House of Delegates Policy Topic Webinar – Biosimilar Drug Products

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Learning Objectives

1. Explain the different regulatory types of biological products
2. Describe the differences between biologic products and small molecule drugs.
3. Describe resources available for evaluating biosimilar drug products.
4. Explain barriers to pharmacy when supplying biosimilar drug products.

Which of the following statements is true?

A. All biosimilars are interchangeable with the originator product and with each other like traditional generic drugs
B. The molecular composition of biologic drugs is virtually impossible to fully characterize
C. The manufacturing process for biologics has minimal impact on stability, structure, or immunogenicity of the product
D. A biosimilar is an exact copy of a reference biologic product and is manufactured in an identical manner

Which of the following aspects of a biosimilar product may be different from the reference product?

A. Formulation (e.g., the vehicle)
B. Route of administration
C. Conditions of use (i.e., indications)
D. Strength

According to the U.S. Food and Drug Administration (FDA) draft guidance on biosimilars, which of the following is "fundamental" for demonstrating biosimilarity?

A. Studies evaluating structure and function
B. Human pharmacokinetics and pharmacodynamics studies
C. Clinical safety and effectiveness
D. Postmarketing studies, including pharmacovigilance

State biosimilars legislation typically has addressed all of the following *except*:

A. Naming of biosimilars
B. Notification of the prescriber and patient
C. Length of recordkeeping
D. Lists of substitutable products

Which of the following statements regarding potential substitution of biosimilars is *false*?

A. The FDA has created a "Purple Book" to help provide information on interchangeable biosimilar products

B. A number of states have passed legislation addressing the substitution of biosimilar products

C. The ACA created a category of "interchangeable biosimilars" that would be able to be substituted in a manner similar to traditional generic drugs

D. Biologic and biosimilar products are both approved through FDA's 351(a) pathway

What Is a Biologic (Biopharmaceutical)?

- 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
- "Therapeutic proteins"

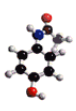
U.S. Code of Federal Regulations Title 21 Subchapter F – Biologics.
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=600.3

Differences Between Chemical Drugs and Biologics

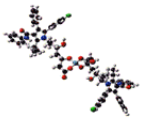
	Chemical Drugs	Biologics
Size	Small, low molecular weight	Large, high molecular weight
Structure	Simple, well-defined	Complex, heterogeneous
Manufacturing	• Reproducible chemical reactions • Identical copies can be made	• Living cells or organisms • Impossible to ensure identical copies
Characterization	Completely characterized	Impossible to fully characterize molecular composition
Stability	Stable	Unstable, sensitive to external conditions
Immunogenicity	Mostly non-immunogenic	Immunogenic

Declerck PJ. *GaBI Journal*. 2012;1(1)13-6.

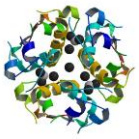
Relative Size and Complexity of Small Molecule Drugs and Biologics



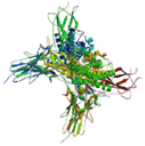
Acetaminophen
151 daltons



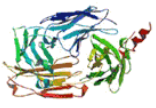
Atorvastatin
558 daltons



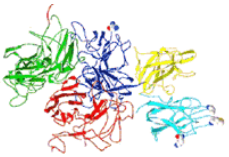
Insulin Glargine
6,063 daltons



Filgrastim
158,880 daltons



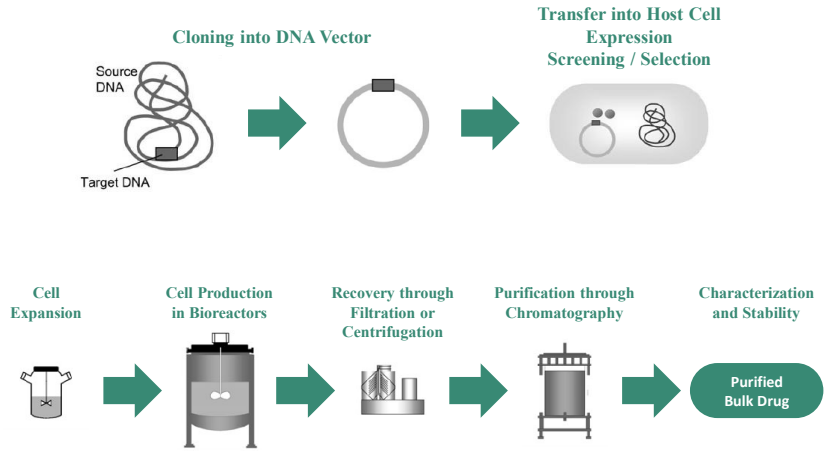
Rituximab
145,000 daltons



Coagulation Factor VIII
264,400 daltons

DrugBank 4.1. www.drugbank.ca

Manufacturing Process for Biologics



Mellstedt H, et al. *Ann Oncol.* 2008;19:411-9.

Biologics Have Varying Risks of Immunogenicity

- Manufactured in living cells
  - Hamster cells, rabbit cells, bacteria *(E. coli)*, etc.
- 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 chance of immunogenicity
- Scientific tools for detecting immunogenicity exist, but they are not precise

U.S. FDA. Immunogenicity Assessment for Therapeutic Protein Products. August 2014. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

Changes in Manufacturing Can Have Real Consequences

- Differences in manufacturing can lead to differences in structure, stability, and impurities as well as excipients
- Changes in the manufacturing of an epoetin alfa resulted in a small change in formulation
  - Decreased protein stability and increased aggregate formation
  - Resulted in cases of pure red cell aplasia
- Excessive host cell protein contamination increased immunogenicity with somatropin
  - Resolved with additional purification

Owens DR, et al. *Diabetes Technol Ther*. 2012;14:989-96.
Schellekens H. *NDT Plus*. 2009;2(suppl_1):i27-i36.

What Is a Biosimilar?

- A biosimilar is a "copy" of a commercially available biologic agent (reference or originator product) that has gone off patent
- A biosimilar is "similar" to the reference product with demonstrated similarity in physicochemical characteristics, efficacy, and safety based on data from analytical studies, animal studies, and clinical study or studies

Weise M, et al. *Nat Biotechnol*. 2011;29:690-3.
Zelenetz AD, et al. *J Natl Compr Canc Netw*. 2011;9(suppl 4):S1–S22.

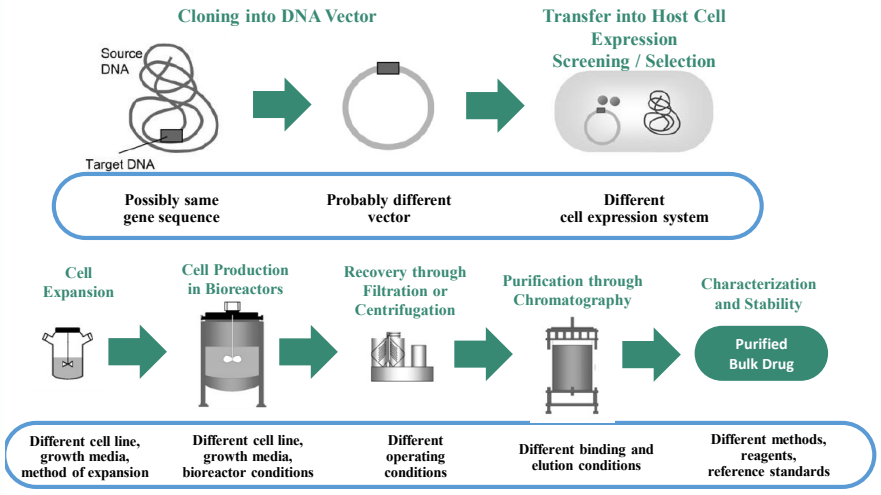
What Is a Biosimilar?

- Approved via an abbreviated pathway
- Exhibits "highly similar" efficacy and safety compared with reference product
- Interchangeable biosimilar
  - Can switch back and forth between biosimilar and reference with no clinical consequences
  - Appropriate for substitution without consulting the prescriber

Weise M, et al. *Nat Biotechnol*. 2011;29:690-3.

Zelenetz AD, et al. *J Natl Compr Canc Netw*. 2011;9(suppl 4):S1–S22.

Manufacturing Process for Biosimilars



Mellstedt H, et al. *Ann Oncol*. 2008;19:411-9.

Potential Differences vs Reference

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

Zelenetz AD, et al. *J Natl Compr Canc Netw*. 2011;9(suppl 4):S1-S22.

Biosimilar vs Generic

- A generic is an identical copy of a chemical drug that has gone off patent
- Biosimilars are **not** generics
  - Biosimilars are not identical to the reference product because of differences in manufacturing processes
- Therefore, an assessment of biosimilarity is much more complex than the assessment of "bioequivalence" for small-molecule generic drugs

Biosimilarity vs Bioequivalence

- **Biosimilarity**[1]
  - Unlikely to have "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 become 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**

1. FDA. Biosimilars: Questions and Answers Implementation of BPCI Act of 2009. April 2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf
2. FDA. Bioavailability and Bioequivalence Studies. March 2003. www.fda.gov/downloads/Drugs/.../Guidances/ucm070124.pdf

General Principles for Demonstrating Biosimilarity

- Biosimilars approved via an abbreviated pathway
- Demonstration of biosimilarity is a comparability exercise and not a therapeutic equivalence study
- The goal of the biosimilarity exercise is to establish that the candidate biosimilar is not significantly different from the reference product and is **unlikely to have any clinically significant differences**
  - Smaller-scale direct comparisons and extrapolation are used

FDA. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. April 2015. http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

Biosimilar vs Reference Product

Characteristic	Comparison with Reference
Stability	May be different
Efficacy	Unlikely to have clinically meaningful differences
Safety	Unlikely to have clinically meaningful differences
Active ingredient	Not exactly the same
Manufacturing	Different process
Immunogenicity	May be different

Understanding Key Differences Between Biosimilars and Small Molecule Generics. Spec Pharm Continuum. 2013:vol 2.
IFPMA. Biotherapeutic Medicines: Grasping the New Generation of Treatments. 2012.
www.ifpma.org/fileadmin/content/Publication/2012/IFPMA_BiotheraputicsWeb4.pdf

FDA Specifications for Biosimilars

Biosimilar Product Specification	Comparison with Reference
Formulation	May be different
Delivery device/container	May be different
Routes of administration	May obtain licensure for fewer than all routes of administration for which reference product is licensed
Indications for use	May obtain licensure for fewer than all conditions of use for which reference product is licensed
Strength	Must be the same

FDA. Biosimilars: Questions and Answers Implementation of BPCI Act of 2009. April 2015.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

Projected U.S. Patent Expirations for Major Biologics

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

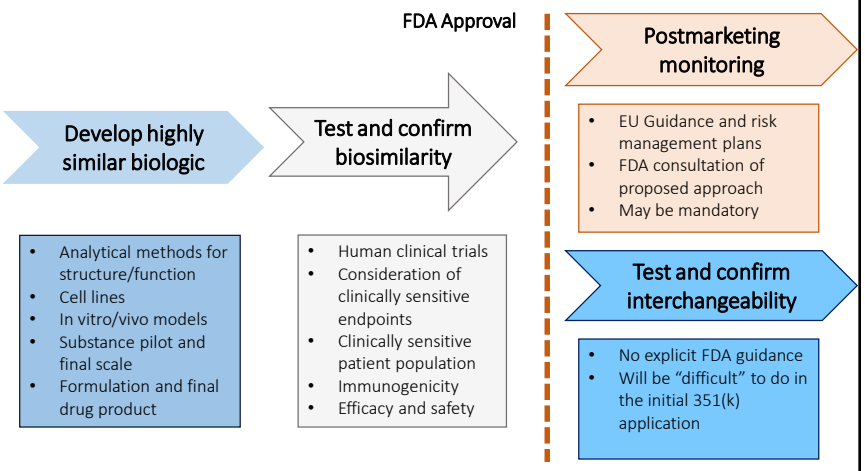
Lucio SD, et al. *Am J Health-Syst Pharm*. 2013;70:2004-17.
www.gabionline.net/Biosimilars/General/US-67-billion-worth-of-biosimilar-patents-expiring-before-2020

Demonstrating Biosimilarity: Things to Keep in Mind

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

FDA. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. April 2015. http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

Biosimilar Development Approach



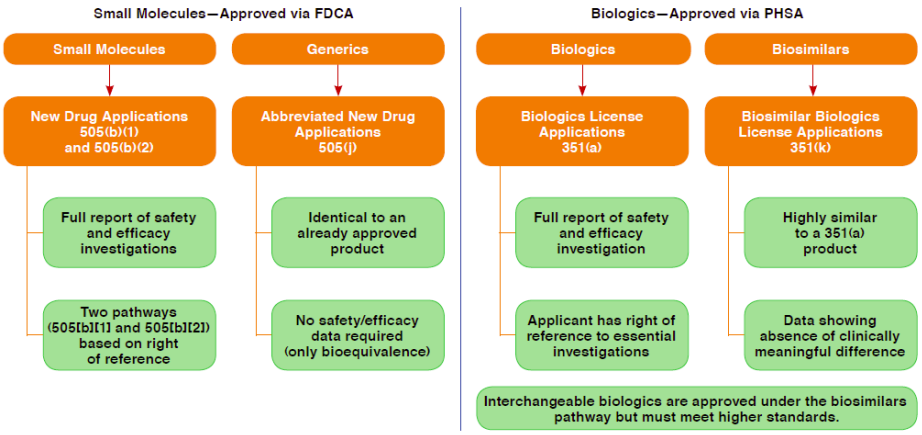
Adapted from: McCamish M, et al. *Clin Pharmacol Ther*. 2012;91:405-17.
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf

Varying Regulatory Types

	351(a) Originator	351(k) Biosimilar	351(k) Interchangeable Biosimilar	351(a) Non-originator biologic
Description	First-to market biologic molecule; will likely be the reference product	"Highly similar" to reference product; approved via Biosimilars pathway	A biosimilar that meets additional standards so that it can be substituted for the reference without permission from prescriber	It is "another brand name" of an already approved biologic
Depth of data submitted to the FDA	"Standard" data package of efficacy and safety	Abbreviated data package for comparability	Abbreviated data package for comparability; more information on switching	"Standard" data package of efficacy and safety
Compared to originator?	N/A	Yes	Yes	Not necessary (yes or no)
Implications		Biosimilar pricing; explicit regulatory oversight on comparison with reference; possible pharmacist substitution (for interchangeable biosimilars)		Different pricing structure and substitution issues

Lucio et al, 2013

Approval Processes



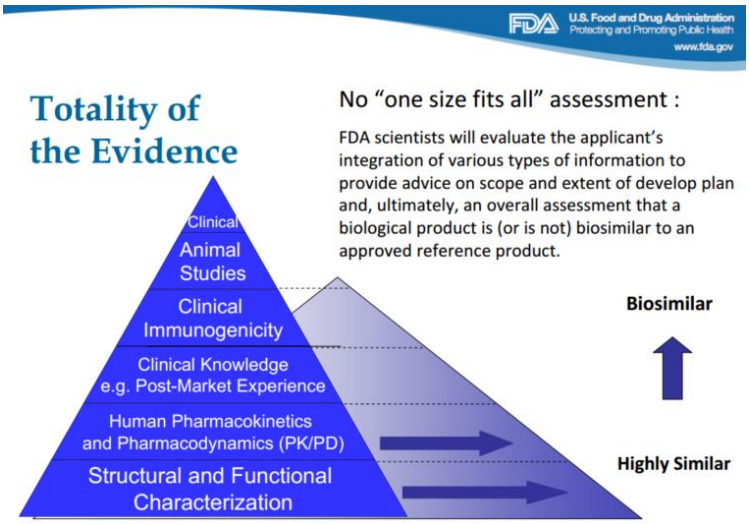
Approval pathways for drugs vs. biologics (from Li et al., 2015)

Demonstrating Biosimilarity: A Stepwise Approach

- Compare proposed biosimilar to reference in terms of:
  1. Structure
  2. Function
  3. Animal Toxicity Studies
  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

FDA. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. April 2015. http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

Biosimilar and Biologic Development



www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM292463.pdf

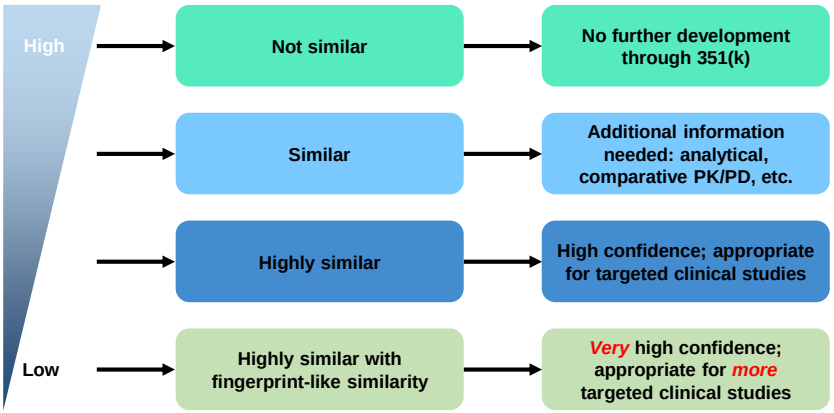
Structure and Function

- Serve as the "foundation" of biosimilar development
- Useful in determining future studies that 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

FDA. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. April 2015. http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

Four Assessments of Analytical Characterization

Studies of Structure and Function: Residual Uncertainty



FDA. Draft guidance for industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. May 2014. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf 33

Human Pharmacokinetics and 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
    - Have the sensitivity to detect clinically meaningful difference
- Ideally correlate exposure to clinical outcomes
- Utilize crossover and parallel designs

PK=pharmacokinetics; PD=pharmacodynamics

FDA. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. April 2015. http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf 34

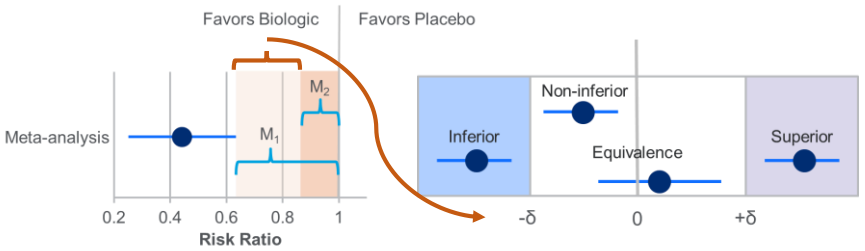
Clinical Studies

- 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
- Efficacy and safety: 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
  - Biosimilar sponsor to justify comparability delta

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

Clinical Trial Design: Equivalence

- Establish the equivalence margin (δ) via the 95-95 method
- 95% CI should fall between -δ and +δ for equivalence



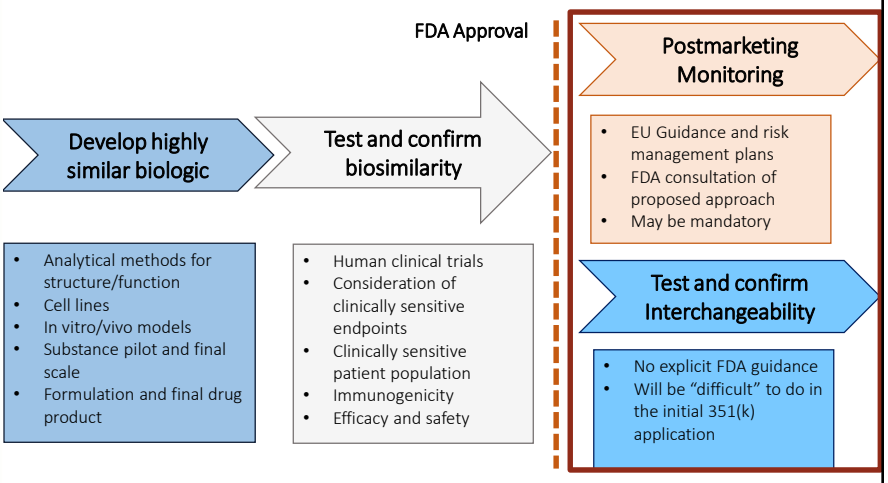
- However, non-inferiority studies may be appropriate if it is well-established that the biologic saturates the receptors at the clinical dose

Adapted from: Dranitsaris G, et al. *Invest New Drugs*. 2013;31(2):479-487 and Greene CJ, et al. *J Trauma Stress.* 2008; 21(5):433-9.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

Biosimilar Products: Summary

- A comprehensive comparability exercise is conducted for biosimilar products in preparation for regulatory approval
  - Physiochemical characterization is foundational to the data package
  - Efficacy and safety studies assess equivalence to the reference product
- Insulins present a challenge in the United States because they are approved via the new drug application (NDA) pathway

Biosimilar Development Approach



Adapted from: McCamish M, et al. *Clin Pharmacol Ther*. 2012;91:405-17.
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf

Postmarket Monitoring: EU Risk Management Plans

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

Step	Description	Risk Management Plan
1. Detection	Identify risk	Pharmacovigilance
2. Assessment	Understand/monitor risk	
3. Communication	HCP education	Risk minimization
4. Minimization	Act to reduce risk	

Zuñiga L, et al. *Pharmacoepidemiol Drug Saf*. 2010;19:661-69.

FDA Guidance: Postmarketing Monitoring for Safety

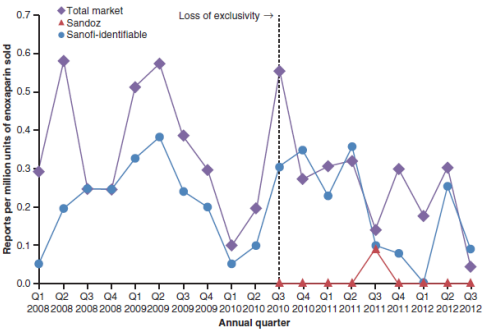
- Important to assure safety for **all** biologics
  - Consider risks seen in reference
  - Are there any new safety concerns?
  - Population-based assessments gives larger N to identify rare safety concerns
  - Might be mandatory for some products
- Biosimilar manufacturers should work with FDA early to discuss approach
- Current pharmacovigilance guidance by FDA

FDA. Guidance for industry. February 2012.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf

Pharmacovigilance Challenges: Enoxaparin Case Study in the United States

- Commercial claims data analysis of patients receiving prescriptions for enoxaparin
  - No statistical difference between branded vs generic with incidence of HIT (1.2% vs 1.5%, *P*<0.0001)
- Increasing market share of generic products after loss of exclusivity in 2010 (to about 44% in 2012)

Enoxaparin thrombocytopenia reports by sponsor: FDA AERS Analysis



Grampp G, et al. *Expert Opin Drug Saf.* 2015;14(3):349-60.

Pharmacovigilance: Challenges in the United States

- Health care providers need to correctly attribute the safety signal
- How?
  - Traceability and attribution
    - Naming
    - Codes: NDC vs HCPCS
  - Data
    - Prospective registries
    - Administrative claims
    - Electronic health record
    - Linked databases
    - Spontaneous adverse event reporting

Interchangeability

- Safety standards for determining interchangeability
  - Must be a biosimilar
  - Produces same clinical result as the reference in any given patient
  - Risk of safety or diminished efficacy due to alternating or switching between biosimilar and reference is no more than using the reference product with no switching
- Will be "difficult" in the initial 351(k) application due to the sequential nature of the assessment
- Appropriate to be "substituted for the reference product without the intervention of the health care provider who prescribed the reference product"

Public Health Service Act, section 351(k)(4).
www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/ucm216146.pdf

Interchangeability Study Design

- FDA interchangeability criteria: switch between reference (R) and biosimilar (B) with no clinical consequences
- What is switching?

R → B	B → R → B
B → R	R → B → R
R → R	
B → B	

- Various designs proposed
  - Standard two-sequence, two-period crossover
  - Balaam's 4 x 2 crossover design

Chow SC, et al. *Stat Med*. 2013;32:442-8.

Key Points thus far…

- There is a robust regulatory pathway for the approval of biosimilar agents in the United States
- A biosimilar's analytical characterization serves as the foundation for further studies
- Interchangeability and pharmacovigilance are important but unresolved issues in the United States

Issues and Considerations: Premise Statements

Biosimilars are not generics

- Different regulatory pathway vs generics
- Different data submitted to FDA to establish efficacy and safety vs originators

Product and data differences create operational and clinical challenges

Operational Challenges

Domain	Elements	Institutional Risk
Formulary analysis	• Product approval pathway and data package • Appropriate indications (on-label and off-label) for use • Extrapolation considerations • Therapeutic interchange +/- guided use policies • Transitions of care • Payer mix	• Institution's use results in poor clinical outcomes • Over-burdensome policies • Poor considerations of transitions of care lead to logistical problems • Off-policy requests (time waste)
Order management and information systems	• Differentiate biosimilar and reference in electronic systems • Order sets, protocols, MARs • Medication reconciliation	• Poor documentation of product actually received and impact on transitions of care • Incorrect attribution for ADE reporting

Adapted from: Lucio et al. *Am J Health Syst Pharm*. 2013; 70(22):2004-17

Operational Challenges

Domain	Elements	Institutional Risk
Inventory management	• Buyer needs adequate information (NDC code, etc.) • Both biosimilar and reference in stock? • Product storage	• Medication errors: wrong product dispensed and/or administered • Procurement delay
Financial analysis	• Pricing information comparison (base, contract, reimbursement, margin) • Staff management time • Patient assistance and out-of-pocket expenses • Determine financial impact	• Margin and time not considered (outpatient) – financial loss • Dollars saved/earned may not be worth the unmitigated risks (above)
Education	• Drug information and education to all providers (clinical info, policies, etc.) • Patient education materials	• Providers provide wrong information to patients • Point-of-care confusion (time waste)

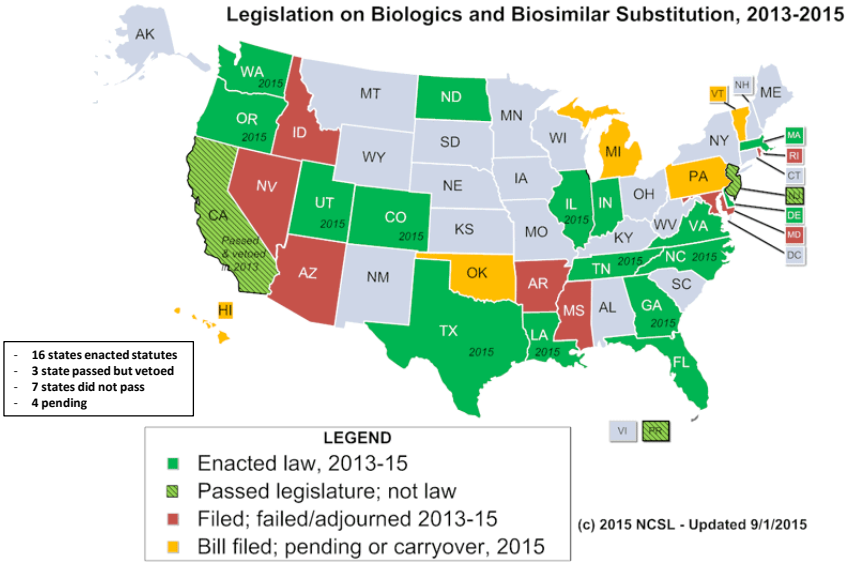
Adapted from: Lucio et al. *Am J Health Syst Pharm*. 2013; 70(22):2004-17

Pharmacist Substitution

- State law gives pharmacists the authority to act independently of the prescriber to dispense the lowest-cost, equivalent medicinal product
- Framework
  - Product criteria
    - Orange book (ANDA generics)
    - Purple book (351(k) biosimilars)
  - DAW
  - Communication with prescriber/patient
  - Record keeping
  - Hospital/health system exemption

Li EC, et al. *J Manag Care Spec Pharm*. 2015;21(7):532-39

Biosimilar Legislation by State



National Conference of State Legislatures. www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx.

Sample of Enacted Biosimilar Substitution Laws

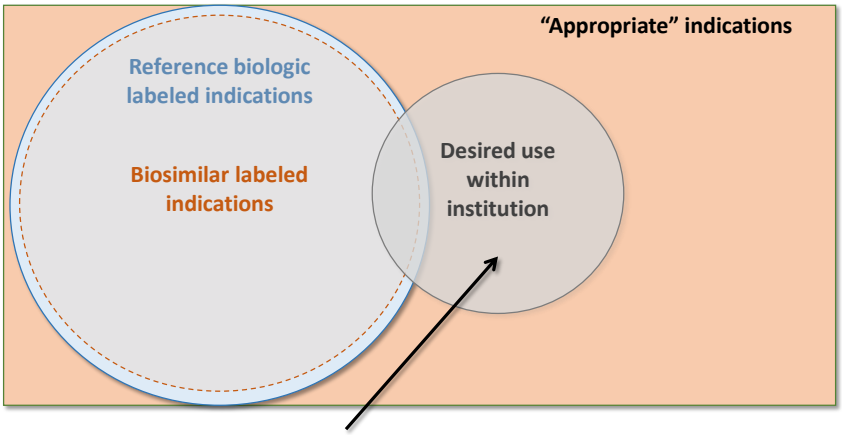
State	DAW	Product's criteria for substitution/interchange	Prescriber/patient communication	Record Keeping
DE	Yes	FDA designated interchangeable or therapeutic equivalent	Inform patient; inform prescriber in 10 days	Same as generic law
FL	Yes	FDA determined interchangeable	Inform patient same as generic; EMR notification for institutions	2 years
VA	Yes	FDA determined interchangeable	Inform patient of cost; inform prescriber within 5 days	2 years
MA	Yes	FDA determined interchangeable	Inform patient and prescriber (no timeline)	1 year

http://delcode.delaware.gov/title24/c025/sc06/index.shtml
http://www.flsenate.gov/Session/Bill/2013/0365/BillText/er/PDF
https://leg1.state.va.us/cgi-bin/legp504.exe?131+ful+CHAP0412
http://www.foleyhoag.com/publications/alerts-and-updates/2014/june/massachusetts-enacts-new-biosimilars-substitution-law

Pharmacy Practice Implications

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

Clinical Issues and the Desired Use of the Biosimilar



P&T determination

Must incorporate patient, disease and endpoint factors with biosimilarity data

Considerations for Formulary Selection of Biosimilars

Efficacy/Safety	Manufacturer Considerations	Product Considerations	Hospital and Patient Factors
• Clinical data • Range of indications • Immunogenicity concerns • Potential for therapeutic interchange • Number of similar agents on formulary • Pharmaco-vigilance requirements	• Supply reliability • History of drug shortages • Supply chain security • Anti-counterfeit measures • Patient assistance programs • Reimbursement support	• Product packaging and labeling • Bedside bar coding • Compatibility with CSTDs*, robotics • Product preparation and administration • Storage requirements	• Economic considerations ✓ Hospital ✓ Payer ✓ Patient • Payer policies • Transitions of care • IT and medication system changes • Educational requirements

CSTDs = closed-system transfer devices

Griffith N, et al. *Hosp Pharm*. 2014;49:813-25.

Major Challenges for P&T Committees With Biosimilars

- Indication extrapolation by the P&T Committee
- Product naming and impact on ordering, errors, traceability, and pharmacovigilance
- Evaluation of overall economic impact of use of biosimilars
  - Combined inpatient and outpatient impact
  - Challenges of portfolio pricing
  - Impact on patient out-of-pocket expense
- How many "similar" products to carry on the formulary
- How to manage transitions of care
  - Desire to minimize switching
    - Reduced chance for error
    - Avoid potential immunogenicity problems
  - Analogy with generic immunosuppressants in transplant recipients?

Recommendations to Pharmacists for Biosimilars

- Utilize existing formulary system and processes to evaluate for formulary inclusion
- Carefully consider scope of indications for use
- Conduct sophisticated economic analysis, considering costs, reimbursement, and patient impact
- Plan for therapeutic equivalence and guided-use policy and processes
- Consider processes for transitions of care
- Prepare information technology (IT) systems to facilitate effective pharmacovigilance programs
- Meet educational needs of patients and providers

Current Resources for Pharmacists

- FDA's "purple book"
- Biosimilars Draft Guidance Documents
- State specific legislation or regulation
- Biosimilars Proposed Rule

FDA, Purple Book
http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm
FDA, Draft Guidance, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm459987.pdf
Federal Register, FDA Proposed Rule,
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm459987.pdf

Conclusion

- Biosimilars present significant opportunities and challenges for pharmacists managing formularies and providing patient care
- A framework for biosimilar introduction is being defined in the United States
- Pharmacists must educate themselves to be prepared to play leadership roles in the safe and appropriate introduction of biosimilars
- Integration of biosimilar agents into clinical practice present many operational and clinical challenges
- Key issues yet to be determined include interchangeability, pharmacovigilance requirements, naming, and traceability
- Pharmacists should take leadership in planning a strategy for successful operational/clinical use of these agents
- Transitions of care and medication reconciliation will be ongoing practice management issues

Which of the following statements is true?

A. All biosimilars are interchangeable with the originator product and with each other like traditional generic drugs
B. The molecular composition of biologic drugs is virtually impossible to fully characterize
C. The manufacturing process for biologics has minimal impact on stability, structure, or immunogenicity of the product
D. A biosimilar is an exact copy of a reference biologic product and is manufactured in an identical manner

Which of the following aspects of a biosimilar product may be different from the reference product?

A. Formulation (e.g., the vehicle)
B. Route of administration
C. Conditions of use (i.e., indications)
D. Strength

According to the U.S. Food and Drug Administration (FDA) draft guidance on biosimilars, which of the following is "fundamental" for demonstrating biosimilarity?

A. Studies evaluating structure and function
B. Human pharmacokinetics and pharmacodynamics studies
C. Clinical safety and effectiveness
D. Postmarketing studies, including pharmacovigilance

State biosimilars legislation typically has addressed all of the following *except*:

A. Naming of biosimilars
B. Notification of the prescriber and patient
C. Length of recordkeeping
D. Lists of substitutable products

Which of the following statements regarding potential substitution of biosimilars is *false*?

A. The FDA has created a "Purple Book" to help provide information on interchangeable biosimilar products
B. A number of states have passed legislation addressing the substitution of biosimilar products
C. The ACA created a category of "interchangeable biosimilars" that would be able to be substituted in a manner similar to traditional generic drugs
D. Biologic and biosimilar products are both approved through FDA's 351(a) pathway