Preparing for Biosimilars: Scientific, Regulatory, and Practice Management Issues for Pharmacists

Presented as a Midday Symposium and Live Webcast at the 47th ASHP Midyear Clinical Meeting and Exhibition

Monday, December 3, 2012
Las Vegas, Nevada

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AGENDA

11:30 a.m. – 11:40 a.m. Welcome and Introductions
James M. Hoffman, Pharm.D., M.S., BCPS

11:40 a.m. – 12:15 p.m. The Role of Biologics in Patient Care and an Overview of Biosimilar Science
Edward Li, Pharm.D., BCOP

12:15 p.m. – 12:45 p.m. Developing the Biosimilar Pathway in the United States
James M. Hoffman, Pharm.D., M.S., BCPS

12:45 p.m. – 1:15 p.m. Introducing Biosimilars to the Health System: The Pharmacist’s and P&T Committee’s Leadership Roles
James G. Stevenson, Pharm.D., FASHP

1:15-1:30 pm Discussion/Questions and Answers

FACULTY

James M. Hoffman, Pharm.D., M.S., BCPS
Program Chair
Medication Outcomes and Safety Officer
St. Jude Children’s Research Hospital
Associate Professor of Clinical Pharmacy
College of Pharmacy
University of Tennessee Health Science Center
Memphis, Tennessee

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

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
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James M. Hoffman, Pharm.D., M.S., BCPS

Dr. Hoffman declares that he has no relationships pertinent to this activity.

Susan R. Dombrowski, M.S., B.S.Pharm.

Ms. Dombrowski declares that she has no relationships pertinent to this activity.

Edward Li, Pharm.D., BCOP

Dr. Li declares that he has no relationships pertinent to this activity.

James G. Stevenson, Pharm.D., FASHP

Dr. Stevenson declares that he has no relationships pertinent to this activity.

Erika Thomas, M.B.A., R.Ph.

Ms. Thomas declares that she has no relationships pertinent to this activity.

ASHP staff has no relevant financial relationships to disclose.
ACTIVITY OVERVIEW

This educational activity will cover in depth the scientific and legislative issues associated with biosimilars, including patient safety concerns, such as immunogenicity, pharmacovigilance programs, substitution rules, and interchangeability. Expert faculty will discuss pertinent issues for pharmacists such as the manufacturing and production process of biopharmaceuticals compared with traditional chemical drugs; EMEA’s 2003 guidelines and lessons learned from biosimilar approvals in Europe; current U.S. legislation and updates on FDA regulations regarding biosimilars.

The activity will discuss the importance of pharmacovigilance programs and the role of providers in that process. The activity will conclude with a review of risks and benefits as they relate to patients and providers and important clinical information that will be required when presenting biopharmaceuticals and biosimilars to decision-making groups, such as the pharmacy & therapeutics committee.

ACTIVITY OBJECTIVES

After attending this application-based educational activity, attendees should be able to

- Review the intricate scientific process used to produce biopharmaceutical agents and compare it with the process used to create traditional chemical drug products.
- Discuss the development of the European Union and the U.S. biosimilar regulatory pathway and the impact of emerging FDA guidance on the evaluation and approval of biosimilars in the U.S.
- Examine potential approaches to monitoring and identifying unique adverse events that could emerge with biosimilars.
- Review key information that will be needed to evaluate biosimilars for formulary consideration.
- Develop a plan for the introduction of biosimilars into routine health system practice, including an approach to transitions of care.
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 # 0204-0000-12-437-L01-P).

Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official statements of continuing pharmacy education credit at the ASHP CE Center at http://ce.ashp.org following the activity.

Complete instructions for receiving your statement of continuing pharmacy education online are on the next page. Be sure to record the session code beginning with “A” announced during the activity.

New! PRACTICE REMINDER EMAIL

During this educational activity, we encourage you to jot down points about what YOU want to remember to do as a result of what you are learning.

- Use your smart device to link directly to the reminder tool and type in your ideas.
- Next month, we will send you an email as a reminder from YOURSELF about what YOU want to do after attending this activity.
- Do it more than once…multiple entries for this activity from the same email address will be combined into one email.
- If you do not have a smart device, go to the reminder tool on the activity website http://www.biosimcentral.org/?remindme=1
PROCESSING CPE ONLINE

The ASHP CE Center allows participants to obtain statements of continuing pharmacy education (CPE) conveniently and immediately using any computer with an internet connection. To obtain CPE statements for ASHP Advantage activities, please visit http://ce.ashp.org

1. Log in to the ASHP CE Center using your e-mail address and password. If you have not logged in to the ASHP CE Center and are not a member of ASHP, you will need to set up an account by clicking on “Become a user” and follow the instructions.

2. Once logged in to the site, click on Process Meeting CE.

3. If you are a registered attendee at the ASHP Midyear Clinical Meeting, click on the start button to the right of ASHP Midyear Clinical Meeting 2012. If you are not registered to attend the ASHP Midyear Clinical Meeting, click on the start link to the right of the activity title. If this activity title does not appear in your meeting list, enter the 5-digit activity code in the box above the list and click submit. The activity code is noted below. Click submit when prompted and then click on the start link to the right of the activity title. Do not click on “remove” next to an activity title unless you did not attend that activity.

4. Click on the click here link to view sessions associated with the day of the activity.

5. Enter the session code announced during the activity (e.g., A12XXX and note that the letter is case sensitive) and select the number of hours equal to your participation in the activity.

6. Click submit to receive the attestation page.

7. Confirm your participation and click submit.

8. Complete the evaluation and click the finish button. You will then be able to view and print your transcript.

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<th>Session Code (announced during the live activity)</th>
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<td>2</td>
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</tbody>
</table>

NEED HELP? Contact ASHP Advantage at support@ashpadvantage.com.
Your educational opportunities related to biosimilars extend beyond today’s symposium…

- **Available in 2013**
  - e-Newsletters featuring tips for incorporating information from this symposium into practice, as well as updates on emerging information on biosimilars
  - Web-based activity based on today’s live symposium (2 hours of CPE, but please note that individuals who claim CPE credit for the live activity are ineligible to claim credit for the web-based activity)
  - CE Discussion Guide highlighting the science behind the development and manufacturing of biological agents and other essential information for practitioners

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

www.biosimcentral.org
Edward Li, Pharm.D., BCOP
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 earned his Doctor of Pharmacy degree from the Philadelphia College of Pharmacy. He also 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. He is also 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, a not-for-profit alliance of 21 of the world’s leading cancer centers, that is dedicated to improving the quality and effectiveness of care provided to patients with cancer.

Dr. Li’s research interests include public health policy issues relating to oncology practice, such as comparative effectiveness and Risk Evaluation and Mitigation Strategies (REMS), as well as utilization of secondary data sources to analyze practice trends and outcomes.
Learning Objectives

- Review the intricate scientific process used to produce biopharmaceutical agents and compare it with the process used to create traditional chemical drug products.
- Discuss the development of the European Union and United States biosimilar regulatory pathway and the impact of emerging FDA guidance on the evaluation and approval of biosimilars in the United States.

Learning Objectives

- Examine potential approaches to monitoring and identifying the unique adverse events that could emerge with biosimilars.
- Review key information that will be needed to evaluate biosimilars for formulary consideration.
- Develop a plan for the introduction of biosimilars into routine health system pharmacy practice, including an approach to transitions of care.

What do you know about biosimilars?

A. This is a topic of great interest to me; I've followed it closely for many years.
B. This is a topic of great interest to me, but I’m having trouble keeping up with the latest information.
C. I’m generally aware of some of the issues surrounding biosimilars and have started paying more attention over the last couple of years.
D. Bio-what?
What is a biologic?

- Technical definition from U.S. Code of Federal Regulations
  "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man."

- Derived from living sources
  - Various cultures of bacteria or viruses
  - Human or animal sources

- Biologics do not always have a therapeutic intent
- For our purposes, think of biologics as "therapeutic proteins"

Biologics are More Complex than Chemical Drugs

- Low molecular weight drugs - chemicals
  - are made by mixing together known chemicals and reagents in a series of controlled and predictable chemical reactions

- Biopharmaceuticals
  - are made by harvesting proteins that are produced and secreted by specially genetically engineered living cells
  - therapeutic protein
  - production process is far more complex
  - The quality of the end product (including therapeutic efficacy and safety) may depend on the manufacturing process

Implications of the Complexity of Biologics
What is a Biosimilar?

- Various definitions - key elements include
  - Copy of a therapeutic protein
  - Not made by innovator company
  - Approved under an abbreviated regulatory process

- Proposed consensus definition:
  - A biosimilar is a copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise.


The Role of Biologics in Patient Care and an Overview of Biosimilar Science

Edward Li, Pharm.D, BCOP

Results from an National Comprehensive Cancer Network (NCCN) Survey

PRIMER: HOW DO WE FEEL (AND WHAT DO WE KNOW) ABOUT BIOSIMILARS?
NCCN Trends™ Survey: Biosimilars

• Administered between March 10-11, 2011 at the NCCN 16th Annual Conference
• Over 1,400 conference attendees
• A convenience sample of 277 people responded to the survey

Respondent Characteristics

<table>
<thead>
<tr>
<th>Response Type</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
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<td>129</td>
<td>46.6%</td>
</tr>
<tr>
<td>Nurse</td>
<td>71</td>
<td>25.6%</td>
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<tr>
<td>Pharmacist</td>
<td>38</td>
<td>13.7%</td>
</tr>
<tr>
<td>Other clinician</td>
<td>7</td>
<td>2.5%</td>
</tr>
<tr>
<td>Clinician not practicing or not a</td>
<td>32</td>
<td>11.6%</td>
</tr>
<tr>
<td>Total</td>
<td>277</td>
<td></td>
</tr>
</tbody>
</table>

Note: percentages may not total 100 because of rounding


Familiarity with Biosimilars Legislation

Note: percentages may not total 100 because of rounding

Interest in Using Biosimilars

![Graph showing interest in using biosimilars among different groups.]


See page 24 for enlarged version of slide.

Importance of Various Types of Information

- Studies that show clinical trial results with biosimilar vs. innovator (50% very important)
- Studies that show pharmacokinetics (e.g., absorption, distribution, metabolism, excretion) (38% very important)
- Studies that directly compare clinical endpoints, such as 50% response rates (38% very important)
- Literature reviews and comparative analyses (41% very important)
- Acquirer cost differences (51% very important)
- Physician and expert opinions (49% very important)
- Need for more information on biosimilars to make a decision (38% not important)
- Would not consider using a biosimilar despite having used it before (22% very important)


See page 25 for enlarged version of slide.

If a biosimilar was FDA-approved and available today for the following biologics, how would you proceed in routinely using the biosimilar instead of the innovator product tomorrow?

- Ruxolitinib: 39% would use, 54% would not use
- Filgrastim: 23% would use, 33% would not use
- Rituximab: 12% would use, 18% would not use
- Bevacizumab: 19% would use, 15% would not use
- Gemcitabine: 11% would use, 17% would not use
- Lenalidomide: 15% would use, 28% would not use
- Imatinib: 11% would use, 43% would not use

In a not too Distant Future...

- Mr. Jones is a patient who is receiving chemotherapy for the treatment of non-small cell lung cancer. He is admitted to your hospital for a pleural effusion.
- Upon performing the medication reconciliation, you identify that the patient has been receiving Retacrit® (epoetin zeta) for the treatment of chemotherapy-induced anemia.

Follow-up Questions

- What is this other product?
- Are the two biologics equivalent?
- What does “equivalent” mean for biologics?
- Can I readily substitute one for the other?

See page 26 for enlarged version of slide.

Why are Biologics Important?

- Table 15: Drug Expenditures in Clinical Trials 2017

Biologics by Therapeutics Category

- Oncology and supportive care
- Erythropoiesis stimulating agents
- Cardiovascular
- Neurology
- Pulmonary
- Rheumatology
- Gastroenterology
- Dermatology
- Immunology

Therapeutic Uses of Biologics


Other Important Definitions

- Biosimilar vs. reference
- Sponsor vs. Innovator
- Biosimilarity vs. Bioequivalence
Biosimilar vs. Reference

- **Biosimilar product**
  - A biologic that has been deemed to be “highly similar” to a reference biologic
  - There are no clinically meaningful differences
- **Reference product**
  - The product to which the biosimilar is being compared
  - Think of current brand-name biologic medications

Sponsor vs. Innovator

- **Sponsor company**
  - The company that submits the application for a candidate biosimilar
- **Innovator company**
  - The company that makes the reference product

Biosimilarity vs. Bioequivalence

- **Biosimilarity**¹
  - No “clinically meaningful” differences between biosimilar and reference product
  - Recognizes that the two molecules are in fact different, but exert highly similar effects
- **Bioequivalence**²
  - “The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.”

Biologics vs. Small Molecule Drugs

• Biologics are far more complex than traditional small molecule drugs
• Examples:
  - Molecular weight
  - Structure (i.e., importance of tertiary and quaternary structures)
  - Manufacturing/production process
  - Immunogenicity

Biologics vs. Small Molecule Drugs

Human EPO
165 amino acids
MW ~ 34,000 Da

Courtesy of: Olgun Guvench, MD, PhD, University of New England College of Pharmacy

Biologics vs. Small Molecule Drugs

• Biologics have a complex manufacturing process
  - Multiple steps; proprietary processes
    • Alteration in processes by the originator requires validation of the product
  - Expected variation between manufacturers
  - Even small differences can result in a different end-product

Biologics vs. Small Molecule Drugs

Cisplatin
(NH₃)₂PtCl₂
MW ~ 300 Da
Manufacturing Process for Biologics

Potential Differences vs. Reference

- Primary amino acid sequence
- Modification of amino acids (e.g., glycosylation)
- Higher-order structure
  - Folding
  - Quaternary structure

Biologics vs. Small Molecule Drugs

- Unlike generic small molecule drugs:
  - Biosimilars will not be identical to the reference product because of differences in manufacturing processes
  - We cannot determine if a biosimilar product is identical to the reference product

- Therefore, an assessment of biosimilarity is much more complex than the assessment of "bioequivalence" for small-molecule drugs
See page 28 for enlarged version of slide.

### Summary of Key Differences

<table>
<thead>
<tr>
<th>Area</th>
<th>Biosimilar</th>
<th>Small Molecule Analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>Not identical to the same active ingredient as the innovator's product.</td>
<td>Identical to the reference product.</td>
</tr>
<tr>
<td>Analytical characterization</td>
<td>The reference product can be fully characterized and compared to the biosimilar.</td>
<td>The biosimilar is demonstrated to be identical to the reference product.</td>
</tr>
<tr>
<td>Manufacturing complexity</td>
<td>May consist of multiple steps and involve several stages of purification, production, and formulation of the final product.</td>
<td>Relatively simple, involving few excipient and excipient concentrations.</td>
</tr>
<tr>
<td>Regulation</td>
<td>The biosimilar is regulated and licensed after full characterization and approval of the final product.</td>
<td>The reference product is already approved for use.</td>
</tr>
</tbody>
</table>


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**FDA Draft Guidance: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product**

**THE SCIENCE BEHIND DEMONSTRATING BIOSIMILARITY**


**Demonstrating Biosimilarity: General Principles**

- The clinical efficacy and safety of the biologic 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
Demonstrating Biosimilarity: A Stepwise Approach

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

Structure and Function

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

Animal Data

- Useful when there are unresolved questions about the safety of the candidate biosimilar
- Utilize comparative animal toxicology
- "In general, nonclinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies are not warranted when the proposed product and reference product have been demonstrated to be highly similar through extensive structural and functional characterization and animal toxicity studies."
The sponsor of a proposed product must include in its submission to FDA information demonstrating that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."

**BIOSIMILARITY CLINICAL STUDIES**


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**Human Pharmacokinetics/Pharmacodynamics**

- "Fundamental" for demonstrating biosimilarity
- Both PK and PD will be necessary
  - PK: patient population considerations
  - PD should study measures that are:
    - Relevant to clinical outcomes
    - Can be quickly assessed with precision
    - Has the sensitivity to detect clinically meaningful difference
- Ideally correlate exposure to clinical outcomes

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**Clinical Immunogenicity**

- Goal is to evaluate potential differences in incidence and severity of immune responses
- FDA recommends a comparative parallel study
- Clinical immunogenicity endpoints include: antibody formation (binding, neutralizing), cytokine levels, etc.
- "Ultimately, only clinical studies and post-authorization pharmacovigilance to monitor potential immunogenicity will provide definitive evidence for product comparability to the innovator product with respect to safety and efficacy"

Clinical Safety/Effectiveness

• Are necessary if there are residual concerns about biosimilarity based on aforementioned data
• Type of clinical trial design will depend on what residual questions remain
• Clinical studies should be designed to demonstrate neither decreased nor increased activity
• Use clinically relevant and sensitive endpoints in the right population (e.g., evaluate INR vs. incidence of bleeds/stroke)

Take Home Message

• The “data package” that allows individual biosimilars to be approved is likely to differ
  - Based on draft FDA Guidance, will minimally have some human data (PK/PD and immunogenicity)
  - Don’t always expect a standard type of clinical safety and effectiveness study
• Can we work on “class-guidance?”

The Case of Epoetin Zeta

• Structure
  - Protein backbone comparable
  - Glycosylation overall comparable with some differences
• Function/animal data
  - Quality/purity assessed and comparable
  - In vivo bioactivity comparable
  - Assessment of reticulocytes after administration to mice

The Case of Epoetin Zeta

• PK/PD
  - PK assessed in healthy volunteers using a crossover design
  - Measured epoetin plasma concentrations
  - Initially showed zeta to be over-available
  - Problems with assay which required a “correction”
  - Comparable in post-hoc analysis


The Case of Epoetin Zeta

• Clinical immunogenicity and clinical safety/effectiveness
  - Double-blind, Phase III RCT in hemodialysis patients
    • Designed to address comparability
    • No issues with immunogenicity
    • Comparable safety/efficacy
  - Open, non-controlled Phase III in patients with chemotherapy-induced anemia
    • It works, but was not designed to address comparability


The Case of Epoetin Zeta

• Approved in Europe for anemia associated with CRF and chemotherapy
• Indication for cancer chemotherapy based on “extrapolation” of the data
  - “Since the mechanism of action of epoetin is the same for all currently approved indications and there is only one known epoetin receptor, demonstration of efficacy and safety in renal anemia will allow extrapolation to other indications of the reference medicinal product with the same route of administration”

Back to Patient Case

- The question is: epoetin alfa or zeta while in the hospital?
- FDA approval via biosimilar pathway means that the threshold for comparability has been met
  - What is your ability to evaluate the data?
- Resolution will depend on many different factors

Which of the following best describes your position about continuing this patient’s ESA treatment while in the hospital?

A. Every effort should be made to continue the patient on epoetin zeta.
B. The ESA on formulary should be used since these products are interchangeable.
C. The complexity of these drugs makes withholding ESAs while in the hospital the best choice.
D. Undecided.
Importance of Various Types of Information

If a biosimilar was FDA-approved and available today for the following biologics, how would you proceed in routinely using the biosimilar instead of the innovator product tomorrow?

<table>
<thead>
<tr>
<th>Biologic</th>
<th>0%</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>100%</th>
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<tbody>
<tr>
<td>Epoetin/darbepoetin</td>
<td>20%</td>
<td>59%</td>
<td>4%</td>
<td>5%</td>
<td>13%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Filgrastim/pegfilgrastim</td>
<td>23%</td>
<td>56%</td>
<td>5%</td>
<td>4%</td>
<td>12%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>22%</td>
<td>55%</td>
<td>8%</td>
<td>1%</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Trastuzumab</td>
<td>19%</td>
<td>58%</td>
<td>8%</td>
<td>0%</td>
<td>11%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cetuximab/panitumumab</td>
<td>17%</td>
<td>61%</td>
<td>7%</td>
<td>5%</td>
<td>11%</td>
<td></td>
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<tr>
<td>Bevacizumab</td>
<td>19%</td>
<td>60%</td>
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<td>4%</td>
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<td>Interferon</td>
<td>18%</td>
<td>57%</td>
<td>8%</td>
<td>5%</td>
<td>12%</td>
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Why are Biologics Important?

### Table: Top 15 Drug Expenditures in Clinics in 2011

<table>
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<tr>
<th>Drug</th>
<th>2010 Expenditures (S Thousands)</th>
<th>Percent Change from 2009</th>
<th>2011 Expenditures (S Thousands)</th>
<th>Percent Change from 2010</th>
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<tbody>
<tr>
<td>Epoetin alfa (Procrit, EpoGen)</td>
<td>2,339,292</td>
<td>2.0</td>
<td>2,339,292</td>
<td>-16.1</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta)</td>
<td>2,164,152</td>
<td>2.5</td>
<td>1,789,829</td>
<td>-11.1</td>
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<tr>
<td>Infliximab (Remicade)</td>
<td>1,845,818</td>
<td>3.1</td>
<td>1,719,424</td>
<td>0.4</td>
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<tr>
<td>Bevacizumab (Avastin)</td>
<td>2,453,275</td>
<td>2.6</td>
<td>1,567,994</td>
<td>16.8</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>1,969,396</td>
<td>3.1</td>
<td>1,553,477</td>
<td>6.0</td>
</tr>
<tr>
<td>Ranibizumab (Lancetica)</td>
<td>1,791,607</td>
<td>33.8</td>
<td>1,173,147</td>
<td>26.6</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>1,243,709</td>
<td>6.7</td>
<td>974,251</td>
<td>4.7</td>
</tr>
<tr>
<td>Oxaliplatin (Elotatin)</td>
<td>665,857</td>
<td>-34.4</td>
<td>806,999</td>
<td>58.7</td>
</tr>
<tr>
<td>Pemetrexed (Alimta)</td>
<td>762,243</td>
<td>16.4</td>
<td>594,267</td>
<td>2.6</td>
</tr>
<tr>
<td>Zoledronic acid (Zometa, Reclast)</td>
<td>836,100</td>
<td>8.2</td>
<td>575,519</td>
<td>-7.1</td>
</tr>
<tr>
<td>Docetaxel (Taxotere)</td>
<td>903,063</td>
<td>8.1</td>
<td>568,714</td>
<td>-37.3</td>
</tr>
<tr>
<td>Varicella vaccine (Varivax)</td>
<td>700,557</td>
<td>-8.7</td>
<td>506,387</td>
<td>-7.5</td>
</tr>
<tr>
<td>Pneumococcal vaccine (Prevnar, Prevnar 13)</td>
<td>654,734</td>
<td>100.0</td>
<td>488,068</td>
<td>2.7</td>
</tr>
<tr>
<td>Darbepoetin alfa (Aranesp)</td>
<td>732,130</td>
<td>-14.8</td>
<td>461,918</td>
<td>-13.3</td>
</tr>
<tr>
<td>Bortezomib (Velcade)</td>
<td>447,729</td>
<td>21.4</td>
<td>385,141</td>
<td>17.8</td>
</tr>
<tr>
<td>All others</td>
<td>15,989,190</td>
<td>10.2</td>
<td>13,095,357</td>
<td>13.7</td>
</tr>
<tr>
<td>Total</td>
<td>26,736,175</td>
<td>6.0</td>
<td>20,653,727</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Manufacturing Process for Biologics

<table>
<thead>
<tr>
<th>Area</th>
<th>Biosimilars</th>
<th>Small-Molecule Generics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>The amino acid sequence is the same, but there is expected to be slight</td>
<td>The active drug is chemically identical to the reference product</td>
</tr>
<tr>
<td></td>
<td>differences in terms of protein folding and glycosylation</td>
<td></td>
</tr>
<tr>
<td>Analytical</td>
<td>The final structure cannot be fully defined based on current analytical</td>
<td>Current techniques are available to ensure that the active drug in the generic product is identical to the reference product</td>
</tr>
<tr>
<td>characterization</td>
<td>techniques; therefore, the degree of structural similarity to the reference product is unknown</td>
<td></td>
</tr>
<tr>
<td>Manufacturing Complexity</td>
<td>Very complex; produced in living cells and involves several stages of</td>
<td>Relatively simple, uses organic medicinal chemistry reactions</td>
</tr>
<tr>
<td></td>
<td>purification, production, and validation of the final product</td>
<td></td>
</tr>
<tr>
<td>Impact of a change in</td>
<td>Small changes in process may alter the final structure and function of the</td>
<td>Likely to be negligible because the end product is identical</td>
</tr>
<tr>
<td>manufacturing process</td>
<td>protein</td>
<td></td>
</tr>
<tr>
<td>Regulation</td>
<td>The Biologics Price Competition and Innovation Act of 2009 establishes</td>
<td>Hatch-Waxman Act allows generics to be approved through an Abbreviated New Drug Application (ANDA)</td>
</tr>
<tr>
<td>Legislation approving an</td>
<td>framework for an abbreviated approval pathway for biosimilars; guidance yet to be released by the FDA</td>
<td></td>
</tr>
<tr>
<td>abbreviated pathway</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dr. James M. Hoffman, Pharm.D., M.S., BCPS, is Medication Outcomes and Safety Officer and Associate Member in Pharmaceutical Sciences at St. Jude Children's Research Hospital in Memphis, Tennessee. Dr. Hoffman is also an associate professor of clinical pharmacy at the University of Tennessee Health Science Center. In his position at St. Jude, Dr. Hoffman leads medication use policy, medication safety, and research pharmacy services.

Dr. Hoffman received both his Bachelor of Science in Pharmacy and Doctor of Pharmacy degrees from the Philadelphia College of Pharmacy. In addition, he received a Master of Science degree in pharmacy administration from the University of Wisconsin-Madison. He also completed a residency in pharmacy administration and a fellowship in outcomes research at the University of Wisconsin Hospital and Clinics.

Dr. Hoffman is a Board Certified Pharmacotherapy Specialist (BCPS). He is an active member of the American Society of Health-System Pharmacists (ASHP), including serving on the Council on Pharmacy Practice, in the ASHP House of Delegates, and on the editorial board of the American Journal of Health-System Pharmacy (AJHP). He is currently a Director-at-Large for the Section of Pharmacy Practice Managers Executive Committee. Additionally, he has served on committees for other national organizations, including the National Quality Forum and The National Comprehensive Cancer Network (NCCN). In 2011, he served on the NCCN biosimilars work group, and he was the senior author of the group’s white paper on biosimilars published in the Journal of the National Comprehensive Cancer Network. Dr. Hoffman also has extensive experience analyzing various aspects of medication use and policy. Since 2004, he has been a lead author of the annual special feature in AJHP that projects medication expenditures.
Europe has led the Development of Regulatory Processes for Biosimilars

- First biosimilar approved in 2006
- 12 biosimilars for reference products on the market in Europe
  - Somatropin
  - Epoetin alfa
  - Filgrastim (six)
- Interferon product declined approval
- Discount of 20 to 35 percent compared to innovator (or more?)

European Regulatory Approach for Biosimilars

- 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
  - Specific: Product Data requirements
  - At least 12 biosimilar products on the market in Europe
Legislation was Needed for a Biosimilar Approval Pathway in the U.S.

- Two federal laws for the approval of pharmaceuticals in the United States
  - Food, Drug, and Cosmetic Act (FDCA)
  - New drug application (NDA)
  - Public Health Service Act (PHSA)
  - Biologics license application (BLA)

- Most biologics approved under PHSA
  - Drug Price Competition and Patent Term Restoration Act (informally known as Hatch Waxman Act) of 1984 does not apply
  - No abbreviated pathway in PHSA

Abbreviated Pathway for Biosimilars Included in 2010 Health Care Reform Law

- Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (the Healthcare Reform Law)

- Subtitle called the: Biologics Price Competition and Innovation Act of 2009
  - Amends the Public Health Service Act to define an abbreviated application process for biosimilars

Highlights of the Biologics Price Competition and Innovation Act of 2009 (BPCI)

- Different standards established for
  - Biosimilarity
  - Interchangeability

- Requirements can vary for abbreviated approval process
  - FDA granted discretion in amount and type of data that must be submitted

- 12 years of data exclusivity for innovator biologics
  - Potential for 6 month pediatric extension
Biosimilarity Standard in BPCI

- The biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components.
- There are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

Interchangeability Standard in BPCI

- It is biosimilar to the reference product
- It can be expected to produce the same clinical result as the reference product in any given patient
- Safe and efficacious to switch between innovator and biosimilar; from the law:
  - “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 is not greater than the risk of using the reference product without such alternation or switch.”

Biosimilar Approval Requirements under BPCI

- The biological product is biosimilar to a reference product based upon data derived from
  - Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
  - Animal studies (including the assessment of toxicity); and
  - A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.

FDA may determine that one or more of these requirements are unnecessary
Potential Exists for Three Distinct Products to Come on the U.S. Market

At this time, challenging to anticipate how many of each product will be approved

Non-innovator biologic approved under full BLA

Interchangeable Biosimilar

Increasing data requirements for approval

Biosimilar

Summary of U.S. Biosimilar Law

• Law provides the necessary legal framework for biosimilar approval

• Gives FDA the necessary flexibility to define the best approach for specific products and classes
  - More biosimilar regulatory details forthcoming

• Europe can be a guide for the U.S. regulations

Biosimilar Law - FDA Guidance

• FDA may issue general or specific guidance, after opportunity for public comment

• The issuance or non-issuance of such guidance does not preclude approval of a biosimilar

• FDA must establish a process through which the public can provide FDA with input regarding priorities for issuing guidance

• Status of FDA guidance

FDA Biosimilars page: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215031.htm
Draft Guidance Documents Address the Process FDA will Use to Approve Biosimilars

- Guidance focused on industry, but still provide important insight for clinicians
  - FDA requirements translate to the data available as biosimilar decisions are made
- Current guidance in draft from
  - Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
  - Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

Key Points of Draft Guidance Documents Reinforce Aspects of BPCI

- FDA emphasizes they will use a “totality of the evidence” approach
- Labeling of the biosimilar product will explicitly state if it is:
  - biosimilar to the reference product for specific indications
  - deemed to be interchangeable to the reference product
- Future directions for guidance

Which statement is true regarding the Biologics Price Competition and Innovation (BPCI) Act of 2009?

A. BPCI amends Hatch Waxman and creates approval process the same as small molecules.
B. BPCI defines a biosimilar and an interchangeable biosimilar differently.
C. BPCI provides five years of exclusivity for innovator products.
D. All applications under BPCI will require the same type and amount of data.
Biologics Have a Different Safety Profile from Chemical Drugs

- Evaluation of safety related regulatory actions in U.S. and European Union (EU)
- 174 products approved between 1995 and 2007
  - 82 actions occurred on 41 of the products
  - First in class products more likely to have regulatory action
- Safety problems often related to infections and immune system disorders
- Careful monitoring encouraged, particularly for new products


Biologics Have Varying Risks of Immunogenicity

- Manufactured in living cells
  - Hamster cells, rabbit cells, bacteria (E. coli), etc.
- Proteins bypass many of the body’s natural defenses
  - The body can detect and attack foreign proteins
  - Neutralizing antibodies can be developed by the body
- The more similar a therapeutic protein is to the human protein, the less the chance of immunogenicity
- Scientific tools for detecting immunogenicity exist, but in some cases they are undeveloped

Factors Affecting the Immunogenicity of Proteins

- Structure
- Impurities
- Formulation
- Route of administration
- Dose
- Immune status of patient
- Characteristics of the therapeutic agent
The Implications of Immunogenicity Vary by Type of Therapeutic Protein

- No effect – insulin, human growth hormone
- Loss of effect – granulocyte macrophage colony stimulating factor (GMCSF), interferon alfa-2a, epoetin
- Antibody-mediated disease
  - Pure red cell aplasia (PRCA) with anti-epoetin antibody

Implications of the Complexity of Biologics

The Primary Cautionary Anecdote for Biosimilars Safety

- Antibody mediated pure red-cell aplasia (PRCA) from epoetin is primary example
  - Primarily occurred with brand of epoetin not used in U. S. (Eprex) in patients with chronic kidney disease
- Cause of immunogenicity
  - Formulation change (removal of albumin) vs. leaching of compounds from rubber stoppers
- Small changes in production can have important safety consequences

Options to Identify Biosimilars to Determine Unique Adverse Events vs. the Reference Product

- Prospective registry
- Billing and/or electronic health record data
  - Would need to identify unique products via NDC or billing codes
  - Ability to do this may vary by setting
- Assign biosimilars unique non-proprietary names


The Naming Process for Non-Proprietary Drug Names in the U.S.

“simple, informative, and unique nonproprietary names [also called generic names] for drugs by establishing logical nomenclature classifications based on pharmacologic and/or chemical relationships”

Non-Proprietary Names for Biosimilars Currently Unresolved

- Primary advantage of unique non-proprietary names is clear differentiation of products for pharmacovigilance
  - But would unique names cause confusion?
  - Are unique names essential for tracking biosimilars?
- Is there a compromise?
  - Use the innovator name with a prefix or suffix?
Biosimilars – Safety Summary

- How much extra risk for biosimilars?
  - What is true risk of patient harm from biosimilars when compared to the innovator?
  - How concerned should we be?
    - Safety of biosimilars in Europe provides some confidence
- Pharmacovigilance
  - Can we design appropriate drug safety systems to detect any unique adverse events with biosimilars?
  - Tracking biosimilars
    - Unique nonproprietary names vs. other approaches
    - Important issue for pharmacists

What do you think is the best way to track biosimilars if a safety concern develops?

A. Unique names.
B. Billing, NDC, or other coding data.
C. Pharmacy records (e.g., lot number records).
D. Uncertain.

The Global View on the Safety of Biosimilars...

Biosimilar regulations exist or are developing in the world’s key regulated markets

<table>
<thead>
<tr>
<th>Australia</th>
<th>Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>Japan</td>
<td>United States</td>
</tr>
</tbody>
</table>

However, limited or no biosimilar regulations in developing countries

<table>
<thead>
<tr>
<th>China</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Areas of South America</td>
<td>[Map image]</td>
</tr>
</tbody>
</table>
James Stevenson, Pharm.D., FASHP
Chief Pharmacy Officer
University of Michigan Health System
Professor and Associate Dean for Clinical Sciences
Chair, Department of Clinical, Social, and Administrative Services
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 Assistant Director for Clinical Services, and subsequently Associate Director for Patient Care, Education and Research Services in the Department of Pharmaceutical Services at West Virginia University Hospitals, before being appointed Director of Pharmaceutical Services. He has also served as 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.

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.
Introducing Biosimilars to Health Systems: The Pharmacist’s and P&T Committee’s Leadership Roles

James Stevenson, Pharm.D., FASHP

Characteristics of Biosimilars

- Successor to a biopharmaceutical for which patent protection no longer exists
- Comparable to the reference product in terms of quality, safety and efficacy
- Likely will be approved for the same indications as the reference product
- Biosimilars are not GENERIC EQUIVALENTS, but may be THERAPEUTIC EQUIVALENTS

Potential Biosimilars in the U.S.

<table>
<thead>
<tr>
<th>Product</th>
<th>Brand Name</th>
<th>US Sales (Billions)</th>
<th>Year Launched</th>
<th>Potential Biosimilar Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>$0.8</td>
<td>1991</td>
<td>2013</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel</td>
<td>$3.3</td>
<td>1998</td>
<td>2014</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Epogen/Procrit</td>
<td>$4.8</td>
<td>1989</td>
<td>2014</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
<td>$2.4</td>
<td>1998</td>
<td>2014</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin</td>
<td>$1.3</td>
<td>1998</td>
<td>2014</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Rituxan</td>
<td>$2.4</td>
<td>1997</td>
<td>2015</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Neulasta</td>
<td>$2.2</td>
<td>2002</td>
<td>2015</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira</td>
<td>$1.2</td>
<td>2003</td>
<td>2019</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Avastin</td>
<td>$2.4</td>
<td>2004</td>
<td>2019</td>
</tr>
<tr>
<td>Darbepoetin alfa</td>
<td>Aranesp</td>
<td>$2.3</td>
<td>2004</td>
<td>2019</td>
</tr>
</tbody>
</table>
Prescription Benefit Implications in U.S.

• Biologicals and specialty pharmaceuticals are the fastest growing pharmaceutical expense in the US.
• Products are expensive. For example, treatment for breast cancer using bevacicizumab costs around $92,000 per year in the U.S.
• Express Scripts, Inc. 2007 study estimated 10-year savings of more than $71 billion from the first four classes of biologics that are expected to have biosimilar competition: interferons, erythropoietins, growth hormones, and insulin.

There will be significant pressure to utilize biosimilars to control health care costs.

Prescription Benefit Implications in U.S.

• The process of evaluating biosimilars will likely be similar to how health plans evaluate new branded products today.
• Challenge is in determining the level of clinical studies necessary to establish therapeutic equivalence.

Prescription Benefit Implications in U.S.

• If two drugs are considered “therapeutically equivalent”, then the plan will decide where on its benefit tier each drug should reside or if it should be covered at all.
• Plans likely to use patient financial incentives to drive the use of biosimilars.
  - For example, a 20% copayment for a biologic on its fourth tier, and a biosimilar on the third tier may mean the difference between $50 per month and $200 or more.
• Plans are likely to use their established formulary-review processes, and each drug will be reviewed on its own merit.
To what degree do you believe that outpatient prescription drug benefit programs will influence the use of biosimilars in health systems?

A. No influence.
B. Very little influence.
C. Some influence.
D. Significant influence.

Pharmacy Practice Implications

- Biosimilars present opportunities and responsibilities for pharmacists
  - Current generic substitution practices are not appropriate for biosimilars
  - Pharmacists should lead the objective evaluation of biosimilars using the formulary process
    - Can therapeutic equivalence be established?
    - Are there safety risks in switching products (efficacy, immunogenicity, etc.)?
    - Is there reasonable dose equivalence for conversion?
  - Formulary system to review biosimilars

Review of the P&T Committee Decision-Making Process

- Consideration of patient care and unbiased reviews of the biomedical literature are cornerstone principles
- Decisions on the management of a formulary system should be founded on the evidence-based clinical, ethical, legal, social, philosophical, quality-of-life, safety, and economic factors that result in optimal patient care

Review of the P&T Committee Decision-Making Process

• The process must include the active and direct involvement of physicians, pharmacists, and other appropriate health care professionals
• The process should be evidence-based and should not be based solely on economic factors

Considerations for Formulary Committees and Prescription Benefit Plans

• Relative Efficacy and Safety
  - Approved indications
  - Non-approved indications
• Dosing Equivalence/Conversion
• Nomenclature/Information system implications
• Immunogenicity
• Pharmacovigilance programs
• Issues at Transitions of Care - as with many chronic medications, consideration of prescription benefit approaches will influence hospital decisions

Financial Implications to be Considered

• Patient out-of-pocket impact
• Health-system financial impact
  - Inpatient cost
  - Outpatient margin
  - Potential additional monitoring costs of interchange
• Impact of bundled contracting approaches
• Impact of patient assistance programs
Potential Scenario

• Biosimilar introduced and felt to be therapeutically equivalent in efficacy/safety across all indications
• Biosimilar introduced at approximately 30% price reduction and is in favorable tier on outpatient prescription drug programs
• Innovator offers a significant discount and bundles other products so that the net cost to the health system is less than if using the biosimilar. Requires a significant market share for this discount

What would be your likely action for patients presenting to your hospital on the biosimilar?

A. Maintain the patient on the biosimilar in order to minimize conversion between products.
B. Convert the patient to the innovator product while inpatient in order to reduce cost to the health system; keep patient on the innovator product after discharge.
C. Convert the patient to the innovator product while inpatient in order to reduce cost to the health system; convert the patient back to the biosimilar at discharge.
D. Other.

Therapeutic Interchange

• "Authorized exchange of therapeutic alternates in accordance with previously established and approved written guidelines or protocols within a formulary system"

– Principles of a Sound Drug Formulary System (ASHP)
Criteria for Effective Therapeutic Interchange

- Therapeutically equivalent
- Comparable safety profile
- Significant cost advantage of one product over another
- Potential for clear process for interchange and understanding by prescribers
- Ability to “opt out” in specific circumstances
- Ability to assess outcomes
  - Is there a means of monitoring efficacy/safety?

Examples of Biological Products with Therapeutic Equivalence Approaches

- Human insulin
- Immune globulin (IVIG)
- Epoetin and analogs

Human Insulin

- Competing long-acting biosimilar insulins will likely enter the market during the next 5-10 years
- Biosimilar insulins projected to save healthcare systems $3.8 billion according to Decision Resources
- Experience with interchange of insulins in hospitals and health systems
  - Automatic interchange, one formulary product in many cases for human insulins. Some interchange of insulin aspart and lispro. Less frequent with long-acting products insulin glargine and detemir
IV Immune Globulin

- Increased utilization for multiple indications, most off-label
- Product supply issues
- High cost; contracting strategies to consolidate purchases
- Varying FDA-approved indications

IVIG Therapeutic Equivalence in Hospitals in U.S.

- Despite difference in products, many hospitals have designated a workhorse formulary agent
- Therapeutic equivalence practices that utilize the formulary agent unless a specific patient need is identified
- Permit use of a specific alternate product for patients with problems such as infusion reactions with a particular product

Epoetin and Analogs

- Epoetin alfa and darbepoetin alfa available in U.S.
- Many hospitals have declared therapeutically equivalent and utilize one product for cost purposes
- Assumptions made on dose equivalence
- Automatic interchange/conversion implemented in many institutions
- Switching studies have supported interchangeability
Planning for the Role of Biosimilars in Health Care

- Unanswered questions for biosimilars in U.S.
  - Details of approval process emerging
  - Safety
  - Interchangeability and equivalence
  - Magnitude of cost savings
- However, there is no doubt that:
  - Despite uncertainties, products will soon be marketed in the U.S.
  - Products present opportunities and responsibilities for pharmacists

Planning for Biosimilars in Hospitals

- Best practice will be to employ the formulary system to evaluate biosimilars for inclusion before use
- Careful and objective evaluation regarding evidence of efficacy, safety, and cost
- Evaluation will be more complex than for small molecule compounds
- Careful consideration in management of patient transitions of care
  - Strategies to minimize switching when patients move between sites of care

Pharmacovigilance

- Pharmacovigilance activities essential in order to further investigate safety and immunogenicity
- Major responsibility for pharmacists and practicing clinicians to identify potential safety/immunogenicity concerns and report
- Naming convention of biosimilars may be barrier to effective reporting (must be able to distinguish specific product and record accurately in information systems)
ASHP Policy Guideline on Approval of Biosimilar Medications

• Encourages the development of safe and effective biosimilars in order to make such medication more affordable and accessible
• Encourages research on the safety, effectiveness, and interchangeability of biosimilars
• Supports legislations and regulation to allow FDA approval of biosimilars
• Requires post marketing surveillance to ensure safety effectiveness, purity, quality, identify, and strength

ASHP Policy Guideline on Approval of Biosimilar Medications

• Advocates for adequate reimbursement for biological medications that are deemed interchangeable
• Promotes education of pharmacists about biosimilars and their appropriate use within hospitals and health systems
• Encourages pharmacist evaluation and the application of the formulary system before biosimilars are used in hospitals and health systems

Conclusion

• Biologics are important therapies and are significantly different compared with traditional small molecules
• A framework for the introduction of biosimilars to the U.S. market is developing and has been in place for several years in Europe
• Pharmacists must play a leadership role in determining the most appropriate use of biosimilars utilizing formulary and practice management tools and principles
Conclusion

- Biosimilars will have important implications for health care; key considerations will include
  - Use in multiple indications
  - Policy on product selection at transitions of care
  - Interchangeability and equivalence
  - Cost and contracting
- Biosimilars will require proactive planning and careful evaluation
- Patients will need to be educated, particularly if interchange of products occurs
- Pharmacists must help assure safe and effective utilization of biosimilars and should lead educational efforts with healthcare providers and patients
SELF–ASSESSMENT QUESTIONS

1. Why are biologics different from small molecule drugs?
   a. Complexity.
   b. Importance of higher-order structure (e.g., secondary, tertiary).
   c. Manufacturing process.
   d. All of the above.

2. Is the following statement true or false? The concept of biosimilarity recognizes that while the biosimilar agent may be different from the reference product, the two products are highly similar and there are no clinically meaningful differences between them.
   a. True.
   b. False.

3. According to the FDA draft guidance, which of the following types of evidence serves as the “foundation” by which the biosimilarity of a product is assessed?
   a. Structure and function.
   b. Human pharmacokinetics and pharmacodynamics.
   c. Clinical immunogenicity.
   d. Clinical safety and effectiveness.

4. Which of the following statements regarding biologics is true?
   a. Biologics are produced using the same process as chemical drugs.
   b. Biologics always have a therapeutic intent.
   c. Biologics are larger and more complex molecules compared to chemical drugs.
   d. Biologics' safety and efficacy are not influenced by formulation and handling.

5. Which of the following types of data will the FDA use in making approval decisions for biosimilars?
   a. Any combination of analytical, animal, and clinical data.
   b. Analytical and animal data only.
   c. Clinical data only.
   d. Guidance will be needed to be finalized to determine the type of data.
6. Which of the following statements on non-proprietary biosimilar names is correct?

a. Will be the same as the innovator product.
b. Will be the same as the innovator product but include a prefix.
c. Will be different than the innovator product.
d. Will be the same, different, or have a prefix/suffix once a decision has been made.

7. Health-system formulary decisions should consider all of the following except:

a. Clinical data.
b. Economic impact on the health system.
c. Economic impact on patients.
d. Processes for patients in transitions of care.
e. Degree of research support provided to the health system by the manufacturer.

8. The ASHP Policy Guideline on Approval of Biosimilar Medications recommends that

a. Biosimilars are not be used because they are not safe.
b. Pharmacists evaluate and apply the formulary system before biosimilars are used in hospitals and health systems.
c. Reimbursement be reduced for biological medications.
d. Legislation be enacted discouraging the development of biosimilars.

1. d
2. a
3. a
4. c
5. a
6. d
7. e
8. b
SELECTED REFERENCES AND READINGS


