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?

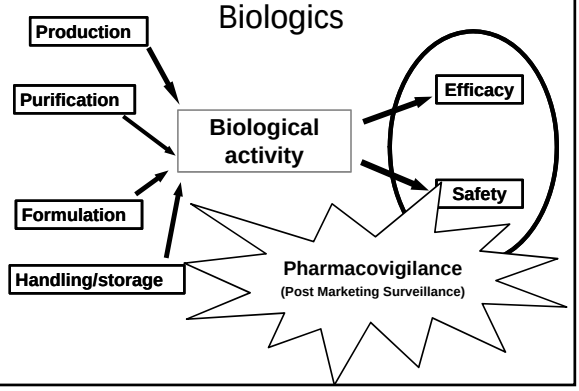
What is a biologic?

- 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.

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

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

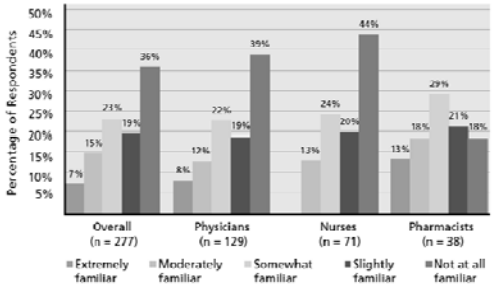
Respondent Characteristics

	n	%
Physician	129	46.6%
Nurse	71	25.6%
Pharmacist	38	13.7%
Other clinician	7	2.5%
Clinician not currently practicing or not a clinician	32	11.6%
Total	277	

Note: percentages may not total 100 because of rounding

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

Familiarity with Biosimilars Legislation



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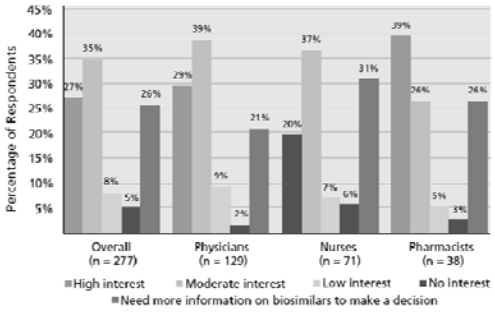
Interest in Using Biosimilars



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

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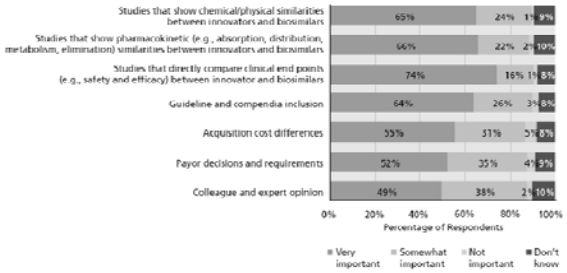
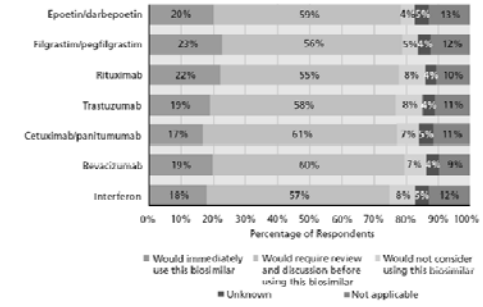
Importance of Various Types of Information



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

See page 10 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?



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

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.

See page 11 for enlarged version of slide.

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?

Why are Biologics Important?

Top 15 Drug Expenditures in Clinics in 2011[a]

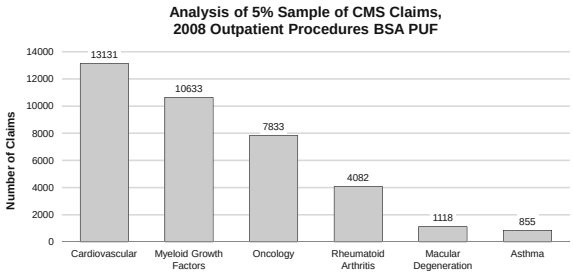
Drug	2010 Expenditures ($ Thousands)	Percent Change from 2009	2011 Expenditures ($ Thousands)[b]	Percent Change from 2010[b]
Epoetin alfa (Procrit, Epogen)	3,733,925	2.9	2,373,824	−16.3
Pegfilgrastim (Neulasta)	2,164,152	2.5	1,789,829	−11.1
Infliximab (Remicade)	2,184,818	3.1	1,719,385	−0.6
Bevacizumab (Avastin)	2,455,275	2.6	1,567,494	−16.8
Rituximab (Rituxan)	1,969,996	3.1	1,553,477	6.0
Ranibizumab (Lucentis)	1,291,607	30.8	1,173,147	26.6
Trastuzumab (Herceptin)	1,243,799	6.7	974,251	4.7
Oxaliplatin (Eloxatin)	665,867	−34.4	806,900	58.7
Pemetrexed (Alimta)	762,248	16.4	594,367	2.6
Zoledronic acid (Zometa, Reclast)	836,100	8.2	575,539	−7.1
Docetaxel (Taxotere)	904,063	−0.1	568,734	−17.3
Varicella vaccine (Varivax)	700,557	−8.7	506,387	−7.5
Pneumococcal vaccine (Prevnar, Prevnar 13)	654,724	100.0	488,068	2.7
Darbepoetin alfa (Aranesp)	732,130	−14.8	481,918	−13.3
Bortezomib (Velcade)	447,729	21.4	385,141	17.8
All others	15,589,198	10.1	13,095,157	11.7
Total	36,736,175	6.0	28,653,727	5.4

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

Biologics by Therapeutics Category

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

Therapeutic Uses of Biologics



Excluded: ESAs (1.4 million claims), vaccines, IVIG

Data available at:
http://cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/BSAPUFS/Outpatient_Proc.html

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

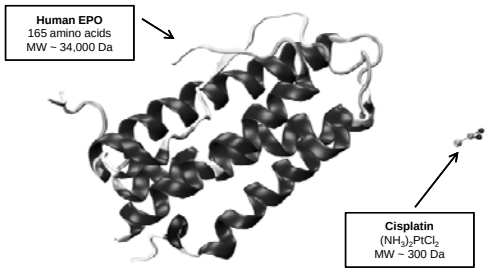
- Biosimilarity[†]
  - No "clinically meaningful" differences between biosimilar and reference product
  - Recognizes that the two molecules are in fact different, but exert highly similar effects
- Bioequivalence[‡]
  - "The absence of a significant difference in the rate and extent to which the active 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



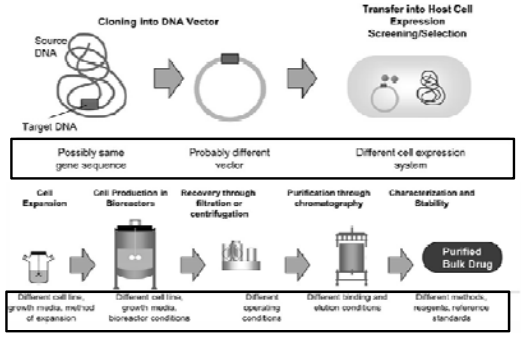
Courtesy of: Olgun Guvench, MD, PhD, University of New England College of Pharmacy

See page 12 for enlarged version of slide.

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

Manufacturing Process for Biologics



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

See page 13 for enlarged version of slide.

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.

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

Structure and Function

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

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

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 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"

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

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

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

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

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

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

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

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"

Barosi G, Bosi A, Abbracchio MP, et al. *Haematologica.* 2011; 96(7):937-42.

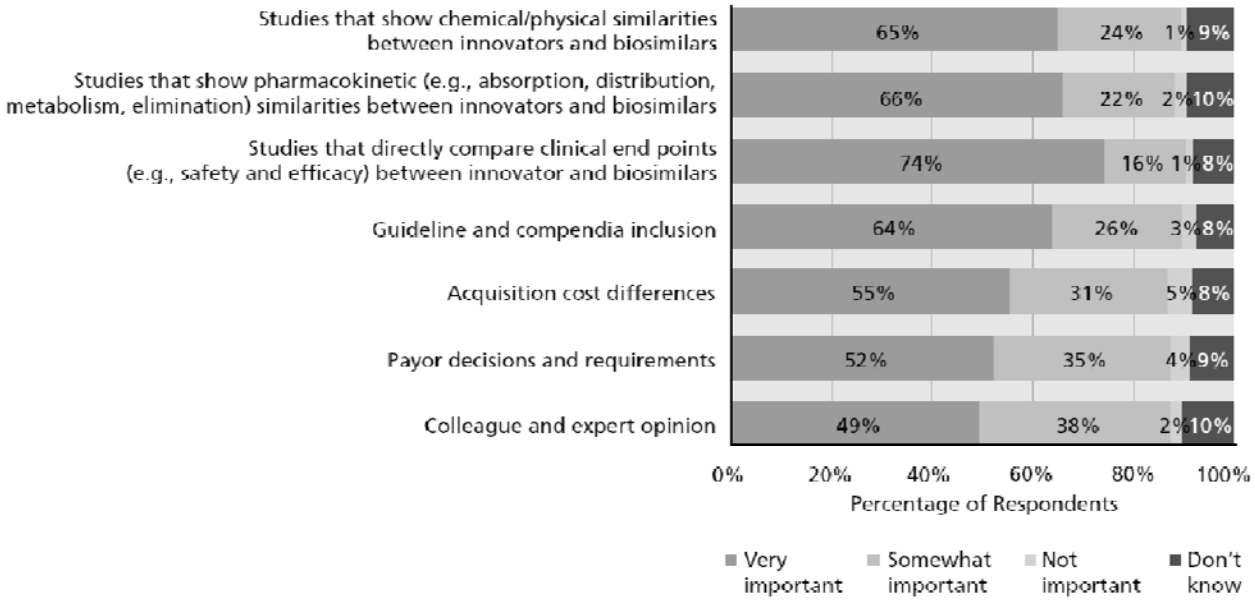
Back to Patient Case

- 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



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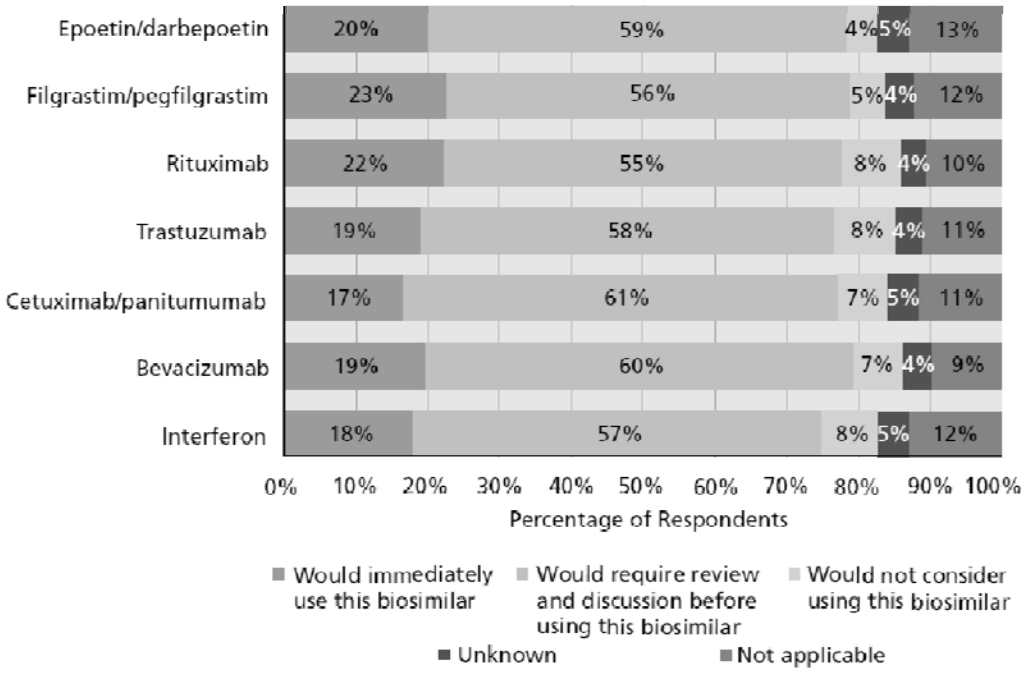

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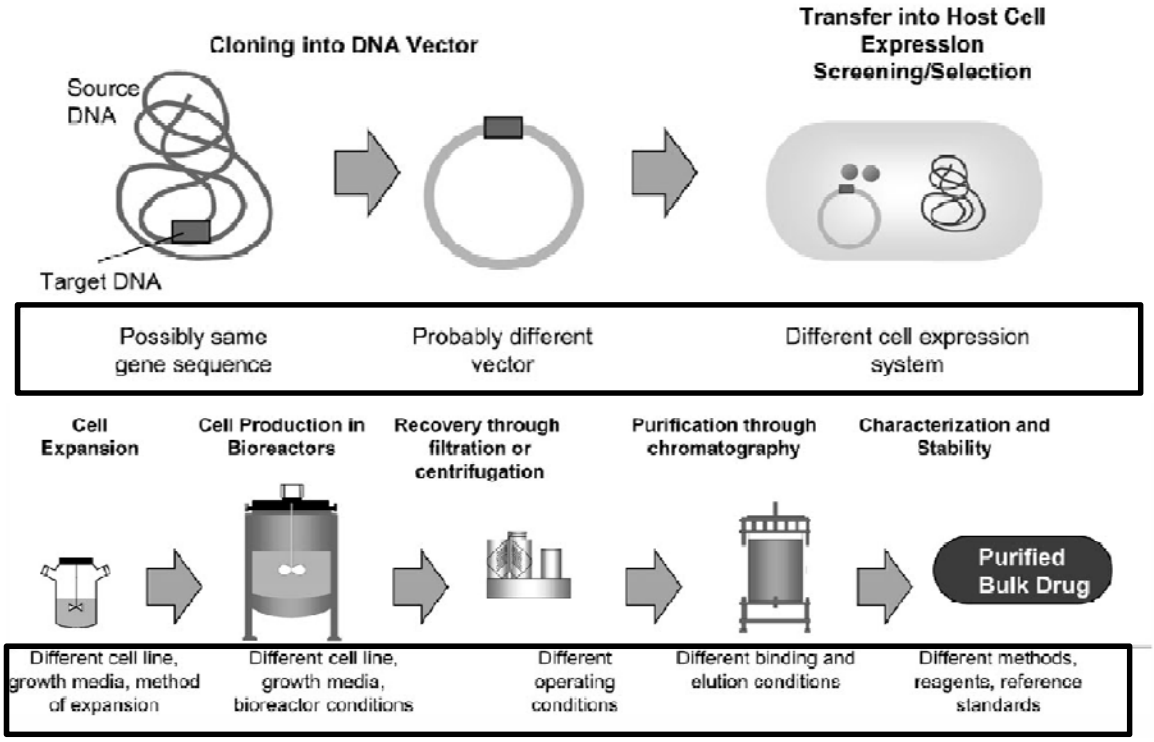
Manufacturing Process for Biologics



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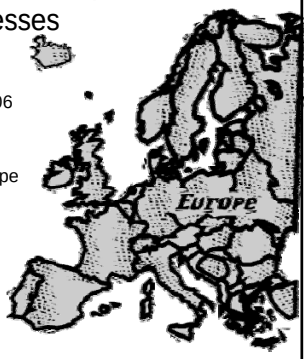
Zelenetz et al. *J Natl Compr Canc Netw*. 2011; 9(Suppl 4):S1-22.

Developing the Biosimilar Pathway in the United States

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

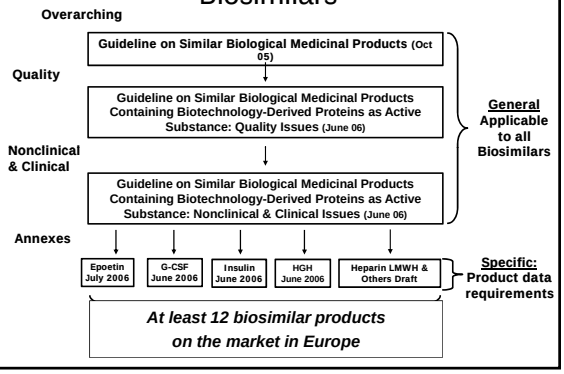
Europe has led the Development of Regulatory Processes for Biosimilars

- 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

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

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.

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

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."

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

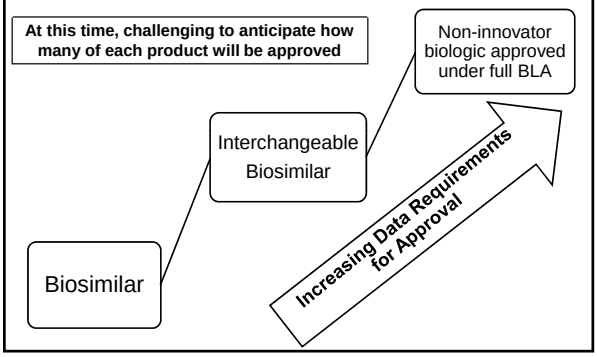
Biosimilar Approval Requirements under BPCI

- 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

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



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

Giezen TJ, et al. *JAMA*. 2008; 300(16):1887-1896.

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

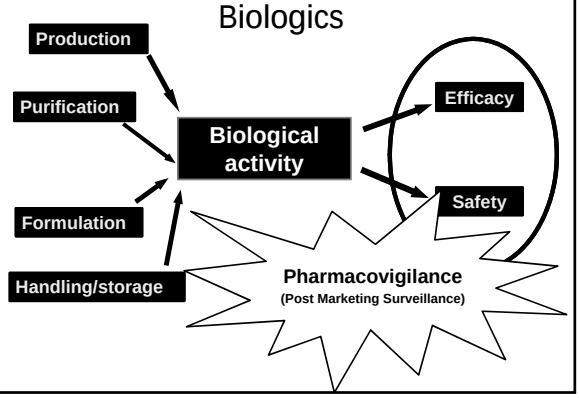
Factors Affecting the Immunogenicity of Proteins

- 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

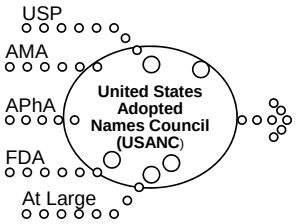
Bennett CL, Luminari S, Nissenson AR et al. Pure red-cell aplasia and epoetin therapy. *N Engl J Med.* 2004; 351:1403–8.

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.

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"

Also, works to harmonize drug names across the world (e.g. WHO INN Expert Committee)

American Medical Association. United States Adopted Names. Available at: http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/about-us.page?

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	

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

Potential Biosimilars in the U.S.

Product	Brand Name	US Sales (Billions)	Year Launched	Potential Biosimilar Entry
Filgrastim	Neupogen	$0.8	1991	2013
Etanercept	Enbrel	$3.3	1998	2014
Epoetin alfa	Epogen/Procrit	$4.8	1989	2014
Infliximab	Remicade	$2.4	1998	2014
Trastuzumab	Herceptin	$1.3	1998	2014
Rituxumab	Rituxan	$2.4	1997	2015
Pegfilgrastim	Neulasta	$2.2	2002	2015
Adalimumab	Humira	$1.2	2003	2019
Bevacizumab	Avastin	$2.4	2004	2019
Darbepoetin alfa	Aranesp	$2.3	2004	2019

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 bevicizumab 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.

- 2008 Congressional Budget Office (CBO) estimated a $200 million reduction in U.S.expenditures on biologics by 2013, and $25 billion by 2018
- 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

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.

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

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 - 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