Biosimilars: An Update on Scientific, Legislative, and Safety Issues

Presented as a Sunday Symposium at the 48th ASHP Midyear Clinical Meeting and Exhibition

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Agenda

10:00 a.m. – 10:10 a.m.  Welcome and Introductions
James G. Stevenson, Pharm.D., FASHP, Activity Chair

10:10 a.m. – 10:20 a.m.  Biosimilars: Overview of a Complex Science
Edward Li, Pharm.D., BCOP

10:20 a.m. – 10:40 a.m.  The European Biosimilars Experience: Focus on Pharmacovigilance and Safety
Edward Li, Pharm.D., BCOP

10:40 a.m. – 11:10 a.m.  Update on Implications of State Biosimilar Legislation
Ben Firschein, J.D., LL.M.

11:10 a.m. – 11:40 a.m.  Preparing for the Introduction of Biosimilars: What Pharmacists and Pharmacy and Therapeutics Committees Need to Know
James G. Stevenson, Pharm.D., FASHP

11:40 a.m. – 12:00 p.m.  Panel Discussion: Questions and Answers

Faculty

James G. Stevenson, Pharm.D., FASHP, Activity Chair
Chief Pharmacy Officer
University of Michigan Health System
Professor and Associate Dean for Clinical Sciences
University of Michigan College of Pharmacy
Ann Arbor, Michigan

Ben Firschein, J.D., LL.M.
Director, Government Affairs and Policy
United States Pharmacopeial Convention (USP)
Rockville, Maryland

Edward Li, Pharm.D., BCOP
Associate Professor
Department of Pharmacy Practice
University of New England College of Pharmacy
Portland, Maine
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- James G. Stevenson, Pharm.D., FASHP, has served as an advisory board member and speaker for Amgen.
- Edward Li, Pharm.D., BCOP, has served as an advisory board member for Amgen and Hospira.

The following faculty and planners report no relationships pertinent to this activity:

- Ben Firschein, J.D., LL.M.
- Susan R. Dombrowski, M.S., B.S.Pharm.
- Erika Thomas, M.B.A., B.S.Pharm.

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Biosimilars: An Update on Scientific, Legislative, and Safety Issues

Activity Overview

Biosimilars are biological medicines that are “highly similar” to an innovator biological product; however, due to their complexity, biosimilars are unlikely to be completely identical to innovator products. Because biosimilars are not the same as the innovator product, the Food and Drug Administration (FDA) approval process used for generic small-molecule drugs is inadequate for biosimilars. The FDA pathway for biosimilars approval was developed to improve affordability of and access to biological therapies, but it remains a work in progress. Concerns about safety must be addressed through postmarketing pharmacovigilance. Health-system pharmacists will play an important role in evaluating biosimilar medicines for the formulary and for ensuring the safe and effective use of biosimilars in health systems.

This activity highlights differences in the scientific, manufacturing, and regulatory processes for biosimilar and small-molecule medications. Faculty will examine the European experience related to biologics and apply lessons learned to the situation in the United States, focusing on pharmacovigilance and safety. Legal implications of recent state legislation on biosimilars will be examined. The evolving role of pharmacists through pharmacy and therapeutics committees, medication use systems, and pharmacovigilance also will be addressed.

Learning Objectives

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

- Compare the scientific, manufacturing, and regulatory processes for biologics and biosimilars with those for traditional small molecule medicines.
- Discuss recent state biosimilar legislation and its possible impact on practitioners.
- Examine considerations for pharmacy and therapeutics committees in evaluating formulary inclusion of biosimilars.
- Review considerations for pharmacovigilance programs, with an emphasis on the pharmacist’s involvement.
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 2 hours (0.2 CEUs) of continuing pharmacy education credit (ACPE activity # 0204-0000-13-478-L03-P).

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If you do not have a smart device, access the Action Reminder for this activity at http://www.ashpadvantagemedia.com/biosims/remindme.php
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- Write down the Attendance Code for each session you attend. These codes are announced during each session. If you miss the code, check with the Room Monitor at the session.
- Click on My Learning Activities. Then click on 2013 – Midyear Clinical Meeting & Exhibition (Orlando, FL) under Conferences.
- At the bottom of the page is a field for redeeming Attendance Codes (formerly called CE codes). Enter the Attendance Code(s) from each session, and click Submit.
  
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- Each session will be listed under Your Sessions. Click Claim Credit for a session.
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   - Click on the Get Started button.
   - Select the 48th ASHP Midyear Clinical Meeting & Exhibition from the dropdown menu.
   - Select your Exhibiting Company from the list of exhibitors. From here, follow the instructions above.

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   *There may be different directions for workshops and review courses.*

| Date of Activity: | Sunday December 8, 2013 | Attendance Code: | M _ _ _ _ | CPE Hours: | 2.0 |

**NEED HELP? Email educserv@ashp.org**
Your educational opportunities related to biosimilars extend beyond today’s symposium…

- **Available in 2014**
  - A **live webinar** on March 20, 2014, where James G. Stevenson, Pharm.D., FASHP, will explore issues raised by participant questions in today’s symposium (1 hour CPE)
  - A **web-based activity** based on today’s live symposium (2 hours of CPE, please note that individuals who claim CPE credit for the live symposium or webcast are ineligible to claim credit for the web-based activity)

For more information and to sign up to receive e-mail updates about this educational series, visit

[www.ashpadvantage.com/biosims](http://www.ashpadvantage.com/biosims)
Edward Li, Pharm.D., BCOP
Associate Professor, Pharmacy Practice
University of New England College of Pharmacy
Portland, Maine

Edward Li, Pharm.D., BCOP, is Associate Professor in the Department of Pharmacy Practice at the University of New England (UNE) College of Pharmacy in Portland, Maine. Dr. Li maintains a clinical practice in ambulatory oncology at the Maine Center for Cancer Medicine in Scarborough. Dr. Li earned his Doctor of Pharmacy degree from the Philadelphia College of Pharmacy. He completed a pharmacy practice residency at the University of Wisconsin Hospital and Clinics in Madison and an oncology pharmacy practice residency at the University of Maryland School of Pharmacy in Baltimore. Dr. Li is a board-certified oncology pharmacist.

Before joining UNE, Dr. Li was a member of the faculty at Wilkes University, Nesbitt College of Pharmacy and Nursing in Wilkes-Barre, Pennsylvania, and most recently was Oncology Pharmacy Manager at The National Comprehensive Cancer Network.

Dr. Li’s research interests include the analysis of practice trends and outcomes research using large claims databases, such as SEER-Medicare data and the Maine All-Payer Claims Database.
Biosimilars: Overview of a Complex Science

Edward Li, Pharm.D., BCOP
Associate Professor
Department of Pharmacy Practice
University of New England College of Pharmacy
Portland, Maine

Topics

• Biosimilar definition, legislation, and manufacturing
  – Differences compared to small-molecule drugs
• Demonstrating biosimilarity
  – FDA guidance

What is a Biosimilar?

• “Copy” of a commercially available therapeutic biologic agent (reference)
• Approved via an abbreviated pathway
• Exhibits “highly similar” efficacy and safety compared with reference product
• Interchangeable biosimilar
  – Can switch back and forth between biosimilar and reference with no clinical consequences
  – Appropriate for substitution without consulting the prescriber

**Biosimilar Legislation**

- **Subtitle:** Biologics Price Competition and Innovation Act (BPCI) of 2009 created an abbreviated FDA approval pathway for biosimilars.
- Before BPCI, there was no abbreviated pathway for FDA approval of copies of biologics.
- According to the FDA, “drugs” are different from “biologics.”

**Pathways for Approval in the USA**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Small molecules</td>
<td></td>
</tr>
<tr>
<td>- Approved via FDCA†</td>
<td></td>
</tr>
<tr>
<td>- Approved via PHSA¥</td>
<td></td>
</tr>
<tr>
<td>New Drug Application (NDA)</td>
<td>Biologics License Application (BLA)</td>
</tr>
<tr>
<td>Safety and Efficacy must be demonstrated</td>
<td>Safety and Efficacy must be demonstrated</td>
</tr>
<tr>
<td>Bioequivalence must be demonstrated</td>
<td>Must demonstrate that it is highly similar to reference</td>
</tr>
</tbody>
</table>

Interchangeable biosimilars require more data

See enlargement p. 22

**We Need Biosimilars!**

- One strategy to potentially reduce healthcare costs
- Experience with traditional generic small molecule drugs: savings up to 80%
- Increase access to expensive therapies
- Foster innovation
Biologics vs. Small Molecule Drugs

Human EPO
165 amino acids
MW ~ 34,000 Da

Cisplatin
(NH3)2PtCl2
MW ~ 300 Da

Biologics Have a Complex Manufacturing Process
• Clone DNA into vector
• Transfer DNA into host cell for expression
• Cell expansion
• Cell production in bioreactors
• Recovery of biologic
  – Filtration
  – Centrifugation
• Purification through chromatography
• Characterization and stability


Similarities and Differences vs. Reference Product

<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>Conditions of 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>

U.S. Food and Drug Administration. Guidance for industry on biosimilars: Q&As regarding implementation of the BPCI Act of 2009: questions and answers part 1. (URL in ref list.)
Demonstrating Biosimilarity: General Principles

- The clinical efficacy and safety of the biologic molecule has already been demonstrated (i.e., by the innovator)
- The biosimilar sponsor only requires evidence that the candidate biosimilar is not significantly different from the reference product.
  - Goal is not to replicate unnecessary clinical trials
  - Smaller scale direct comparisons and extrapolation

U.S. Food and Drug Administration. Draft guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. (URL in ref list).

Audience Polling Question

Based on the information presented so far, what type of comparability information do you feel is necessary for demonstrating biosimilarity?

a. Structure and function only.
b. Structure, function, and human PK/PD only.
c. Structure, function, human PK/PD, and clinical safety (including immunogenicity) only.
d. Structure, function, human PK/PD, and clinical safety and efficacy.

Demonstrating Biosimilarity: A Stepwise Approach

- Compare proposed biosimilar with reference in terms of:
  - Structure
  - Function
  - Animal Data
  - Human Pharmacokinetics (PK) and Pharmacodynamics (PD)
  - Clinical Immunogenicity
  - Clinical Safety and Effectiveness
- FDA intends to utilize a “totality of the evidence” approach

U.S. Food and Drug Administration. Draft guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. (URL in ref list).
Biosimilar Development


Biosimilar Development Approach


Develop highly similar biologic

Test and confirm biosimilarity

Post-Marketing Monitoring

• Analytical methods for structure/function
• Cell line analyses
• In vitro/vivo models
• Substance pilot and final scale analyses
• Formulation and final drug product analyses
• Human clinical trials
• Consideration of clinically sensitive endpoints
• Clinically sensitive patient populations
• Immunogenicity
• Efficacy and safety

Test and confirm Interchangeability

• EU Guidance and risk management plans
• FDA consultation about proposed approach
• May be mandatory

• No explicit FDA guidance
• Will be "difficult" to do in the initial 351(k) application

See enlargement p. 22

The European Biosimilar Experience: Focus on Pharmacovigilance and Safety

Edward Li, Pharm.D., BCOP
Associate Professor
Department of Pharmacy Practice
University of New England College of Pharmacy
Portland, Maine
Topics

- European Post-Marketing Experience
  - Risk Management
  - Pharmacovigilance
  - Case Studies: growth factors (myeloid and erythroid)
- Applications and challenges in the USA

European Union Biosimilar Postmarketing Principles and Issues

- Risk Management Plans
- Pharmacovigilance (PV)
  - Finalized seven different modules on PV (not specific to biosimilars)
- Role of Product Names


European Medicines Agency. European Medicines Agency finalises first set of guidelines on good pharmacovigilance practices (URL in ref list).

EU Risk Management Plans (RMP)

- Principles:
  - Manufacturer has responsibility to ensure biosimilar is safe and effective
  - Pre-market clinical studies insufficient to identify all potential differences
  - Must monitor safety on an ongoing basis; plan to reduce risks
  - RMP needs to be submitted with new marketing authorization application
- Objective:
  - Risk-benefit assessment to quantify risk
  - Biosimilar should be no worse than reference product
  - RMP should focus on:
    - PV measures
    - How to identify immunogenicity risk?
    - Special postmarket surveillance

EU Risk Management Plans

- "Comprehensive and proactive application of scientifically based methodologies to identify, assess, communicate, and mitigate risk throughout a drug’s life cycle so as to establish and maintain a favorable benefit-risk profile."
- Mandatory for biologics (immune reactions)
- Four steps for a particular risk:

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Risk Management Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Detection</td>
<td>Identify risk</td>
<td>Pharmacovigilance</td>
</tr>
<tr>
<td>2. Assessment</td>
<td>Understand/monitor risk</td>
<td></td>
</tr>
<tr>
<td>3. Communication</td>
<td>Healthcare provider education</td>
<td>Risk minimization</td>
</tr>
<tr>
<td>4. Minimization</td>
<td>Act to reduce risk</td>
<td></td>
</tr>
</tbody>
</table>


EU Pharmacovigilance Issues

- Committee for Medicinal Products for Human Use emphasizes need for PV to detect rare but serious adverse effects
- PV systems should differentiate between sources of biological products
- Need for traceability
- Need to submit a detailed description of the biosimilar PV system when submitting application for market authorization

EU Pharmacovigilance Issues

- Elements of the detailed description of PV:
  - Qualified person responsible for PV (QPPV)
  - Organizational structure (relevant to PV)
  - Documented procedures
  - Databases
  - Contractual arrangements to fulfill PV activities
  - Training of staff
  - Quality management system
  - Supporting documentation
# Biosimilar Case 1: Tevagrastim (i.e., tbo-filgrastim)

<table>
<thead>
<tr>
<th>Phase Study</th>
<th>XM02-02-INT</th>
<th>XM02-03-INT</th>
<th>XM02-04-INT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor type</td>
<td>Breast cancer</td>
<td>Lung cancer</td>
<td>Non Hodgkin Lymphoma</td>
</tr>
<tr>
<td>Intervention</td>
<td>Tbo vs. G-CSF vs. placebo</td>
<td>Tbo vs. G-CSF</td>
<td>Tbo vs. G-CSF</td>
</tr>
<tr>
<td>Mean duration of severe neutropenia (days)</td>
<td>1.1 vs. 1.1 vs. 3.8</td>
<td>0.5 vs. 0.3</td>
<td>0.5 vs. 0.9</td>
</tr>
<tr>
<td>Mean ANC nadir (10^6/L)</td>
<td>700 vs. 700 vs. 200</td>
<td>2100 vs. 2900</td>
<td>1700 vs. 1100</td>
</tr>
<tr>
<td>Mean time to ANC recovery (days)</td>
<td>8 vs. 7.8 vs. 14</td>
<td>6.3 vs. 4.5</td>
<td>6.0 vs. 6.7</td>
</tr>
<tr>
<td>Incidence of febrile neutropenia (%)</td>
<td>12.1 vs. 12.5 vs. 36.1</td>
<td>15 vs. 8.8</td>
<td>11.1 vs. 20.7</td>
</tr>
</tbody>
</table>

## EU Risk Management Plan

- Risks to track (most are routine):
  - Hypersensitivity, acute respiratory distress syndrome, Sweet’s syndrome, sickle cell crisis, exacerbation of rheumatoid arthritis, cutaneous vasculitis, splenic rupture/splenomegaly, increased graft-versus-host disease risk, osteoporosis, transformation to leukemia/myelodysplasia, myalgia, immunogenicity, heme malignancies in normal donors, off-label use
  - Most have “Routine PV” (+/- extra studies)
  - Routine risk minimization includes product labeling

- “The only area of uncertainty is the mobilization of peripheral blood progenitor cells”
  - Unknown whether the efficacy in oncology can be fully extrapolated to this area of use.
  - Due to the lack of complete understanding of the mechanism of peripheral blood progenitor cell mobilization
  - “This issue has now been satisfactorily addressed by the RMP.”

- RMP:
  - “Long-term safety follow-up of donors is ongoing. A risk of promotion of a malignant myeloid clone cannot be excluded. It is recommended that the aphaeresis centre perform a systematic record and tracking of the stem cell donors for at least 10 years to ensure monitoring of long-term safety.”
Biosimilar Case 2: Epoetin Zeta

- Clinical immunogenicity and clinical safety/efficacy
  - Double-blind, Phase 3 RCT in hemodialysis patients
    - Designed to address comparability
    - Comparable safety/efficacy
  - Open, non-controlled Phase III in patients with chemotherapy-induced anemia
    - It works, but RCT was not designed to address comparability


Biosimilar Case 2: Epoetin Zeta

EU Risk Management Plan

- Risks to track:
  - Pure red cell aplasia, VTE, tumor growth, general safety & long-term use
  - Risk-benefit assessment not considered positive for major orthopedic surgery indication (SC injection): no comparative studies with SC route
- Routine PV
- Extra:
  - "Prospective open non-controlled multi-centre study to evaluate safety and tolerability of epoetin zeta administered sc for the treatment of anaemia in cancer patients (CT-830-05-0009)"
  - "Post-authorisation cohort study of epoetin zeta for the treatment of renal anaemia (PMS-830-07-0043)"


Nomenclature Issues

- Naming should allow the practitioner to quickly understand the relationship between the biosimilar and reference product
- Use of same name for multiple sources of product may be problematic for PV purposes
- EU naming
  - Allows the biosimilar to use the same nonproprietary name as reference
  - Can lead to unmonitored substitution
  - UK has advised physicians to prescribe by brand name to prevent auto-substitution
- Can the use of codes help pharmacovigilance efforts?

FDA Guidance: Postmarketing Monitoring (for Safety)

- Important to assure safety
  - Consider risks seen in reference product
  - Are there any new safety concerns?
  - Population-based assessments gives larger N to identify rare safety concerns
  - PV might be mandatory for some products
- Biosimilar manufacturers should work with FDA early to discuss approach
- See current PV guidance documents by FDA

Pharmacovigilance: Challenges in the United States

- Traceability and attribution
  - Naming
  - Codes: National Drug Code vs. Healthcare Common Procedure Coding System
- Data
  - Prospective registries
  - Administrative claims
  - Electronic health records
  - Linked databases
- Beyond “routine” PV, what will be required of biosimilars?

Coding Issues: Claims Data

- NDA: Leuprolide Acetate (depot formulations)
  - Lupron Depot: intramuscular injection
  - Eligard: subcutaneous injection
  - 2013 HCPCS code:
    - J1950: Injection, leuprolide acetate (for depot suspension), per 3.75 mg
- BLA: Epoetin alfa
  - Procrit® and Epogen®
  - 2013 HCPCS codes:
    - J0885: Injection, epoetin alfa, (for non-ESRD use), 1000 units
    - J0886: Injection, epoetin alfa, 1000 units (for end on dialysis)

ESRD = End stage Renal Disease
Coding Issues

- Administrative claims data can be a useful source for pharmacovigilance
  - Used for many studies
  - Limitations in collecting outcomes exist
- Unable to differentiate between products (and sources) based on billing data
- Currently not a big deal because small molecules are considered equivalent
- How will current infrastructure handle different sources of biologics?

Pharmacist involvement in PV

- Must know the source of the product
  - Accurate patient records
  - Use technology and codes to facilitate
  - Naming issues
- ADR reporting (FDA MedWatch)
  - Burden of correct attribution is on the HCP
- Participation in studies/registries

EU Biosimilar Experience: Summary

Concerns about biosimilars
1. Low quality
2. Similar ≠ identical
3. Safety unknown
4. Postmarketing surveillance
5. Unsure of efficacy
6. Indications
7. Interchangeability

http://en.wikipedia.org/wiki/Keep_Calm_and_Carry_On

EU Biosimilar Experience

1. Biosimilars are high-quality products with strict regulations in manufacturing and scientific development.
2. Similar vs. identical debate is not unique to biosimilars (applies to each biologic for lot-to-lot comparability).
3. Safety data is required pre-approval (including immunogenicity).
4. Postmarketing surveillance seeks to identify residual concerns; not unique to biosimilars.
5. Efficacy comparison trials will use the most clinically sensitive endpoint.
6. Be aware of indication differences and extrapolate if appropriate (already done for lot-to-lot variations).
7. Interchange.


AudIENCE Polling Question

How do you think biosimilar pharmacovigilance programs will affect your daily workflow?

a. Minimally; it’s not a big deal.
b. Somewhat, but we are ready!
c. Great, another thing to do!
d. I hope this doesn’t become a REMS.
Pathways for Approval in the USA

**Drugs**
- Small-molecules
- Approved via FDCA†

**Biologics**
- Proteins
- Approved via PHSA¥

- **New Drug Application (NDA)**
  - Safety and Efficacy must be demonstrated

- **Abbreviated New Drug Application (ANDA)**
  - Bioequivalence must be demonstrated

- **Biologics License Application (BLA)**
  - Safety and Efficacy must be demonstrated

- **Biosimilar Biologics License Application**
  - Must demonstrate that it is highly similar to reference

**Interchangeable biosimilars require more data**

†FDCA = Federal Food Drug and Cosmetic Act
¥PHSA = Public Health Service Act

Biosimilar Development Approach

- **Develop highly similar biologic**
  - Analytical methods for structure/function
  - Cell line analyses
  - In vitro/vivo models
  - Substance pilot and final scale analyses
  - Formulation and final drug product analyses

- **Test and confirm biosimilarity**
  - Human clinical trials
  - Consideration of clinically sensitive endpoints
  - Clinically sensitive patient populations
  - Immunogenicity
  - Efficacy and safety

Post-Marketing Monitoring

- EU Guidance and risk management plans
- FDA consultation about proposed approach
- May be mandatory

Test and confirm Interchangeability

- No explicit FDA guidance
- Will be “difficult” to do in the initial 351(k) application

Ben Firschein, J.D., LL.M.
Director, Government Affairs and Policy
United States Pharmacopeial Convention (USP)
Rockville, Maryland

Ben Firschein, J.D., LL.M., is Director of Government Affairs and Policy for the United States Pharmacopeial Convention (USP), an independent, nonprofit global scientific organization that sets standards for drugs, dietary supplements, and food ingredients. In this role he works closely with policymakers to foster an appreciation of the value of public standards in helping to assure quality care and drug and food purity.

Prior to coming to USP, Mr. Firschein served as Legislative Director and Counsel in the United States House of Representatives and as staff to committees of the California State Legislature.

Mr. Firschein received his Bachelor of Arts degree in social sciences from the University of California, Berkeley. He received his Juris Doctor degree in law from the Columbia University School of Law in New York, New York and a Masters of Law degree in law and government from the American University in Washington, D.C. He is admitted to practice law in Washington, D.C.
Update on State Biosimilar Legislation

Ben Firschein, J.D., LL.M.
Director, Government Affairs and Policy
The United States Pharmacopeial Convention (USP)
Rockville, Maryland

Topics
- Federal law’s role in state bills
- Status of state legislation
- Common elements in state legislation
- Where is this going? How can pharmacists prepare?
- Polling questions (Review)

Audience Polling Question
What State are you from?
- Florida, North Dakota, Oregon, Utah, Virginia.
- California.
- Another State.
What State are you from?

a. Florida, North Dakota, Oregon, Utah, Virginia – All have enacted legislation on biosimilars.

b. California – Vetoed bill on biosimilars.

c. Arizona, Arkansas, Colorado, Delaware, Illinois, Indiana, Maryland, Massachusetts, Mississippi, Pennsylvania, Texas, Washington State – Biosimilars proposals died or pending.

d. Another State – No proposals yet.

State Proposals Are Driven By BPCI Act...

- The healthcare reform law amended the Public Health Service (PHS) Act to create an additional approval pathway targeted specifically at biosimilar and interchangeable biological products (the Biologics Price Competition and Innovation Act of 2009, or BPCI Act):
  - Allows the submission of a biologics license application (BLA) for a biosimilar or interchangeable biological
  - Requires a biosimilar applicant to demonstrate that there are no clinically meaningful differences in safety, purity, and potency between a biosimilar product and a reference product
  - Allows approval by FDA of a biosimilar product as “interchangeable,” as specified

State Proposals Are Driven By BPCI Act...Definitions (from BPCI):

- “Biological Product” defined as
  - “a virus, ... vaccine, blood, ... protein (except any chemically synthesized polypeptide), or analogous product, ... applicable to the prevention, treatment, or cure of a disease or condition of human beings.”

- “Biosimilar” means:
  - “highly similar to the reference product notwithstanding minor differences in clinically inactive components,” and “no clinically meaningful differences” in terms of “safety, purity and potency”

- “Interchangeable” biosimilar means a biosimilar that:
  - “can be expected to produce the same clinical result” in “any given patient,” and (if administered more than once) has no greater risk “in terms of safety or diminished efficacy” than the reference product
State Proposals Are Driven by BPCI Act

- As FDA continues work on implementing BPCI Act, States have been considering proposals to restrict substitution of biologic medications that are deemed similar/interchangeable, but have not been cleared for marketing by FDA as literally being “generic” in the FD&C Act sense
- Supporters of state proposals believe the ultimate decision on substitution should be left to the patient’s prescribing physician
- Opponents believe state proposals are restrictive/inconsistent with forthcoming national standards

Status of State Legislation

- Enacted
  - Florida, HB 365 (2013), Chapter 2013-102
  - North Dakota, SB 2790 (2013)
  - Oregon, SB 460 (2013), Chapter 342, 2013 Laws
    https://olis.leg.state.or.us/LIZ/2013R1/Measures/Text/SB0460/Enrolled (contains sunset clause)
  - Utah, SB 76 (2013),
    http://le.utah.gov/~2013/bills/sbills/sb0076.pdf (contains sunset clause)

- Other
  - California, SB 598 (2013) - vetoed
  - Arizona, SB 1439 (2013) - died
  - Arkansas, SB 149 (2013) - died
  - Colorado, House Bill 13-121 (2013) - died
  - Delaware, SB 116 (2013) - died
  - Illinois, SB 1934 (2013) - died
  - Indiana, SB 372 (2013) - died
  - Maryland, SB 781 (2013) - died
  - Massachusetts, H. 1927 (2013) - pending
  - Mississippi, SB 2085 (2013) - died
  - Pennsylvania, SB 405 (2013) - pending
  - Texas, SB 190 (2013) - died
  - Washington State, SB 5469 (2013) - died
California Governor’s Veto Message

Senate Bill 598 would effect two changes to our state’s pharmacy law. First, it would allow interchangeable “biosimilar” drugs to be substituted for biologic drugs, once these interchangeable drugs are approved by the federal Food and Drug Administration (FDA).

This is a policy I strongly support.

Second, it requires pharmacies to send notifications back to prescribers about which drug was dispensed. This requirement, which on its face looks reasonable, is for some reason highly controversial. Doctors with whom I have spoken would welcome this information. CaPERS and other large purchasers warn that the requirement itself would cast doubt on the safety and feasibility of these cost-effective alternatives to biologics.

The FDA, which has jurisdiction for approving all drugs, has not yet determined what standards will be required for biosimilars to meet the higher threshold for “interchangeability.” Given this fact, to require physician notification at this point strikes me as premature.

For these reasons, I am returning SB 598 without my signature.

Sincerely,


See enlargement p. 31

Common Elements in State Bills

- Definitions from BPCI/FDA
  - Biological Product
  - Biosimilar
  - Interchangeable biosimilar (so far, FDA has received no biosimilar applications, therefore no interchangeability requests either)

(continued)

- Prescriber preference
- Patient choice: notification of patient/prescriber if substitution occurs
- Labeling
- Recordkeeping (years required vary by state)
- Pricing (not more than product originally prescribed)
- Liability protections
- List of substitutable products (State Board of Pharmacy)
Where Is This Going?..Considerations

- Veto of California bill may have slowed down legislative activity- California a bellwether; more negotiation may take place nationally between supporters/opponents
- Is there a need to reconcile biosimilar substitution with existing state laws on substitution of generic drugs (although very existence of BPCI underscores similar and interchangeable biologics are not classified as "generic")?
- Are Federal/State roles in practice of medicine and pharmacy affected by BPCI or further FDA guidance? (Reminiscent of compounding issue)

How Can Pharmacists Prepare?

- Familiarize yourself with applicable laws (see handout- a reference and resource list will be provided)
- Much may hinge on future FDA determinations of biosimilarity and interchangeability– not expected soon; additionally, some laws are being adopted with sunset clauses and may expire in whole or in part before applications/determinations occur
- Closely follow your State Board of Pharmacy’s guidance
- Pharmacy/healthcare organizations are a good resource for updates

Audience Polling Question

What States have enacted legislation on biosimilars?

c. Florida, North Dakota, Oregon, Utah, Virginia.
d. Kansas, Massachusetts, Nebraska, Wyoming.
What States have enacted legislation on biosimilars?

Answer:

c. Florida, North Dakota, Oregon, Utah, Virginia.

State Biosimilars Legislation Covers What Areas?

a. Definitions (e.g. "interchangeable"), prescriber preference, notification of patient/prescriber, labeling, recordkeeping, pricing, liability protections, list of substitutable products.

b. Packaging, naming, procedures for preparation, pharmacy inspection, supply chain.

c. Licensing, certification, discipline for violations, appeals.

d. Confidentiality, enforcement.
So far, how many biologic drugs have been determined by FDA to be interchangeable under BPCI?

a. 5.
b. 2.
c. 1.
d. 0.

**Answer**
d. 0.
Status of State Legislation

• Enacted
  – Florida, HB 365 (2013), Chapter 2013-102
    http://www.flsenate.gov/Session/Bill/2013/0365/BillText/er/PDF
  – North Dakota, SB 2190 (2013)
  – Oregon, SB 460 (2013), Chapter 342, 2013 Laws,
    https://olis.leg.state.or.us/LIZ/2013R1/Measures/Text/SB0460/Enrolled (contains sunset clause)
  – Utah, SB 78 (2013),
    http://le.utah.gov/~2013/bills/sbiller/sb0078.pdf (contains sunset clause)
  – Virginia, SB 1285, (2013), Chapter 544 (contains sunset clause),
    http://lis.virginia.gov/cgi-bin/legp604.exe?131+ful+CHAP0544

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Senate Bill 598 would effect two changes to our state’s pharmacy law. First, it would allow interchangeable “biosimilar” drugs to be substituted for biologic drugs, once these interchangeable drugs are approved by the federal Food and Drug Administration (FDA). This is a policy I strongly support.

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The FDA, which has jurisdiction for approving all drugs, has not yet determined what standards will be required for biosimilars to meet the higher threshold for “interchangeability.” Given this fact, to require physician notification at this point strikes me as premature.

For these reasons, I am returning SB 598 without my signature.

Sincerely,

[Signature]

Edmund G. Brown Jr.

James G. Stevenson, Pharm.D., FASHP
Chief Pharmacy Officer
University of Michigan Health System
Professor and Associate Dean for Clinical Sciences
University of Michigan College of Pharmacy
Ann Arbor, Michigan

James G. Stevenson, Pharm.D., FASHP, is Chief Pharmacy Officer at the University of Michigan Health System, as well as Professor and Associate Dean for the Department of Clinical Sciences at the University of Michigan College of Pharmacy.

Dr. Stevenson received his Bachelor of Science and Doctor of Pharmacy degrees from Wayne State University in Detroit, Michigan. He then joined the faculty at the West Virginia University School of Pharmacy in Morgantown.

Dr. Stevenson’s previous appointments include Director of Pharmaceutical Services at West Virginia University Hospitals, Director of Pharmacy Services at Detroit Receiving Hospital and University Health Center, Director of the Graduate Program in Health Systems Pharmacy Management in the Wayne State University College of Pharmacy, and Executive Director of Pharmacy Services for the Detroit Medical Center.

Dr. Stevenson will receive the Award for Distinguished Leadership in Health-System Pharmacy Practice at the 48th Midyear Clinical Meeting, December 2013. The Award for Distinguished Leadership in Health-System Pharmacy Practice recognizes the contributions of practitioners who have achieved excellence in health-system pharmacy practice leadership. He is a Fellow of the American Society of Health-System Pharmacists (ASHP) and has been recognized as Pharmacist of the Year by both the Michigan Society of Health-System Pharmacists and the Michigan Pharmacists Association. He has also been honored with the Distinguished Alumnus Award by the Wayne State University College of Pharmacy and the Joseph Oddis Leadership Award by the Michigan Society of Health-System Pharmacists. He recently completed a term of service on the ASHP Board of Directors and received the John W. Webb Lecture Award in 2010. In 2012, Dr. Stevenson was appointed to the Michigan Board of Pharmacy.

Dr. Stevenson’s major research interests include pharmacy practice management, pharmacoeconomics, pharmacy informatics, and medication safety.
Preparing for the Introduction of Biosimilars: What Pharmacists and Pharmacy and Therapeutics Committees Need to Know

James G. Stevenson, Pharm.D., FASHP
Chief Pharmacy Officer
University of Michigan Health System
Professor and Associate Dean for Clinical Sciences
University of Michigan College of Pharmacy
Ann Arbor, Michigan

Topics

- Evaluation of biosimilars vs. reference products
- Factors for formulary consideration
- Strategies and challenges in integrating biosimilars into the health-system medication-use process
- Considerations at transitions of care
- Importance of pharmacovigilance

Types of Biologics

<table>
<thead>
<tr>
<th>Description</th>
<th>Reference</th>
<th>Biosimilar</th>
<th>Interchangeable Biosimilar</th>
<th>Full BLA Copy</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-to-market biologic</td>
<td>N/A</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>molecule approved by full</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLA pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly similar to reference</td>
<td>N/A</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>product approved via the</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abbreviated biosimilars</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biosimilar deemed</td>
<td>N/A</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>interchangeable that can be</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>substituted for the</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>reference product</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without permission from</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prescriber</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approved via the full</td>
<td>N/A</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>BLA pathway; &quot;Biobetters&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Depth of data submitted to the FDA

<table>
<thead>
<tr>
<th>Standard data package</th>
<th>Abbreviated data package</th>
<th>Abbreviated data package, more information on efficacy and safety of switching</th>
<th>Standard data package</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Compared to reference?

- N/A
- Yes
- Yes
- Not necessarily

Current examples in USA

- None
- None
- N/A/Not available

See enlargement p. 44
Potential Differences Between Biosimilar and Reference Product

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

Financial Drivers for Biosimilar Use

- Average biologic cost of > $34K per year
- Payers expected to drive utilization through reimbursement policies, co-payment or co-insurance tiers
- Payers/P&T Committees will need to address use for off-label indications
- Innovator companies expected to offer payers/providers quantity/market-share discounts

Pharmacy Practice Implications

- Generic substitution may not be appropriate for biosimilars, but therapeutic equivalence programs are likely within health systems
- Pharmacists will need to lead evaluation of biosimilars for formulary inclusion
  - Range of indications
  - Therapeutic equivalence
  - Process for interchange within health systems
  - Information systems to enable pharmacovigilance


Financial Drivers for Biosimilar Use

Considerations for Formulary Inclusion of Biosimilars

<table>
<thead>
<tr>
<th>Efficacy/Safety</th>
<th>Manufacturer Considerations</th>
<th>Product Considerations</th>
<th>Hospital and Patient Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical data</td>
<td>• Supply reliability</td>
<td>• Product packaging and labeling</td>
<td></td>
</tr>
<tr>
<td>• Range of indications</td>
<td>• History of drug shortages</td>
<td>• Bedside bar coding</td>
<td></td>
</tr>
<tr>
<td>• Immunogenicity concerns</td>
<td>• Supply chain security</td>
<td>• Compatibility with CSTDs*</td>
<td></td>
</tr>
<tr>
<td>• Potential for therapeutic interchange</td>
<td>• Anti-counterfeit measures</td>
<td>• Robotics</td>
<td></td>
</tr>
<tr>
<td>• Number of similar agents on formulary</td>
<td>• Patient assistance programs</td>
<td>• Product preparation and administration</td>
<td></td>
</tr>
<tr>
<td>• Pharmacovigilance requirements</td>
<td>• Reimbursement support</td>
<td>• Storage requirements</td>
<td></td>
</tr>
</tbody>
</table>

* CSTDs = closed system transfer devices

Major Challenges for P&T Committees with Biosimilars

• If approved for a specific indication, will use be allowed for other indications?
• Decisions around product naming critical to provide clarity when ordering, prevent errors, ensure traceability, and enable P&V
• Evaluation of overall economic impact of use of biosimilars
  – Combined inpatient and outpatient impact
  – Challenges of portfolio pricing
  – Impact on patient out-of-pocket expense

Biosimilar Economic Evaluation

• Step 1: clinically evaluate the biologic/biosimilar → which product do you propose to use and in which populations/indications
• Step 2: estimate market share/volume of each product and gather acquisition pricing information based on projected market share/volume
• Step 3: estimate margin (outpatient) and/or cost savings (inpatient) based on pricing/reimbursement to calculate total economic impact
• Step 4: consider patient out-of-pocket cost
• Step 5: consider formulary conversion/management costs

See enlargement p. 44
Which of the following best describes your institution's approach to economic analysis?

a. Only the cost of the drug is considered.
b. Both the cost (inpatient) and the margin (outpatient) are considered.
c. A combination of cost, margin, and patient impact is considered.
d. Don’t know or not involved in this aspect.

Major Challenges for P&T Committees with Biosimilars

• How many “similar” products to carry on the formulary
  – Desire to minimize switching
    • Reduced chance for error
    • Avoid potential immunogenicity problems
  – Analogy with generic immunosuppressants in transplant recipients?

Audience Polling Question

How many products do you anticipate including on your formulary for a similar biologic?

a. Only the reference product.
b. Only the biosimilar.
c. Both the reference product and the biosimilar.
d. The reference product and multiple biosimilars.
Audience Polling Question

What do you anticipate your approach will be to a biosimilar that has fewer indications than the reference product?

a. Only use the biosimilar for indications for which it is approved.
b. Use the biosimilar for all indications for which the reference product is currently used.
c. Use the biosimilar for all indications for which it is approved plus some selected indications for which it is not approved.
d. Will not use a biosimilar.

Generic or Therapeutic Substitution Policy

• ASHP Guideline definitions:
  – Generic equivalents: drugs considered to be bioequivalent by FDA
  – Therapeutic equivalents: products differing in composition or drug entity considered to have similar therapeutic profile
• Best Practices:
  – Pharmacist is responsible for product selection (pursuant to the order)
  – Prescriber opt-out (justification must be scientifically and clinically sound)
• Address interchangeable biosimilar requirements (if state law allows) or utilize therapeutic equivalence

Therapeutic Interchange for Biosimilars

• FDA categorization as “interchangeable biosimilar” or “biosimilar”
  – Potential impact of state laws on implementation
• Prepare a monograph for the biosimilar and policy for review by the P&T committee
  – Describe the data comparing the biosimilar with reference product
  – Expected outcomes
    – Clinical: efficacy, safety, immunogenicity
    – Economic
• Many examples:
  – Non-biologics: analgesic, anti-infective, cardiovascular, CNS, GI
  – Biologics: Insulins, IV/G, Erythropoietic stimulating proteins

Therapeutic Interchange for Biosimilars

Explicit review of similarity data by the FDA will make interchange decisions easier for these indications

Expected level of scrutiny by P&T committee

- Full BLA copy or approval
  - Efficacy, safety (immunogenicity), financial
  - Consider appropriate indications

- Non-interchangeable Biosimilar
  - Efficacy, safety (i.e., immunogenicity), financial
  - Consider appropriate indications (non-approved vs non-addressed)

- Interchangeable Biosimilar
  - Consider range of indications, state laws, financial

Use of the Formulary System to Manage Biosimilars

- Tools
  - Generic substitution policy
  - Therapeutic interchange policies
  - Guided-use policies
  - Clinical practice guidelines
  - Off-label policies
  - Medication use evaluations

- Implementation
  - Education
  - Communication
  - Technology

Therapeutic Interchange

- Therapeutic interchange “provides pharmacists with the authorization to use a formulary therapeutic alternative in place of a non-formulary medication or a non-preferred formulary medication”
  - Automatic or with prescriber pre-notification
  - Notification is done in a systematic manner

- Appropriate for drugs with different chemical structures and similar safety/efficacy profile

- Endorsed by PhRMA and AMA

- Guidelines available from the American College of Clinical Pharmacy

References:
Therapeutic Interchange Challenges

- Biosimilarity (and interchangeability) data may not be available for all indications
  - May need to extrapolate; or
  - Limit use to specific indications
- Transitions of care
  - Risk of immunogenicity
  - Patient cost burden/preference
  - Prescriber preference

Guided-Use Policy (GUP) Considerations

- More narrow than an across-the-board Therapeutic Interchange
- Specific tools:
  - Established-use policy
  - Restricting use to a service
  - Limiting use to specific prescribers
  - Prior approval of medical director
- Many biologics already have GUPs

Established-Use Policy for the Biosimilar

- Patient must meet established criteria for use
- Criteria can be based on:
  - Indication
  - Patient’s history of use of that biologic
- Example (hypothetical):
  - Rituximab biosimilar for de novo patients
  - Reference rituximab for patients already on the drug
Restrict Use of the Biosimilar or Reference Product by Service

- Restricted to a specific service (e.g., hematology/oncology), or approval
- Potential tool if service lines disagree
- Example:
  - Rituximab is used in many disease areas: heme/onc, rheumatology
  - Hypothetically use biosimilar rituximab for rheumatology orders and reference rituximab for heme/onc

Limit Use of the Biosimilar to Specific Providers

- Commonly used for chemotherapy
- More restrictive than restricting by service line
- Many of the anti-cancer biologics fall under chemotherapy already
- Hypothetical example: only heme/onc attending physicians are allowed to order reference rituximab

Require Prior Approval of Medical Director

- Often used for high-cost medications or for non-formulary agents
- Example: situation where the attending physician wishes to “opt-out” of an interchange program and use the reference product
Audience Polling Question

Which of the following are tools that you may use for incorporating biosimilars into your institution?

a. Restricted use policies.
b. Therapeutic interchange.
c. Guided use policies.
d. All of the above.

Post-Marketing Surveillance

- Pharmacovigilance activities essential in order to further assess ongoing safety and immunogenicity
- Major responsibility for pharmacists and practicing clinicians to identify and report potential safety/immunogenicity concerns
- Naming convention for biosimilars is a concern for effective reporting (must be able to differentiate specific product)
- Importance of configuring IT systems to be able to track specific products

Recommendations For Biosimilars in Health Systems

- Utilize existing formulary system and processes to evaluate for formulary inclusion
- Carefully consider scope of indications for use
- Conduct sophisticated economic analysis considering costs and reimbursement, patient impact
- Plan for therapeutic equivalence and guided use policy 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

- ASHP Resource Center on Biosimilars
- ASHP Advantage Site
  - http://www.ashpadvantage.com/biosimcentral/
- American Journal of Managed Care Resource Center

Conclusion

- Biosimilars present significant opportunities and challenges for pharmacists managing formularies and patient care
- A framework for biosimilar introduction has existed in Europe and is being defined in the US
- Pharmacists must educate themselves to be prepared to play leadership roles in the safe and appropriate introduction of biosimilars into health systems
- Existing principles of sound formulary management can be applied to biosimilars
Types of Biologics

<table>
<thead>
<tr>
<th>Description</th>
<th>Reference</th>
<th>Biosimilar</th>
<th>Interchangeable Biosimilar</th>
<th>Full BLA Copy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>First-to-market biologic molecule, approved by full BLA pathway</td>
<td>“Highly similar” to reference product; approved via the abbreviated biosimilars pathway</td>
<td>A biosimilar deemed interchangeable that can be substituted for the reference product without permission from prescriber</td>
<td>Approved via the full BLA pathway; “Biobetters”</td>
</tr>
<tr>
<td>Depth of data submitted to the FDA</td>
<td>&quot;Standard&quot; data package</td>
<td>Abbreviated data package</td>
<td>Abbreviated data package, more information on efficacy and safety of switching</td>
<td>“Standard” data package</td>
</tr>
<tr>
<td>Compared to reference?</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
<td>Not necessarily</td>
</tr>
<tr>
<td>Current examples in USA</td>
<td>None</td>
<td>None</td>
<td>Tbo-filgrastim</td>
<td></td>
</tr>
</tbody>
</table>

Considerations for Formulary Inclusion of Biosimilars

- Efficacy/Safety
- Manufacturer Considerations
- Product Considerations
- Hospital and Patient Factors

* CSTDs = closed system transfer devices
References & Suggested Readings

21 C.F.R. 600.3. [http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=6b7fc67bc5c5eb7e826639e3aa2114ab&ty=HTML&h=L&r=PART&n=21y7.0.1.1.1#21:7.0.1.1.1.1.1.2](http://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=6b7fc67bc5c5eb7e826639e3aa2114ab&ty=HTML&h=L&r=PART&n=21y7.0.1.1.1#21:7.0.1.1.1.1.1.2), (access 2013 Nov 7).


Biosimilars: An Update on Scientific, Legislative, and Safety Issues


2011; 29:690-3.

2011; 9(suppl 4):S1-22.


**Other Resources**

ASHP Biosimilars Resource Center  
http://www.ashp.org/menu/PracticePolicy/ResourceCenters/Emerging-Sciences/Biosimilars.aspx

ASHP Advantage Preparing for Biosimilars: Scientific, Regulatory, and Practice Management Issues for Pharmacists initiative  
http://www.ashpadvantage.com/biosimcentral/

*American Journal of Managed Care* Biosimilars Website  
http://www.ajmc.com/resource-center/biosimilars

Lucio SD, Stevenson JG, Hoffman JM. Biosimilars: implications for health-system pharmacists.  

Silverman E. Controversial biosimilar legislation heats up in California, August 22, 2013.  
Self–Assessment Questions

1. According to the Food and Drug Administration, which of the following characteristics of biosimilars and reference (innovator) products must be the same?
   a. Formulation.
   b. Delivery device.
   c. Strength.
   d. Container.

2. Which of the following is the greatest safety concern associated with biosimilars?
   a. Transformation to leukemia.
   b. Immunogenicity.
   c. Anemia.
   d. Myalgia.

3. Which of the following laws established the abbreviated pathway for approval of biosimilars in the United States?
   a. Affordable Care Act.
   d. Public Health Service Act.

4. The level of scrutiny by the pharmacy and therapeutics committee is least for
   a. A non-interchangeable biosimilar.
   b. An interchangeable biosimilar.
   c. A “biobetter” approved via the full biologics license application pathway.
   d. A reference (innovator) biological product.

Answers

1. c
2. b
3. b
4. b