Biosimilars in the United States: Critical Updates for Pharmacists

Presented as a Midday Symposium and Live Webinar at the 49th ASHP Midyear Clinical Meeting and Exhibition

Monday, December 8, 2014
Anaheim, California

Planned and conducted by ASHP Advantage and supported by an educational donation provided by Amgen.
Please be advised that this activity is being audio and/or video recorded for archival purposes and, in some cases, for repurposing of the content for enduring materials.
Agenda

11:30 a.m. – 11:40 a.m.  Welcome and Introduction  
Edward Li, Pharm.D., BCOP

11:40 a.m. – 12:00 p.m.  There and Back Again: Comparability of Biological Products vs. Small-Molecule Drugs  
Ali McBride, Pharm.D., M.S., BCPS, BCOP

12:00 p.m. – 12:25 p.m.  Biosimilars: Current Activity at the National and State Level and the Debate and Implications of Naming Biosimilars  
Philip E. Johnson, M.S., B.S.Pharm., FASHP

12:25 p.m. – 12:50 p.m.  Considerations for Using Biosimilars in Practice: Pharmacist Substitution, Indication Extrapolation, and Pharmacovigilance  
Edward Li, Pharm.D., BCOP

12:50 p.m. – 1:00 p.m.  Panel Discussion: Questions and Answers

Food and beverage are no longer provided at Midday Symposia. This ASHP policy considers the varied internal policies of commercial supporters related to the Physician Payments Sunshine Act.
Faculty

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

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Premier Inc.
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Disclosure Statement

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- Edward Li, Pharm.D., BCOP has served as an advisory board member for Amgen and Hospira and speaker for Amgen and Pfizer.
- Ali McBride, Pharm.D., M.S., BCPS, BCOP has served as an advisory board member for Hospira and Amgen
- All other faculty and planners report no financial relationships relevant to this activity.
Activity Overview

In light of the impending arrival of biosimilars in the United States, this timely educational activity will briefly review the processes used to produce biologics compared with traditional drug products. An in-depth overview of the current legislative status of biosimilars in the United States and abroad will be presented. The activities will cover in depth the scientific and legislative issues associated with biosimilars. Patient safety concerns will be reviewed and the roles that pharmacists can assume in pharmacovigilance programs will be described. Expert faculty will also address factors to consider with respect to the interchangeability of biosimilars, indication extrapolation, as well as explain key considerations in naming biosimilars, including the long-term ramifications.

Learning Objectives

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

- Describe how the process of manufacturing biological agents differs from the process for manufacturing traditional small-molecule drugs.
- Discuss the current status of biosimilars in the United States, including recent activity by the FDA, state and federal legislators, and other agencies on the approval of these agents.
- Assess the factors to consider with respect to the interchangeability of biosimilars and pharmacist substitution or interchange of biological products.
- Develop a conceptual framework during the formulary review process that considers appropriate off-label indications for biosimilars.
- Explain the rationale for and key components of a successful pharmacovigilance program, including roles the pharmacist can assume in ensuring success.

Your educational opportunities related to biosimilars in the United States extend beyond today’s symposium...

- Available in 2015
  - On-demand activity based on today’s live symposium (1.5 hours of CPE, please note that individuals who claim CPE credit for the live symposium or webinar are ineligible to claim credit for the on-demand activity)

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

www.ashpadvantage.com/biosiminfo
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 1.5 hours (0.15 CEUs – no partial credit) of continuing pharmacy education credit (ACPE activity #0204-0000-14-711-L04-P for the live activity and ACPE activity #0204-0000-14-711-H04-P for the on-demand activity).

Complete instructions for receiving your statement of continuing pharmacy education credit online are on the next page.

Webinar Information

Visit [http://ashpadvantagemedia.com/biosiminfo/webinar](http://ashpadvantagemedia.com/biosiminfo/webinar) to find
- Webinar registration link
- Group viewing information and technical requirements

**ACTION REMINDER EMAIL**

Have ideas about what YOU want to remember to do as a result of what you are learning in this educational session? Use the Action Reminder tool via your smart device, and you will be sent an email reminder from YOURSELF next month.

If you do not have a smart device, access the Action Reminder for this activity at [http://www.ashpadvantage.com/go/biosiminfo/remindme](http://www.ashpadvantage.com/go/biosiminfo/remindme)
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1. Access the e-Learning site at http://elearning.ashp.org/my-activities

2. If you already have an ASHP account, log in using your username and password.

   If you do not have an ASHP account, click on the Register link and follow the registration instructions. You do not have to be a member to create an account.

For Midyear Attendees in Anaheim

- Once logged in, select “Conferences” and click on the conference name under Your Conferences.

- Under Add Sessions enter your attendance code announced during the activity, and click Submit.

  Helpful Tip: If your code is not redeeming successfully, verify that you have clicked on the title of your conference to access the Attendance Code field, not the Enrollment Code field.

- Each session will be listed under Your Sessions. Click Claim Credit for a particular session.

- Complete any requirements for each session by clicking on the name of the activity and following the instructions.

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- Once logged in, enter the enrollment code (announced during the webinar) into the “ENROLLMENT CODE” box for the activity and click Redeem.
Biosimilars in the United States: Critical Updates for Pharmacists

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- Complete all required elements. A green check should appear as each required element is completed. You can now claim your credit.

3. 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 do not see your profession listed.

4. 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.

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**NEED HELP? Contact eLearning@ashp.org**

<table>
<thead>
<tr>
<th>Date of Activity:</th>
<th>Code:</th>
<th>CPE Hours:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday December 8, 2014</td>
<td>- - - - -</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Edward Li, Pharm.D., BCOP, *Activity Chair*
Associate Professor
Department of 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.
Philip E. Johnson, M.S., B.S.Pharm., FASHP
Director of Oncology
Premier Inc.
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Philip E. Johnson, M.S., B.S.Pharm., FASHP is the Oncology Director for Premier Inc. Mr. Johnson received Bachelor of Science degrees in pharmacy and chemistry at the University of Illinois, and a Master of Science in Administration and Organizational Development degree at George Williams College.

Previously he served for 26 years as the founding Director of Pharmacy, and later the Pharmacy Advocacy Director at the Moffitt Cancer Center and Research Institute, a National Cancer Institute (NCI) Designated Comprehensive Cancer Center at the University of South Florida in Tampa. During his career he has opened three new hospitals where he developed patient focused, multidisciplinary services that focus on quality, safety, and financial outcomes. Mr. Johnson has faculty appointments with several colleges of pharmacy, has served as Assistant Dean for the University of Florida Tampa Bay College of Pharmacy program and the steering committee to establish the University of South Florida College Of Pharmacy. Mr. Johnson has numerous publications and was a contributing editor to AJHP. He has served on more than 40 advisory boards and committees of professional organizations. He was a founding Director of the Florida Cancer Pain Initiative (FCPI), and the Hematology Oncology Pharmacy Association (HOPA) which he served as President. Mr. Johnson had a gubernatorial appointment to the Florida Department of Health serving as Chairman of the Drug Wholesaler Distribution Advisory Committee (DWDAC) that oversees Florida drug pedigree legislation. He represents ASHP on the American Hospital Association (AHA) Committee on Clinical Leadership, has served on guidelines committees for the Association of Community Cancer Centers (ACCC) and HOPA, has chaired the National Comprehensive Cancer Network (NCCN) taskforce on REMS, and chaired the Institute for Safe Medication Practices (ISMP) international taskforce to develop an oncology medication self-assessment tool. Mr. Johnson is the pharmacist representative to the Florida School Health and Education Consortium (SHEC) where he focuses on medication safety and compliance in our nation’s school systems, an effort that has been grant funded, and was awarded an ISMP Cheers Award. He is also a Founding Partner for Safe School Meds (SSM) that is dedicated to improving the use of medication in school systems.

Mr. Johnson is actively involved with developing education programs that address professional leadership and was the lead faculty member for the ASHP Foundation, Pharmacy Leadership Academy module on Leading People.
Ali McBride, Pharm.D., M.S., BCPS, BCOP
Clinical Coordinator, Hematology/Oncology
Department of Pharmacy
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Tucson, Arizona

Ali McBride, Pharm.D., M.S., BCPS, BCOP, is Clinical Coordinator, Hematology/Oncology, in the Department of Pharmacy at the University of Arizona Cancer Center in Tucson, Arizona. Dr. McBride earned his Bachelor in Science in Neurobiology and Physiology from Purdue University, a Master of Science in Biochemistry from Indiana University-Purdue University at Indianapolis, and his Doctor of Pharmacy Degree from the University of Arizona. He completed his PGY-1 residency at Carl T. Hayden VA in Phoenix and his PGY-2 residency at the H. Lee Moffitt Cancer Center. Dr. McBride is a board-certified pharmacotherapy specialist and a board-certified oncology pharmacist.

Previously he served as a stem cell transplant pharmacist at The Arthur G. James Cancer Hospital and Richard J. Solove Research Institute at The Ohio State Medical Center and as the hematologic malignancies/stem cell transplant pharmacist at Siteman Cancer Center at Barnes-Jewish Hospital.

He has been actively involved with the Association of Community Care Centers (ACCC), Missouri Society of Health-System Pharmacists (MSHP), the American Society of Health-System Pharmacy (ASHP) and the Hematology Oncology Pharmacy Association (HOPA). Dr. McBride has been engaged in advocacy with ASHP and has served on the ASHP Student Forum, The ASHP Council on Administrative Affairs, the ASHP New Practitioner Forum serving on both the Science and Research Group and the Communication and Technology Advisory Group after graduation. He currently serves on the ASHP Section Advisory Group on Emerging Sciences and the ASHP Council on Therapeutics.
There and Back Again: Comparability of Biological Products vs. Small-Molecule Drugs

Ali McBride, Pharm.D., M.S., BCPS, BCOP
Clinical Coordinator, Hematology/Oncology
Department of Pharmacy
University of Arizona Cancer Center
Tucson, Arizona

Topic
- Differences in manufacturing biological agents vs. manufacturing traditional small-molecule drugs.

Which of the following molecules would not be considered an agent for which a biosimilar could be developed?

a. Trastuzumab
b. Filgrastim
c. Rituximab
d. Lovastatin
Small Molecule Drugs

• A small molecule is a low molecular weight compound
  – Less than 900 daltons
• Mechanism of action
  – Often binds to a specific effector
    • Protein
  – Inhibit a specific function or signaling mechanism


Chemical Structure of Small Molecules


Hatch-Waxman Amendments to Federal Food Drug and Cosmetic Act (FDCA)- 1984

• Considered one of the most successful pieces of legislation ever passed
• Created the generic drug industry
• Increased availability of generics
  • 1984 12% prescriptions were generic
  • 2000 44% prescriptions were generic
  • 2012 80% prescriptions were generic

FDA. Facts about Generic Drugs. Updated: 09/19/2012.
Hatch-Waxman Amendments to FDCA- 1984

- Allowed generic firms to rely on findings of safety and efficacy of innovator drug after expiration of patents and exclusivities (do not have to repeat expensive clinical and pre-clinical trials)
- A generic must have the same indications, strength, purity and quality as the original product.
- It must be prepared in the same formulation and be bioequivalent

Generic Requirements

- Components and composition
- Manufacturing and controls
- Batch formulation and records
- Specifications
- Packaging
- Bioequivalence

Manufacturing of Small Molecules

1. Comprised of the addition of chemicals and reagents
2. Developed products based on a series of controlled and predictable chemical reactions
3. Production is the same as the innovator product
4. Process is standardized
5. Contaminants are quantifiable
**Chemical Synthesis of Aspirin**

![Chemical Synthesis of Aspirin](image)

**Small Molecule Drugs**

![Small Molecule Drugs](image)

**Biologic Agents**

- Monoclonal antibodies
- Complex sugars
- Blood derivatives
- Vaccines
- Recombinant or purified proteins
  - Cytokines
  - Thrombolytic agents
  - Enzymes
### Biologic Agents

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human insulin</td>
<td>Several</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Interferons: α, β, γ</td>
<td>Several</td>
<td>Several</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Procrit, Epogen, Aranesp</td>
<td>Anemias</td>
</tr>
<tr>
<td>Darbepoetin alfa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Neupogen, Neulasta, Leukine</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td></td>
<td></td>
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<tr>
<td>Sargramostim</td>
<td></td>
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</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin</td>
<td>Her2 cancers</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Rituxan</td>
<td>Lymphomas, NHL</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erbitux, Avastin</td>
<td>EGFR-expressing cancers</td>
</tr>
</tbody>
</table>

### Small Molecules vs. Biologics

<table>
<thead>
<tr>
<th>Small Molecule Drugs</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (MW)</td>
<td>Small (&lt;1000 Daltons)</td>
</tr>
<tr>
<td>Source</td>
<td>Chemical synthesis</td>
</tr>
<tr>
<td>Structure</td>
<td>Simple, well defined, independent of manufacturing process</td>
</tr>
<tr>
<td>Characterization</td>
<td>Easy to characterize</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Mostly non-immunogenic</td>
</tr>
</tbody>
</table>

**Example**

Atorvastatin

MW = 558.64

Trastuzumab

MW = 185,000

### Biosimilar Manufacturing

- Several major steps included in development
  - Modifying the selected gene of interest
  - Inserting the desired gene into a specific cell line or host
  - Replicating cell line and increased protein expression
  - Harvesting protein products from the cell
  - Purifying the selected protein
Biosimilar Manufacturing


Manufacturing Challenges

- Large molecular structures, increased molecular weight
- Complex three-dimensional structure
- Utilize cell-based systems for drug production
- Potential variations among biologic products
  - Minor changes can occur during cell production.


Differences in Biologic Products

Differences between Proteins

- Amino acid substitution
- N- and C-terminal modifications
- Mismatched disulfide bonds
- Post-translation modifications folding
  - Carboxylation
  - Formylation
  - Glycosylation
  - Methylation
  - Phosphorylation
- PEGylation
Differences in Biologic Products

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Comparator</th>
<th>Difference</th>
<th>Molecular Difference or Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiglucerase (Cerezyme), velaglucerase alfa (VPRIV), taliglucerase alfa (Elelyso)</td>
<td>Natural glucocerebrosidase</td>
<td>Clinically superior</td>
<td>Enhanced glycosylation</td>
</tr>
<tr>
<td>Somatropin (Genotropin, Nutropin, Norditropin)</td>
<td>Natural human growth hormone</td>
<td>Varying half-lives (1.5 to 10 hours)</td>
<td>None</td>
</tr>
<tr>
<td>Coagulation Factor VII</td>
<td>Natural Factor VII</td>
<td>Antibody production</td>
<td>Pasteurization process</td>
</tr>
<tr>
<td>Interferon alfa-2a (Intron-A, Schering)</td>
<td>Interferon alfa-2b (Roferon-A)</td>
<td>Antibody production</td>
<td>Human serum albumin diluent and room storage</td>
</tr>
<tr>
<td>Epakin alfa (Eprex)</td>
<td>Same protein, different formulation</td>
<td>Antibody production causing anemia (pure red blood cell aplasia)</td>
<td>Change in stabilizer from human serum albumin to glycine and polysorbate 80</td>
</tr>
</tbody>
</table>

Antibody Formation: “Immunogenicity”

- Potential increases with changes in amino acid sequence
- Some antibodies produce neutralizing effect against rDNA product (interferon alfa)
- Human antibody formation seen with some monoclonal antibodies (Mabs), especially human anti-mouse antigen (HAMA)
- HAMA: neutralizing effect or hypersensitivity reactions
- Macromolecules (proteins), such as biologic drugs, can trigger immune responses with varying consequences, e.g.
  - Antibodies may neutralize the molecule, making it therapeutically ineffective
  - There may be no clinical effect
  - Rare but serious autoimmune responses can be life-threatening
- Immunogenicity of biologic drugs is unpredictable, unforeseeable


Immunogenicity

- Up to 60% of enrolled patients developed antibodies to Omnitrope (somatropin [rDNA origin] in first European phase III study
- Problem was high concentration of protein in host cells, which is known to enhance antibody reaction against growth hormone
- Additional purification steps were introduced
- New phase III studies were conducted
- Antibody levels were significantly reduced to within authorized ranges

Summary of Differences Between Small Molecule and Biologic Agents

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Small Molecule Drugs</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production</td>
<td>Chemical synthesis</td>
<td>Through biotechnology and host cell lines</td>
</tr>
<tr>
<td>Physiochemical properties</td>
<td>Low molecular weight</td>
<td>High molecular weight</td>
</tr>
<tr>
<td></td>
<td>Well defined</td>
<td>Complex</td>
</tr>
<tr>
<td></td>
<td>Stable</td>
<td>Sensitive to heat, sheer stress (aggregation)</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>Single entity, high chemical purity, standards well established</td>
<td>Heterogeneous mixture, broad specifications, may change during development, difficult to standardize</td>
</tr>
<tr>
<td>Analytic assays</td>
<td>Completes characterized by analytic methods</td>
<td>Difficult to characterize, assays not standardized</td>
</tr>
<tr>
<td>Decontamination</td>
<td>Easy to verify</td>
<td>Lengthy and complex purification process</td>
</tr>
<tr>
<td></td>
<td>Contaminants can be removed and easily detected and removable</td>
<td>High possibility of contamination; detection difficult, and removal impossible</td>
</tr>
<tr>
<td>Pharmacokinetic properties</td>
<td>Administered through different routes</td>
<td>Parenteral route of administration most common</td>
</tr>
<tr>
<td></td>
<td>Rapidly enters systemic circulation through capillaries</td>
<td>Larger molecules enter circulation through lymphatic system, subject to proteolysis and lymphatic tank</td>
</tr>
<tr>
<td></td>
<td>Distributed to all organs and tissues</td>
<td>Distribution limited to plasma and extracellular fluid</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Organ specific toxicity</td>
<td>Mostly receptor mediated toxicity</td>
</tr>
<tr>
<td>Allergenicity</td>
<td>Often not antigenic</td>
<td>Usually antigenic</td>
</tr>
</tbody>
</table>
Disclosures

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• Develop a conceptual framework during the formulary review process that considers appropriate off-label indications for biosimilars.
• Explain the rationale for and key components of a successful pharmacovigilance program, including roles the pharmacist can assume in ensuring success.
Biosimilars: Current Activity at the National and State Level and the Debate and Implications of Naming Biosimilars

Philip E. Johnson M.S., B.S.Pharm., FASHP
Director, Oncology Services
Premier Inc.
Tampa, Florida

Topics

• Current status of biosimilars in the United States
  – Approval process
  – State legislative initiatives

• Factors to consider for interchangeability and pharmacist substitution or interchange of biological products
  – Naming
  – Dosing
  – Coding
  – Companion Diagnostics

Are biosimilar drug issues new?

Which, if any, are relevant to current discussion?

• Human Growth Hormone
  – First to be substituted
• Human Insulin
  – Many choices, little hesitation to interchange
• Interferon Alpha 2a, 2b, Beta, Gamma
  – Payer directed formulary equivalence / interchange
• Influenza Vaccine
  – Multiple manufacturers; you provide what you can get
• Heparin
  – Harvested, purified, equivalence by batch
• Low molecular weight heparin (LMWH)
  – Significant dosing issues when interchanged
• Anti-infectives
  – Therapeutic Class representative for sensitivity tests
• CMS considered erythropoietin and darbepoetin “Functional Equivalents”
Evolution of Biosimilar Approval Pathway in U.S.

- Two federal laws for the approval of pharmaceuticals in the United States
  - Food, Drug, and Cosmetic Act (FDCA)
  - New drug application (NDA)
  - Abbreviated NDA (ANDA)
  - Public Health Service Act (PHSA)
  - Biologics license application (BLA)
- Most biologics approved under PHSA
  - Drug Price Competition and Patent Term Restoration Act (aka Hatch-Waxman Act) of 1984 does not apply
  - Biologics Price Competition and Innovation Act (BPCI) of 2009 created an abbreviated FDA approval pathway for biosimilars
- According to the FDA, "drugs" are different from "biologics"


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

Does approval path impact therapeutic interchange (TI) decision?

- Increasing data requirements for approval
- Decreasing safety concerns
- Increased potential for TI

Unknown which market strategy will prevail

Interchangeable Biosimilar
- New Biologic under full BLA

Biosimilar
- Increasing potential for TI
State initiatives: warranted or not?

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 biosimilars 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

See page 49 for enlarged view
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, ...”

- **“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

- FDA continues work on implementing BPCI Act
- States have considered proposals to restrict substitution of biologic medications that are deemed similar/interchangeable, but have not been cleared by FDA for interchange
- Supporters of state proposals believe the ultimate decision on substitution should be left to the patient’s prescribing physician
  - Perhaps concern for patient safety
  - Perhaps desire to protect use of “originator” drug
- Opponents believe state proposals are restrictive and inconsistent with forthcoming national standards

Frequent Features of State Legislation

- Any biological product under consideration for substitution must be certified and listed as approved for substitution by the FDA
- No products have gained such approval as biosimilars in the United States
- Prescriber would be able to prevent substitution by stating “dispense as written” or “brand medically necessary”
- Prescriber must be notified of any allowable substitution made at a pharmacy
- Individual patient must be notified that a substitute or switch has been made; in some cases, state law requires patient consent before any such switch is made
- Pharmacist and the physician must retain records of substituted biologic medications
- State must maintain a public list of permissible interchangeable products
Enacted State Legislation
October 2014


Enacted by the Legislature of the State of Florida
(Key Points)

- Section 1. Subsection (6) of section 465.019, Florida 18 Statutes, is amended to read:
  (6) In a Class II institutional pharmacy, an institutional formulary system may be adopted with approval of the medical staff for the purpose of identifying those medicinal drugs, and proprietary preparations, biologics, biosimilars, and biosimilar interchangeables that may be dispensed by the pharmacists employed in such institution. …shall establish policies and procedures for the development of the system in accordance with the joint standards of the American Hospital Association and American Society of Hospital Pharmacists for the utilization of a hospital formulary system…..

- Section 2. Section 465.0252, Florida Statutes, is created to read:
  465.0252 Substitution of interchangeable biosimilar products.
  (3) A pharmacist who practices in a class II or modified class II institutional pharmacy shall comply with the notification provisions of paragraph (2)(c) by entering the substitution in the institution’s written medical record system or electronic medical record system.

http://www.flsenate.gov/Session/Bill/2013/0365/BillText/enPDF

State Legislation Status

Where is this going? ...Considerations For Pharmacy

- Familiarize yourself with state and federal laws
  - Much may hinge on future FDA determinations of biosimilarity and interchangeability (not expected soon)
  - Some laws are being adopted with sunset clauses and may expire before applications/determinations occur
  - Seek amendments that exempt institutional practice
- Closely follow your state Board of Pharmacy’s guidance
  - Is there a need to reconcile biosimilar substitution with existing state laws on substitution of generic drugs?

Has your P&T Committee adopted policies and procedures for biosimilar addition to the formulary and automatic substitution?

a. Biosimilar addition to formulary
b. Biosimilar automatic substitution
c. Both
d. Neither

History of Naming
Selected Terms Used to Describe "Generic" Biologics

- Post patent biologicals
- Biogenerics
- Subsequent entry protein pharmaceuticals
- Second-generation biologicals
- **Follow-on biologicals**
- Follow-on protein products
- Bio-betters
- **Biosimilars**
**Names and Numbers**

- **Originator Manufacturer (Reference Product)**
  - Trade Name
  - Generic is "Reference Name"
- **United States Adopted Names (USAN)**
  - Provided by AMA
  - Generally adopted by FDA
  - The generic name
- **United States Pharmacopeia (USP)**
  - Monographs and consistency concerns
- **Institute for Safe Medication Practices (ISMP)**
  - Naming clarity / Safety concerns
  - Labeling standards
- **Food and Drug Administration (FDA)**
  - Ultimately approves name
  - Assigns National Drug Code (NDC)
- **Centers for Medicare & Medicaid Services (CMS)**
  - Assigns HCPCS codes which could be the same between biosimilars

**HCPCS=Healthcare Common Procedure Coding System**

**Recent Naming Events (Precedents?)**

- **Teva (US)**
  - Filgrastim (tbo-Filgrastim), Full NDA approval
- **Sanofi (US)**
  - Zaltrap (ziv-ELPANH
- **Tyrosine Kinase Inhibitors naming convention**
  - PONATinib and PANOPanib
- **WHO (Oct 2013)**
  - Leaning toward "Generic + Suffix"
- **EU naming**
  - Allows the biosimilar to use same non-proprietary name as reference
- **HER-2 targeted Kadcyla (ado-trastuzumab emtansine)**
  - Trastuzumab: 8mg/kg loading; 6mg/kg q 3 weeks maintenance
  - Ado-trastuzumab: no loading; 3.6mg/kg q 3 weeks
  - FDA rejected trastuzumab emtansine and added prefix "ado"
  - ISMP Alert 4-17-13: Use both brand and full generic name to avoid confusion
  - International Medication Safety Network (IMSN) Alert 5-8-14: USAN and WHO did not approve FDA name, leading to international confusion
  - Confusion documented as leading to overdoses of ado-trastuzumab
  - FDA working on naming resolution

"IMSN Alert – Risk of confusion between the names trastuzumab emtansine and trastuzumab", May 8, 2013, IMSN Alert
"Confusion regarding the generic name of the HER2-targeted drug KADCYLA (ado-trastuzumab emtansine)", April 17, 2013, IMSN Alert

**Importance of a Naming Strategy**

**Goal:**
- Identify relationship between the biosimilar and reference/originator
  - Therapeutic category
  - Dosing
- Differentiate products
  - Support pharmacovigilance (PV)
  - Intended product administered to patient
  - Outcomes and ADEs attributed to correct product
- Avoid "sound alike" and "look alike" errors
- Facilitate effective product tracking and tracing (anti-counterfeiting)
Importance of a Naming Strategy

- Options
  - Totally different names from originator
    - Preferred by originator pharmaceutical companies
  - Same USAN name as originator
  - Unique suffix attached to originator’s USAN
    - Error prone because some computer fields truncate long names
  - Unique prefix attached to originator’s USAN
    - Precedent with some new drugs
    - Supported by ISMP and Hematology/Oncology Pharmacy Association (HOPA)

Does coding help differentiate?

- NDC and HCPCS codes can support accurate differentiation
- Billing claims data can be a useful data source for pharmacovigilance
  - Outcomes
  - Adverse Events
- Problems sometimes exist with using billing 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
  - BIA: 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 ESRD on dialysis)

Is dosing an issue?

- Molecular size differs among biosimilar drugs
  - Will “gram” based dosing be equivalent?
- Should “international unit” dosing be required?
  - “Vial contains 123 mcg (equivalent to 250 units) per mL”
  - Should “units” only be required when molecular size difference is greater than __%?
  - Erythropoietin is 34,000 daltons, typical dose = 10,000 units
  - Filgrastim is 18,800 daltons, typical dose = 300 mcg
- Should all prescribing and dosing be based on units?
- Should dose equivalent be based on originator dosing?
  - What if the originator stops production?
- Should pharmacy advocate for standards or just monitor the emerging market?
Should pharmacy advocate for dosing standards now, or just monitor the emerging market to see if this is a significant issue?

a. Advocate for standards now
b. Monitor issue and see what happens
c. Neither

Will companion diagnostics be an issue?

- FDA Guidance for Industry and FDA Staff, August 6, 2014
- For regulators (and payers?)
  - Determine which patients will benefit
  - Decrease the chance of a drug being used off-label...
- For drug makers
  - Easier to obtain approval...
- Key points in guidance:
  - “In most circumstances, an IVD companion diagnostic device and its corresponding therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling.”
  - In cases where the drug cannot be used safely or effectively without the companion diagnostic (CDx), FDA will not approve it.
  - FDA will, however, approve some drugs without a CDx in certain circumstances.
  - Therapy is intended to treat a serious or life-threatening disease

13 Drugs with FDA Required Companion Diagnostics

- Erbitux (cetuximab)
- Vectibix (panitumumab)
- Exjade (deferasirox)
- Gleevec/Glivec (imatinib mesylate)
- Herceptin (trastuzumab)
- Perjeta (pertuzumab)
- Kadcyla ( ado-trastuzumab emtansine)
- Mektansin (tramebutin)
- Tafinlar (dabrafenib)
- Tarceva (erlotinib)
- Xalkori (crizotinib)
- Zelboraf (vemurafenib)

Will CDx apply to a single drug or a therapeutic class?
Will this affect interchangeability?

http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm
Summary

• A framework for biosimilar introduction has existed in Europe and is being defined in the U.S.
  – FDA needs to enact rules
  – State initiatives, when adopted, must be rendered appropriate for institutional practice, and “sunset” when FDA guidance is finalized

• Pharmacists must play leadership roles in the safe and appropriate introduction of biosimilars into health systems
  – Naming that supports differentiation of product for pharmacovigilance
  – Dosing issues
  – Coding issues
  – Companion diagnostic issues
Considerations for Using Biosimilars in Practice: Pharmacist Substitution, Indication Extrapolation, and Pharmacovigilance

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Associate Professor
Department of Pharmacy Practice
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Portland, Maine

Topics

• Factors to consider for the interchangeability of biosimilars and pharmacist substitution or interchange of biological products
• Formulary review process that considers appropriate off-label indications for biosimilars
• Key components of a successful pharmacovigilance program, including roles the pharmacist can assume in ensuring success.

Which of the following statements about interchangeability is TRUE?

a. All biosimilars will be interchangeable with their respective reference products and other biosimilars of the same reference product
b. The FDA recognizes that an interchangeability designation, while possible, will be difficult to obtain with the original biosimilar application
c. The Biologics Price Competition and Innovation Act gives pharmacists the authority to substitute one biological product for another
d. Interchangeability is a European concept and does not apply to the United States
### Biosimilar Development Approach

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

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

**Postmarketing Monitoring**
- EU Guidance and risk management plans
- FDA consultation of proposed approach
- May be mandatory

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

### Interchangeability Definition

- **Interchangeability definition**
  - “Biosimilar to the U.S.-licensed reference biological product and can be expected to produce the same clinical result as the reference product in any given patient.”
  - “For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product will not be greater than the risk of using the reference product without such alternation or switch”

### Interchangeability

- **Safety standards for determining interchangeability**
  - Major risk is immunogenicity
  - Residual questions about diminished efficacy or increased immune-related reactions
  - Will be “difficult” in the initial 351(k) application due to the sequential nature of the assessment
    - Immune reactions are highly variable and sensitive to many different factors
    - Data package to be submitted will generally not be sufficiently sensitive to detect rare/serious adverse events
Interchangeability Study Design

- FDA interchangeability criteria: switch between reference (R) and biosimilar (B) with no clinical consequences
- What is switching?
  - R → B
  - B → R
  - B → B
- Various designs proposed
  - Standard two-sequence, two-period crossover
  - Balaam’s 4 x 2 crossover design

Practice Implications for Interchangeable Biosimilars

- “Interchangeable biological products may be substituted at the pharmacy level without the intervention of a healthcare provider.”
- Product substitution by the Pharmacist
  - Community practice
  - Institutional practice
  - Will a formal P&T committee review be necessary?
- Impact on transitions of care

FDA “Purple Book”

- Lists biological products approved by FDA and dates of approval
- Lists approval pathway: e.g., 351(a), 351(k)
- Lists if a biosimilar is interchangeable
- Defines exclusivity period
Purple Book: Clinician Perspectives

- One source for a list of biosimilar/interchangeable products
- Will this be tied to state pharmacy practice laws (drug product selection)?
- For biosimilars, will the data regarding the comparability exercise be published (e.g., highly similar with fingerprint-like similarity, highly similar, etc.)

Interchangeability and Biosimilars Substitution: Considerations

- The basis for drug/biologic product selection by the pharmacist
  - Orange Book
  - Purple Book
- Patient & prescriber communication
  - Notification vs. counseling vs. written communication
- Provisions to exclude hospitals/health-systems with a formulary system
- Documentation of substitution
- Does current pharmacy practice law apply to biologics & biosimilars?

What is your desired use of the Biosimilar within your institution?

See page 50 for enlarged view
**Biosimilar Indication Extrapolation**

- **Definition**
  - Extending information and conclusions from one population to make inferences in another target population
  - Examples: across diseases (types, stage, etc.), age groups, in combination with other drugs, impaired organ function

- **Purpose (regulatory)**
  - Avoid unnecessary studies or reduce the number of studies
  - Limited feasibility in studying the target population
  - Industry/regulator extrapolation to reference's labeled indications
  - Extrapolation of data is already an established regulatory principle
  - Manufacturing changes with originator biologics

---

**Biosimilar Indication Extrapolation: Clinician’s Perspective**

- **Clinician’s purpose**
  - Appropriately use a biological product that optimizes efficacy, safety, cost, and access

- **Situations for extrapolation**
  - Clinician extrapolation to appropriate off-label indications
    - P&T committee
    - What is the framework for extrapolation?

---

**Indication Extrapolation: FDA**

- Reference Biologic
  - Indication #1 (FDA-approved)
  - Indication #2 (FDA-approved)
  - Indication #3 (Off-label, compendia support)

- Comparability and Biosimilarity Studies
  - Indication Extrapolation

- Biosimilar
  - Indication #1 (FDA-approved)
  - Indication #2 (FDA-approved)
  - Indication #3 (Off-label, compendia support)
Indication Extrapolation: You

Reference Biologic  
Comparability and Biosimilarity Studies  
Biosimilar

Indication #1 (FDA-approved)

Indication #2 (FDA-approved)

Indication #3 (Off-label, compendia support)

Your Extrapolation Discussion

Indication #1 (FDA-approved)

Indication #2 (FDA-approved)

Indication #3 (Off-label, compendia support)

Indication Extrapolation: FDA

Reference Biologic  
Comparability and Biosimilarity Studies  
Biosimilar

Indication #1 (FDA-approved)

Indication #2 (FDA-approved)

Indication #3 (Off-label, compendia support)

No FDA Extrapolation

Indication #1 (FDA-approved)

Indication #2 (Not FDA-approved)

Indication #3 (Off-label, compendia support)

Indication Extrapolation: You

Reference Biologic  
Comparability and Biosimilarity Studies  
Biosimilar

Indication #1 (FDA-approved)

Indication #2 (Not FDA-approved)

Indication #3 (Off-label, compendia support)

Your Extrapolation Discussion

Indication #1 (FDA-approved)

Indication #2 (Not FDA-approved)

Indication #3 (Off-label, compendia support)
## Key Principles for Indication Extrapolation Justification

- **Physiologic & clinical factors**
  - Clinical experience with reference product
  - MOA & receptors for each indication
  - Differences in safety & immunogenicity between patient populations
  - Degree to which functional moieties of biologic can be characterized and compared

- **Biosimilar data package (extent of data)**
  - Physicochemical and functional comparison
  - Potential uncertainties
  - Acceptable safety profile including immunogenicity
  - Extrapolate from high- to low-risk groups for immunogenicity concerns
  - Recognize that additional tests/studies may be required

---

### Possible Conceptual Framework for Indication Extrapolation

- **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 Biosimilar

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

---

### Scenario A

- The P&T Committee is considering indication extrapolation for a biosimilar from last-line treatment for metastatic cancer (FDA-approved indication – Indication 1) to first-line treatment (not FDA-approved but supported by compendia – Indication 2)
- The biosimilar is “highly similar with fingerprint-like similarity” with good follow-up studies for indication 1

---

See page 51 for enlarged view
Scenario A

What do we know about indication 1 vs. indication 2 for the following domains?

<table>
<thead>
<tr>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Factors</td>
</tr>
<tr>
<td>Disease Factors</td>
</tr>
<tr>
<td>Endpoint Factors</td>
</tr>
<tr>
<td>Biosimilar Evidence</td>
</tr>
<tr>
<td>Structure &amp; Function</td>
</tr>
<tr>
<td>Clinical studies</td>
</tr>
<tr>
<td>Final extrapolation determination</td>
</tr>
</tbody>
</table>

Scenario B

- The P&T Committee is considering indication extrapolation from a non-malignant disease (FDA-approved indication – Indication 3) to adjuvant treatment of a curable cancer (not FDA-approved but supported by compendia – Indication 4).
- The biosimilar is “similar” with clinical data addressing residual concerns for indication 3; no information for indication 4

Scenario B

What do we know about indication 3 vs. indication 4 for the following domains?

<table>
<thead>
<tr>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Factors</td>
</tr>
<tr>
<td>Disease Factors</td>
</tr>
<tr>
<td>Endpoint Factors</td>
</tr>
<tr>
<td>Biosimilar Evidence</td>
</tr>
<tr>
<td>Structure &amp; Function</td>
</tr>
<tr>
<td>Clinical studies</td>
</tr>
<tr>
<td>Final extrapolation determination</td>
</tr>
</tbody>
</table>
Indication Extrapolation: Challenges for Clinicians

- Framework and discussion at the P&T committee
  - It is likely that many will reject the framework for extrapolation
  - May not feel that the “risk” of unknown is worth the “benefit”
- Payers
  - How will payers make their coverage determinations?
  - Compendia

Which of the following statements about biosimilar pharmacovigilance is TRUE?

a. Pharmacovigilance is something that only manufacturers have to worry about
b. Pharmacovigilance will only be required for products that have serious safety concerns
c. The purpose of biosimilar pharmacovigilance is to show that the products are indeed different
d. None of the above are true

Biosimilar Development Approach

- Develop highly similar biologic
- Test and confirm biosimilarity
- Postmarketing monitoring
  - EU Guidance and risk management plans
  - FDA consultation of proposed approach
  - May be mandatory
- Test and confirm interchangeability
  - No explicit FDA guidance
  - Will be “difficult” to do in the initial 351(k) application

Biosimilar Pharmacovigilance

• Rationale
  – Evaluate post-approval safety signals
  – Differences in immunogenicity?
  – Detection of rare events associated with one unique product

• Challenges
  – “Unambiguous product identifiers [to] distinguish all biologics from one another to accurately trace adverse events to the correct product and to identify potential differences in safety profiles after approval”


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

Risk minimization
• Healthcare provider communication
• Recalls and alerts
• REMS?

Risk Identification and characterization

Nome: Integracion into electronic medical record (EMR)
• Drug codes: HCPCS, NDC, etc.
• Prospective registries

FDA Approval

Biosimilar Pharmacovigilance: Role of the Pharmacist

• Monitor and report
  – Adverse events: FDA MedWatch
  – Medication errors

• Correct attribution of safety event
  – What was ordered vs. what did the patient receive?
    • Maintenance of EMR
    • Bar code administration
  – Medication reconciliation
    • Consider transitions of care
Summary

- An interchangeability designation requires data that switching between the biosimilar and reference is appropriate; these products will be declared as such in the FDA “Purple Book” and are candidates for pharmacist substitution.
- A conceptual framework for indication extrapolation should include patient, disease, and endpoint factors as well as the quantitative data for the biosimilar compared to the reference product.
- Pharmacovigilance is necessary to verify safety and identify rare but serious adverse effects; pharmacists should take the lead in establishing systems to ensure correct attribution of adverse effects to specific products during the reporting process.

Resources for Pharmacists

- ASHP Resource Center on Biosimilars
- American Journal of Managed Care Resource Center
Chemical Structure of Small Molecules


Chemical Synthesis of Aspirin

Benzene $\xrightarrow{H_2SO_4} \text{Salicylic acid} \xrightarrow{\text{Sodium phenolate}} \xrightarrow{\text{Kolbe-Schmidt reaction}} \text{Aspirin}$
### Small Molecules vs. Biologics

<table>
<thead>
<tr>
<th></th>
<th>Small Molecule Drugs</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size (MW)</strong></td>
<td>Small (&lt;1000 Daltons)</td>
<td>Large (&gt;10,000 Daltons)</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Chemical synthesis</td>
<td>Cultures of living cells</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Simple, well defined, independent of</td>
<td>Complex (heterogeneous), defined</td>
</tr>
<tr>
<td></td>
<td>manufacturing process</td>
<td>by the exact manufacturing process</td>
</tr>
<tr>
<td><strong>Characterization</strong></td>
<td>Easy to characterize</td>
<td>Cannot be characterized completely</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Mostly non-immunogenic</td>
<td>Immunogenic</td>
</tr>
</tbody>
</table>

**Example**

- **Atorvastatin**
  - MW = 558.64

- **Trastuzumab**
  - MW = 185,000


---

### Biosimilar Manufacturing

**Cloning and Protein Expression**

1. Cloning into DNA Vector
2. Transfer into Host Cell Expression
3. Screening/Selection

**Protein Production, Purification, and Validation**

- Cell Expansion
- Cell Production in Bioreactors
- Recovery Through Filtration or Centrifugation
- Purification Through Chromatography
- Characterization and Stability

### Summary of Differences Between Small Molecule and Biologic Agents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Small Molecule Drugs</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Production</strong></td>
<td>Chemical synthesis</td>
<td>Through biotechnology and host cell lines</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Low molecular weight</td>
<td>High molecular weight</td>
</tr>
<tr>
<td><strong>Physiochemical properties</strong></td>
<td>Well defined</td>
<td>Complex</td>
</tr>
<tr>
<td><strong>Stable</strong></td>
<td></td>
<td>Sensitive to heat, shear stress (aggregation)</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Single entity, high chemical purity, standards</td>
<td>Heterogeneous mixture, broad specifications</td>
</tr>
<tr>
<td><strong>well established</strong></td>
<td>Not affected by slight changes in production</td>
<td>which may change during development, difficult to standardize</td>
</tr>
<tr>
<td><strong>process and environmental conditions</strong></td>
<td></td>
<td>Highly susceptible to changes in production process and environmental conditions</td>
</tr>
<tr>
<td><strong>Analytic assays</strong></td>
<td>Completely characterized by analytic methods</td>
<td>Difficult to characterize, assays not standardized</td>
</tr>
<tr>
<td><strong>Decontamination</strong></td>
<td>Easy to purify</td>
<td>Lengthy and complex purification process</td>
</tr>
<tr>
<td><strong>Quality assurance and contamination detection</strong></td>
<td>Contamination can be avoided and easily detected and removable</td>
<td>High possibility of contamination, detection difficult, and removable impossible</td>
</tr>
<tr>
<td><strong>Pharmacokinetic properties</strong></td>
<td>Administered through different routes</td>
<td>Parenteral route of administration most common</td>
</tr>
<tr>
<td><strong>Rapidly enters systemic circulation through capillaries</strong></td>
<td>Larger molecules enter circulation through lymphatic system, subject to proteolysis and lymphatic transit</td>
<td>Distribution limited to plasma and extracellular fluid</td>
</tr>
<tr>
<td><strong>Distributes to any organ and tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Organ specific toxicity</td>
<td>Mostly receptor mediated toxicity</td>
</tr>
<tr>
<td><strong>Allergenicity</strong></td>
<td>Often not antigenic</td>
<td>Usually antigenic</td>
</tr>
</tbody>
</table>
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

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**EMA Model: Biosimilars Regulations**

www.ema.europa.eu

**Overarching**
Guideline on Similar Biological Medicinal Products (Oct 05)

**Quality**
Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (June 06)

**Nonclinical & Clinical**
Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical & Clinical Issues (June 06)

**Annexes**
- Epoetin: July 2006
- G-CSF: June 2006
- Insulin: June 2006
- HGH: June 2006
- Heparin LMWH & Others Draft

13 biosimilar marketing authorizations have been granted

*EMA* = European Medicines Agency
Biosimilar Development Approach

Develop highly similar biologic

Test and confirm biosimilarity

• Analytical methods for structure/function
• Cell lines
• In vitro/vivo models
• Substance pilot and final scale
• Formulation and final drug product

Test and confirm interchangeability

• Human clinical trials
• Consideration of clinically sensitive endpoints
• Clinically sensitive patient population
• Immunogenicity
• Efficacy and safety

Postmarketing Monitoring

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

Test and confirm interchangeability

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

FDA Approval


What is your desired use of the Biosimilar within your institution?

“Universal Truth” for Appropriate Use

Compendia listing for appropriate use

Desired use within institution

Reference biologic labeled indications

Biosimilar labeled indications

P&T determination

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**Possible Conceptual Framework for Indication Extrapolation**

**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 Biosimilar**
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


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**Biosimilar Development Approach**

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

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

**Postmarketing Monitoring**
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**FDA Approval**

References and Suggested Readings

http://www.gphaonline.org/issues/stateinitiatives  


Other Resources

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

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

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

1. Which of the following is NOT characteristic of biologic drugs?
   a. Proteins derived from genetically engineered living cells
   b. Complex structure
   c. Low molecular weight
   d. Variation from lot to lot in end product

2. The FDA guidance requires which of the following to be the same between the biosimilar and the reference product?
   a. Formulation
   b. Routes of administration
   c. Indications
   d. Strength of the product

3. Post-marketing surveillance is important in detecting potential adverse events with biologics and biosimilars. What is another common term for this?
   a. Pharmacokinetics
   b. Pharmacodynamics
   c. Pharmacovigilance
   d. Pharmacoepidemiology

Answers

1. c
2. d
3. c