Preparing your Practice for Biosimilars

An application-based CPE activity presented during the
2013 MSHP-ICHP Spring Meeting

Saturday, April 13, 2013
St. Charles, Missouri

Planned and conducted by ASHP Advantage and supported by
an educational donation provided by Amgen.

Preparing your Practice for Biosimilars

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ACTIVITY FACULTY

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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.

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ACTIVITY OVERVIEW

This educational activity will cover the practical scientific, legal, and practice issues associated with biosimilars, including patient safety concerns, 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, lessons learned from biosimilar approvals in Europe, current U.S. legislation, and updates on Food and Drug Administration 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 and therapeutics committee.

There will be time for questions and answers at the end of the presentation.

LEARNING OBJECTIVES

At the conclusion of this application-based CPE 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.
- Examine potential approaches to monitoring and identifying unique adverse events that could emerge with biosimilars.
- Discuss 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 1 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity # 0204-0000-13-415-L01-P).

Attendees must complete a Continuing Pharmacy Education Request online and may print their official ASHP statements of continuing pharmacy education credit at the ASHP eLearning site (elearning.ashp.org) immediately following this activity.

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Instructions for Processing CE Credit with Enrollment Code

Pharmacists and Technicians: All ACPE accredited activities which are processed on the eLearning site will be reported directly to CPE Monitor. To claim pharmacy credit, you must have your NABP e-Profile ID, birth month, and birth day. If you do not have an NABP e-Profile ID, go to www.MyCPEMonitor.net for information and application. Please follow the instructions below to process your CPE credit for this activity.

1. The **ASHP eLearning** site allows participants to obtain statements of continuing education credit conveniently and immediately using any computer with an internet connection. Type the following link into your web browser to access the e-Learning site: **http://elearning.ashp.org/my-activities**
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3. Once logged in to the site, enter the enrollment code for this activity in the field provided and click **Redeem**.

   Note: The Enrollment Code was announced at the end of the live activity.
   Please record the Enrollment Code in the grid below for your records.
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Date of Activity	Activity Title	Enrollment Code	Credit Hours
04-13-2013	Preparing your Practice for Biosimilars	_ _ _ _ _	1.0

NEED HELP? Contact ASHP Advantage at **eLearning@ashp.org.**

Preparing Your Practice for Biosimilars

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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.
- Examine potential approaches to monitoring and identifying unique adverse events that could emerge with biosimilars.
- Discuss 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.

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?

NCCN Trends™ Survey: Biosimilars

- Administered March 2011 at the NCCN Annual Conference
- Convenience sample of 277 people responded
- Results
  - Overall, 36% were not familiar with biosimilars legislation (pharmacists were 18%)
  - Over 60% indicated high to moderate interest in using biosimilars (about 25% needed more information)
  - Studies evaluating clinical endpoints, PK/PD, biochemical properties are important to respondents
  - If a biosimilar product were available today, most would review data before deciding to use it

NCCN Biosimilars White Paper:Regulatory, Scientific, and Patient Safety Perspectives JNCCN 2011; 9(Suppl 4):S1–S22.

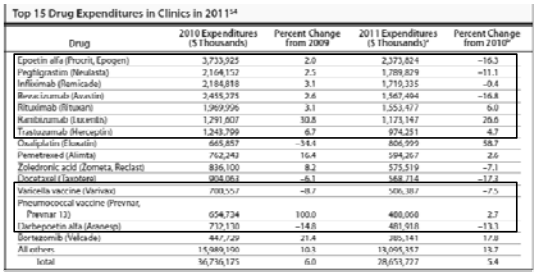
What is a Biologic?

- 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 vs. Drugs

- Small molecule drugs (chemicals)
  - are made by mixing together known chemicals and reagents in a series of controlled and predictable chemical reactions
- Biologics (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

Why are Biologics Important?



Top 15 Drug Expenditures in Clinics in 2011[34]

Drug	2010 Expenditures ($ Thousands)	Percent Change from 2009	2011 Expenditures ($ Thousands)*	Percent Change from 2010*
Epoetin alfa (Procrit, Epogen)	3,733,925	2.0	2,373,824	−16.3
Peglilgrastim (Neulasta)	2,164,152	2.5	1,789,829	−11.1
Infliximab (Remicade)	2,184,818	3.1	1,719,335	−0.4
Bevacizumab (Avastin)	2,455,375	3.6	1,567,494	−16.8
Rituximab (Rituxan)	1,969,996	3.1	1,553,477	6.0
Ranibizumab (Lucentis)	1,291,607	30.8	1,123,147	26.6
Trastuzumab (Herceptin)	1,243,799	6.7	974,251	4.7
Oxaliplatin (Eloxatin)	665,857	−34.4	806,999	58.7
Pemetrexed (Alimta)	762,249	16.4	594,267	2.6
Zoledronic acid (Zometa, Reclast)	836,100	8.2	575,519	−7.1
Docetaxel (Taxotere)	904,061	−6.1	568,714	−17.2
Varicella vaccine (Varivax)	703,557	−8.7	506,387	−7.5
Pneumococcal vaccine (Prevnar, Prevnar 13)	654,734	100.0	488,068	2.7
Darbepoetin alfa (Aranesp)	713,130	−14.8	481,918	−13.1
Bortezomib (Velcade)	447,429	21.4	285,141	17.8
All others	15,989,190	10.3	13,095,357	13.7
Total	36,736,175	6.0	28,653,727	5.4

Hoffman J et al. *Am J Health-Syst Pharm*. 2012; 69(5):405-421.

Biologics by Therapeutic Category

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

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.

Weise M, et al. *Nat Biotechnol*. 2011; 29:690-3.
Zelenetz AD, et al. *JNCCN* 2011; 9(Suppl 4):S1–S22.

Other Important Definitions

- Biosimilar vs. reference
  - Biosimilar: deemed to be "highly similar" to a reference biologic
  - Reference: the product to which the biosimilar is being compared
- Sponsor vs. Innovator
  - The company that submits the application for a candidate biosimilar
  - The company that makes the reference product

Biosimilarity vs. Bioequivalence

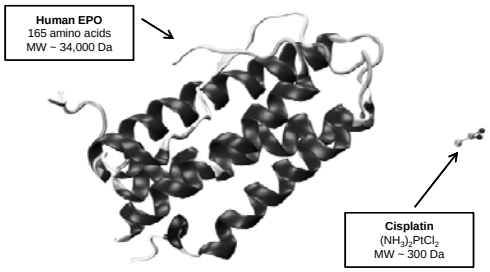
- Biosimilarity†
  - No "clinically meaningful" differences between biosimilar and reference product
  - Recognizes that the two molecules are in fact different, but exert highly similar effects
- Bioequivalence‡
  - "The absence of a significant difference in the rate and extent to which the active 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."
- These terms are not equal

†http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf
‡http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070124.pdf

Biologics vs. Small Molecule Drugs

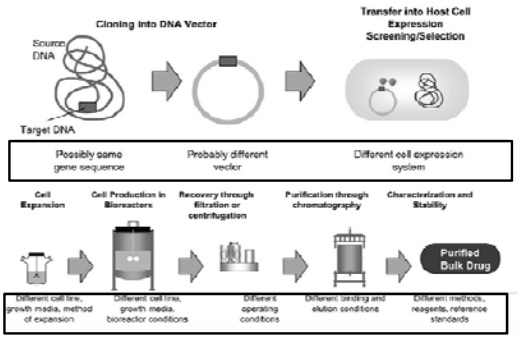
- Biologics are far more complex than traditional small molecule drugs
- Examples:
  - Molecular weight
  - Structure (i.e., importance of tertiary and quaternary structures)
  - Manufacturing/production process
  - Immunogenicity

Biologics vs. Small Molecule Drugs



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

Biologics Have a Complex Manufacturing Process



Mellstedt H, et al. *Ann Oncol* 2008; 19:411-419.

Potential Differences vs. Reference

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

Zelenetz et al. *J Natl Compr Canc Netw.* 2011; 9(Suppl 4):S1-22.

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

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

THE SCIENCE BEHIND DEMONSTRATING BIOSIMILARITY

Available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

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

*"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

FDA Draft Guidance. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

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

Clinical Studies

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

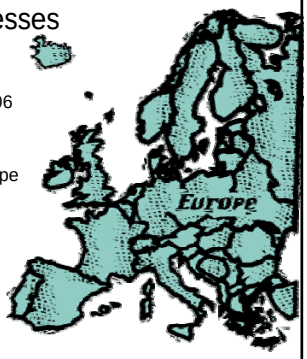
Schellekens H. *NDT Plus*. 2009; 2(Suppl 1):i27-i36.

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?"

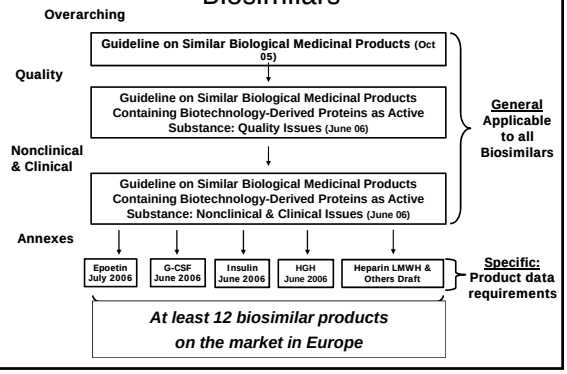
Europe has led the Development of Regulatory Processes for Biosimilars

- 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?)



http://www.ema.europa.eu/ema/
http://www.managedcaremag.com/archives/1210/1210.medmgmt.html

European Regulatory Approach for Biosimilars



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

NCCN Biosimilars White Paper:Regulatory, Scientific, and Patient Safety Perspectives JNCCN 2011; 9(Suppl 4):S1–S22.

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

H.R.3590 Patient Protection and Affordable Care Act
TITLE VII--IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES Subtitle A--Biologics Price Competition and Innovation
http://thomas.loc.gov/cgi bin/query/F?c111:5:./temp/~c111MPoyiX:e2193341:

FDA Biosimilars page: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215031.htm

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

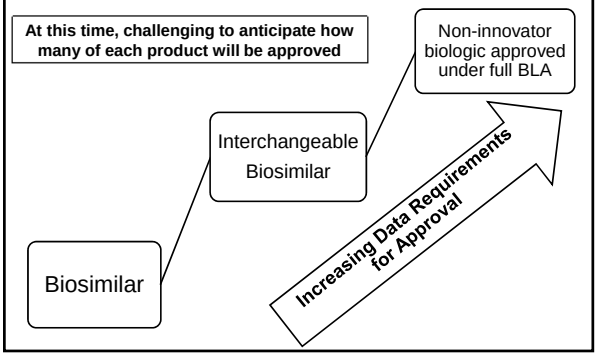
FDA Biosimilars page: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215031.htm

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

- Different standards established for
  - Biosimilarility
  - 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

FDA Biosimilars page: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215031.htm

Potential Exists for Three Distinct Products to Come on the U.S. Market



Biosimilar Law – FDA Guidance

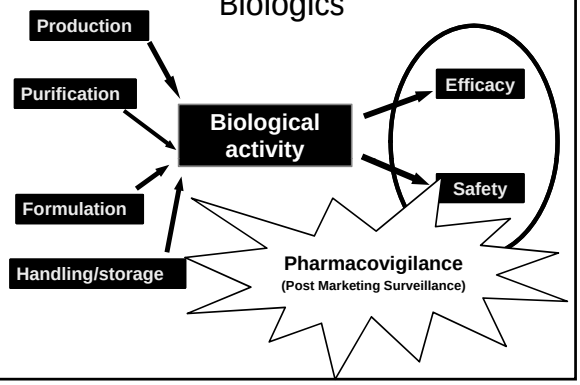
- FDA may issue general or specific guidance, after opportunity for public comment
- The issuance or non-issuance of such guidance does not preclude approval of a biosimilar
- FDA must establish a process through which the public can provide FDA with input regarding priorities for issuing guidance
- Status of FDA guidance

FDA Biosimilars page: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215031.htm

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

Implications of the Complexity of Biologics



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

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

Bennett CL, Luminari S, Nissenson AR et al. Pure red-cell aplasia and epoetin therapy. *N Engl J Med.* 2004; 351:1403–8.

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

Hennessy S et al. *Clin Pharmacol Ther.* 2010 Feb; 87(2):157-9.

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 <u>true</u> 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	***However, limited or no biosimilar regulations in developing countries***
Australia	China
Europe	India
Canada	Areas of South America
World Health Organization	
Japan	"Biopharmaceutical not subject to regulatory approval – B-NSRA"
United States	

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 <u>not</u> GENERIC EQUIVALENTS, but may be THERAPEUTIC EQUIVALENTS**

Projected US Patent Expirations for Major Biologicals

Generic Name	Brand Name	Potential Biosimilar Entry
Filgrastim*	Neupogen	2013
Epoetin alpha	Epogen/Procrit	2014
Pegfilgrastim	Neulasta	2015
Palivizumab	Synagis	2015
Rituxumab	Rituxan	2016
Cetuximab	Erbitux	2016
Adalimumab	Humira	2016
Infliximab	Remicade	2018
Trastuzumab	Herceptin	2019
Bevacizumab	Avastin	2019
Darbepoetin	Aranesp	2024
Etanercept	Enbrel	2028

*tbo-filgrastim product is approved and expected to be marketed in late 2013; product approved as a full BLA and therefore not a biosimilar per BPCI Act

Prescription Benefit Implications in U.S.

- Biologicals and specialty pharmaceuticals are the fastest growing pharmaceutical expense in the US
- Biosimilars bring savings opportunities
  - 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
  - 2008 Congressional Budget Office (CBO) estimated a $200 million reduction in U.S. expenditures on biologics by 2013, and $25 billion by 2018

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

Prescription Benefit Implications in U.S.

- Expect plans to use established formulary-review processes to review each drug on its own merit
- 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

Pharmacy Practice Implications

- Biosimilars present opportunities and responsibilities for pharmacists
  - Current generic substitution practices are not appropriate for biosimilars, but therapeutic equivalence could be considered
  - 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

- Decisions 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
- The process must include physicians, pharmacists, and other appropriate health care professionals
- The process should be evidence-based and should not be based solely on economic factors

American Society of Health-System Pharmacists. ASHP guidelines on the pharmacy and therapeutics committee and the formulary system. *Am J Health-Syst Pharm. 2008; 65:1272–83.*

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
  - Like other chronic medications, prescription benefit approaches may influence hospital decisions

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

Planning for Biosimilars in Health Systems

- 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
- Consideration of pharmacovigilance in naming conventions and information systems
- Careful consideration in management of patient transitions of care
  - Strategies to minimize switching when patients move between sites of care

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
- ASHP Policy Guidance exists

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

APPENDIX

Summary of Key Differences

Table 6 Summary of Key Differences Between How Biosimilars and Small-Molecule Generics Compare With Their Respective Reference Product

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

Zelenetz et al. *J Natl Compr Canc Netw*. 2011; 9(Suppl 4):S1-22.

Demonstrating Biosimilarity: 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
- Pharmacokinetics (PK)/Pharmacodynamics (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
- 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

Preparing your Practice for Biosimilars

- 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
- 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”

Schellekens H. *Drug Discov Today. 2009; 14(9-10):495-9.*
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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. 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.

4. 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.

5. 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.

Answers

1. d
2. a
3. c
4. a
5. e