to the sequential nature of the assessment  
• Appropriate to be “substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product”  
• FDA is in process of developing guidance  
• The biological is biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient, and the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its reference product is not greater than the risk of using the reference product without such alteration or switch  
• State substitution laws will impact practice

www.fda.gov/Drugs/ GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm  
(all accessed 2015 Oct 30)

Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations

• Designed to enable a user to determine if a biological product is biosimilar or interchangeable with a reference biologic per FDA evaluation  
• Cross-references biological products licensed under 351(a) with biosimilar or interchangeable products licensed under 351(k)


Legislation on Biologics and Biosimilar Substitution, 2013-2015

Typical Features of State Legislation

- Prescriber can prevent substitution with DAW
- Prescriber must be notified of substitution
- Patient must be notified and consent
- Records of substitution must be retained
- State should keep a list of interchangeable products


FDA Proposed Guidance on Naming

- INN with an added random four-letter suffix for all biologics (including reference products)
  - Example: replicamab-cznn, replicamab-hxif
- Benefits
  - Ability to differentiate products for pharmacovigilance purposes
    - Some biosimilars may be licensed for fewer indications than reference product
    - Common INN will group similar biologics in electronic systems
    - Reduces perception that biosimilar is inferior to reference product
- Concerns
  - Without same suffix, interchange will be inhibited
  - Potential for errors with use of four-letter suffix “devoid of meaning”
  - Need to change name of current biologics on market


What’s in a Name?
Two Differing Viewpoints

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosimilars should have the same exact nonproprietary name as their respective reference</td>
<td>Communicate that these products are “highly similar”</td>
</tr>
<tr>
<td>Ability to differentiate products for pharmacovigilance purposes</td>
<td>May impede adoption</td>
</tr>
<tr>
<td>Some biosimilars may be licensed for fewer indications than reference product</td>
<td>Issues with substitution</td>
</tr>
<tr>
<td>Common INN will group similar biologics in electronic systems</td>
<td></td>
</tr>
<tr>
<td>Reduces perception that biosimilar is inferior to reference product</td>
<td></td>
</tr>
</tbody>
</table>

Pros
- Improved pharmacovigilance
- Recognize that these are distinct products
- Confusion about whether they are “interchangeable”
- May impede adoption
- Issues with substitution


See enlargement, p. 21

Operational Challenges:
Education

- Education of all providers to avoid confusion (clinical information, policies, appropriate use, etc.)
- Patient education
- Managing transitions of care


What strategies will you use to track the appropriate product the patient is taking in your electronic system and during medication reconciliation?

a. Order & document with full product name (INN plus suffix)
b. Order & document with full product name PLUS brand name
c. Order and document with INN (minus suffix) PLUS brand name
d. Other

Recommendations for Biosimilars for Health System Pharmacy

- Use existing formulary system and processes to evaluate for formulary inclusion
- Carefully consider scope of indications for use
- Conduct sophisticated economic analysis, considering costs, reimbursement, and patient impact
- Plan for therapeutic equivalence and guided-use policy and processes
- Consider processes for transitions of care
- Prepare IT systems to facilitate effective pharmacovigilance programs
- Meet educational needs of patients and providers
### Resources for Pharmacists and Technicians

- ASHP Resource Center on Biosimilars  
- American Journal of Managed Care Resource Center  

### Key Takeaways

- The European experience with biosimilars has seen a reduction in biological prices with an increase in access to medications  
- FDA has developed a pathway to assess the comparability of a biosimilar to the reference product
- Biologics are complex drugs that should not be considered “generic”
- Switching and indication extrapolation (off-label) are residual concerns that P&T committees need to address

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### Key Takeaways

- Integration of biosimilar agents into clinical practice presents many operational and clinical challenges
- European biosimilar experience has been good from a safety perspective
- Federal and state regulatory actions, pricing, and reimbursement policies will play key roles in determining future use of biosimilars and product selection in the U.S.

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### Key Takeaways

- Transitions of care and medication reconciliation will be ongoing practice management issues
- Key issues yet to be resolved include naming, interchangeability criteria and requirements, and pharmacovigilance requirements
- Pharmacists should assume leadership in planning a strategy for successful operational and clinical use of these agents
Biosimilars Market Uptake in Europe: Erythropoiesis Stimulating Agents (ESAs)


Biologics: More Complex than Traditional Small Molecule Drugs

Biologics
- Produced by living systems
- High molecular weight
- Complex & heterogeneous structure
- Impossible to fully characterize
- Sensitive to external conditions & manufacturing changes
- Relatively high immunogenicity

Small-molecule drugs
- Produced by chemical reactions
- Relatively low molecular weight
- Final structure independent of process
- Able to be characterized fully
- Stable
- Mostly non-immunogenic

Human EPO
165 amino acids
MW ~ 34,000 Da

Cisplatin
(NH$_3$)$_2$PtCl$_2$
MW ~ 300 Da

Illustration courtesy of Olgun Guvench, M.D., Ph.D., University of New England College of Pharmacy.
Manufacturing Biosimilars: Sources of Variation

Cloning and Protein Expression

Protein Production, Purification, and Validation

Originator Manufacturing Process Changes

- Small modifications may result in gradual changes

- Despite these differences, when the products are within a prespecified acceptable range, the products are marketed with no change in label

- If large alterations occur, analytical studies (and possibly additional clinical studies) are required to compare post-change product with existing pre-change product

Biosimilar and Biologic Development

Totality of the Evidence

No “one size fits all” assessment:
FDA scientists will evaluate the applicant’s integration of various types of information to provide advice on scope and extent of develop plan and, ultimately, an overall assessment that a biological product is (or is not) biosimilar to an approved reference product.

351(a)
Clinical Animal Studies
Clinical Immunogenicity
Clinical Knowledge, e.g. Post-Market Experience
Human Pharmacokinetics and Pharmacodynamics (PK/PD)
Structural and Functional Characterization

351(k)
Biosimilar
Highly Similar

Clinical Trial Design: Equivalence

- Establish the equivalence margin ($\delta$) via the 95-95 method
- 95% CI should fall between -$\delta$ and $+\delta$ for equivalence

- However, non-inferiority studies may be appropriate if it is well-established that the biologic saturates the receptors at the clinical dose


Indication Extrapolation Framework

Patient Factors
- Similarity of biologic disposition: PK/PD
- Organ function
- Age, ethnicity, etc.

Disease Factors
- Clear MOA?
- Similarity of disease (e.g., histology, stage, pathophysiology, etc.)
- Single vs. combo therapy
- Clinical manifestation

Endpoint Factors
- Efficacy and toxicity
- Short-term vs. long-term
- Sensitivity of surrogate outcomes

Quantitative Evidence of Biosimilarity
In vitro, preclinical, epidemiological studies, diagnostic studies, clinical trials, and observational studies

Indication Extrapolation Determination
No extrapolation; extrapolation to some indications; extrapolation to all indications


Biosimilar Pharmacovigilance

Risk Identification and Characterization

Pharmacovigilance
- Practical to encourage healthcare provider reporting
- Real-time data
- Ensure traceability

Risk minimization
- Healthcare provider communication
- Recalls and alerts
- FDA REMS?

FDA Approval

Healthcare Provider Responsibility for Reporting
- Correct attribution of safety event
- Maintenance of electronic medical record
- Bar code administration
- Medication reconciliation
- Consideration of transitions of care


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### There Will Be Many Types of Biologic Products

<table>
<thead>
<tr>
<th>Description</th>
<th>351(a) Originator</th>
<th>351(k) Biosimilar</th>
<th>351(k) Interchangeable Biosimilar</th>
<th>351(a) Non-originator biologic</th>
<th>351(a) Next-generation “Bio-better”</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-to market biologic molecule; will likely be the reference product</td>
<td>“Highly similar” to reference product; approved via biosimilars pathway</td>
<td>A biosimilar that can be switched to and from the reference with no clinical consequences</td>
<td>It is “another brand name” of an already approved biologic</td>
<td>Biologic that has been altered to achieve improved clinical outcomes</td>
<td></td>
</tr>
<tr>
<td>Data package</td>
<td>Demonstrate safety &amp; efficacy</td>
<td>Abbreviated data package</td>
<td>Abbreviated data package, more information on switching</td>
<td>Demonstrate safety &amp; efficacy</td>
<td>Demonstrate safety &amp; efficacy</td>
</tr>
<tr>
<td>Practice implications</td>
<td>Biosimilar reimbursement per CMS (same margin as reference)</td>
<td>Biosimilar reimbursement per CMS; possible automatic substitution without contacting prescriber</td>
<td>Lower margin if lower cost; automatic substitution issues</td>
<td>New entity</td>
<td></td>
</tr>
</tbody>
</table>

### Why are Biologics Important?

**Table 4. Top 15 Drugs by Expenditures in Clinics in 2014**

<table>
<thead>
<tr>
<th>Drug (Brand Name)</th>
<th>2013 Expenditures ($ Thousands)</th>
<th>Percent Change in 2013</th>
<th>2014 Expenditures ($ Thousands)</th>
<th>Percent Change in 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (Remicade)</td>
<td>2,670,586</td>
<td>7.1</td>
<td>2,245,189</td>
<td>12.8</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta)</td>
<td>2,577,038</td>
<td>2.4</td>
<td>2,044,069</td>
<td>4.0</td>
</tr>
<tr>
<td>Epoetin alfa (Procrit, Epogen)</td>
<td>2,508,126</td>
<td>5.2</td>
<td>2,033,361</td>
<td>5.8</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>2,307,286</td>
<td>5.1</td>
<td>1,777,743</td>
<td>3.3</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>2,097,323</td>
<td>2.5</td>
<td>1,660,714</td>
<td>7.5</td>
</tr>
<tr>
<td>Ranibizumab (Lucentis)</td>
<td>1,707,227</td>
<td>15.3</td>
<td>1,342,183</td>
<td>5.8</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>1,538,357</td>
<td>4.6</td>
<td>1,270,581</td>
<td>10.9</td>
</tr>
<tr>
<td>Denosumab (Prolia)</td>
<td>932,423</td>
<td>27.3</td>
<td>824,607</td>
<td>27.3</td>
</tr>
<tr>
<td>Pemtrexed (Alimta)</td>
<td>932,188</td>
<td>5.8</td>
<td>715,352</td>
<td>5.1</td>
</tr>
<tr>
<td>Immune globulin</td>
<td>517,412</td>
<td>13.1</td>
<td>488,254</td>
<td>32.3</td>
</tr>
<tr>
<td>Varicella vaccine (Zervax, Zostavax)</td>
<td>592,886</td>
<td>-30.7</td>
<td>476,574</td>
<td>4.1</td>
</tr>
<tr>
<td>Influenza virus vaccines</td>
<td>617,999</td>
<td>117.8</td>
<td>475,613</td>
<td>14.5</td>
</tr>
<tr>
<td>Pneumococcal vaccine (Prevnar, Prevnar 13)</td>
<td>637,430</td>
<td>3.4</td>
<td>460,824</td>
<td>-0.2</td>
</tr>
<tr>
<td>Nataizumab (Tysabri)</td>
<td>412,975</td>
<td>204.2</td>
<td>424,361</td>
<td>277.4</td>
</tr>
<tr>
<td>HPV vaccine for types 6,11,16,18 (Gardasil)</td>
<td>523,209</td>
<td>14.8</td>
<td>420,850</td>
<td>-0.6</td>
</tr>
<tr>
<td>All others</td>
<td>21,997,663</td>
<td>7.0</td>
<td>19,335,538</td>
<td>20.6</td>
</tr>
<tr>
<td>Total</td>
<td>42,660,130</td>
<td>7.6</td>
<td>30,017,813</td>
<td>15.5</td>
</tr>
</tbody>
</table>

The Patent Cliff and Growth Potential for the Biosimilars Market

<table>
<thead>
<tr>
<th>Global Sales 2013, US$ Billion</th>
<th>EU Expiry Date</th>
<th>U.S. Expiry Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>2018</td>
<td>2016</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>Expired</td>
<td>2018</td>
</tr>
<tr>
<td>Rituximab (Rituxan, Mabthera)</td>
<td>Expired</td>
<td>2016</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>Expired</td>
<td>2013/2028*</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>2022</td>
<td>2019</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Expired</td>
<td>2019</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta)</td>
<td>2017</td>
<td>Expired</td>
</tr>
</tbody>
</table>

*Expiry date uncertain.

www.gabionline.net/Biosimilars/General/Top-8-blockbuster-biologicals-2013.

What’s in a Name? Two Differing Viewpoints

Biosimilars should have the same exact nonproprietary name as their respective reference

Pros
• Communicate that these products are “highly similar”
• Facilitate adoption and substitution of interchangeable biologics

Cons
• Hard to trace for [rare] adverse events

Biosimilars should each have a distinct nonproprietary name to differentiate them from the originator and other biosimilars

Pros
• Improved pharmacovigilance
• Recognize that these are distinct products

Cons
• Confusion about whether they are “interchangeable”
• May impede adoption
• Issues with substitution

Biosimilars: Current Challenges and Opportunities for Pharmacists

Self-assessment Questions

1. Which of the following best describes the European experience with biosimilars?
   a. Increase in prices of biologicals, increase in access to medications.
   b. Increase in prices of biologicals, decrease in access to medications.
   c. Reduction in prices of biologicals, increase in access to medications.
   d. Reduction in prices of biologicals, no change in access to medications.

2. According to Food and Drug Administration (FDA) guidance documents, which of the following domains serves as the “foundation” for biosimilar development?
   a. Animal studies.
   b. Structural and functional characterization.
   c. Human pharmacokinetics/pharmacodynamics studies.
   d. Clinical safety and effectiveness.

3. The P&T committee’s responsibility in the pharmacovigilance of biologics and biosimilars is to
   a. Oversee that records are maintained such that clinicians can correctly attribute safety signals to specific products when reporting events.
   b. Ensure that a biosimilar is as safe as the reference product as related to immune-mediated adverse events.
   c. Investigate whether a biosimilar is interchangeable to its reference product.
   d. Communicate to healthcare providers when there is a manufacturing process change with a biologic so that they can be aware of any safety issues.

4. The P&T committee at ABC Hospital is considering biosimilar-abcd for formulary inclusion, and it must evaluate manufacturer, product, payer, provider, and patient factors as part of its decision-making process. Which of the following is a product-related factor that the P&T committee should consider?
   b. Supply reliability.
   c. Manufacturer’s expertise in manufacturing biologics.
   d. Compatibility of product with bar code systems.

Answers: 1. c, 2. b, 3. a, 4. d
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1. Type the following link into your web browser to access the e-Learning site: http://elearning.ashp.org/my-activities
2. If you already have an account registered with ASHP, log in using your username and password.
   If you have not logged in to any of the ASHP sites before and/or are not a member of ASHP, you will need to set up an account. Click on the Register link and follow the registration instructions.
3. Once logged in to the site, enter the enrollment code for this activity in the field provided and click Redeem.
   Note: The Enrollment Code was announced at the end of the live activity. Please record the Enrollment Code in the grid below for your records.
4. The title of this activity should now appear in a pop-up box on your screen. Click on the Go button or the activity title.
5. Complete all required elements. A green ✓ should appear as each required element is completed. You can now claim your credit.
6. Available credit(s) will appear beneath the completed required activities. Look for your profession in the list of available credits and click the appropriate Claim button. You might have to click to see more credit options if you don’t see your profession listed.
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7. Review the information for the credit you are claiming. If all information appears to be correct, check the box at the bottom and click Claim. You will see a message if there are any problems claiming your credit. Your credit will be reported directly to CPE Monitor.

<table>
<thead>
<tr>
<th>Date of Activity</th>
<th>Activity Title</th>
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<th>Credit Hours</th>
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<tr>
<td>Biosimilars: Current Challenges and Opportunities for Pharmacists</td>
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<td>1.0</td>
</tr>
</tbody>
</table>

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