BIOSIMILAR INSULINS: ISSUES AND CONSIDERATIONS BEFORE CLINICAL USE

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Learning Objectives

- Outline the differences between biopharmaceuticals, biosimilars, and generic medications
- Discuss the FDA guidance documents and abbreviated regulatory pathway available for the licensing of “biosimilar” products and the implications for insulin products
- Describe the potential impact that changes in manufacturing and sourcing of ingredients for biosimilar products may have on immunogenicity, safety, and efficacy
- Discuss the critical issues of naming, interchangeability, and pharmacovigilance with biosimilar products including biopharmaceuticals with a narrow therapeutic window such as insulin
- Identify the issues and considerations for clinical use of biosimilar insulin products
Disclosures

• Curtis Triplitt, PharmD, CDE has served on a speaker bureau for Boehringer Ingelheim and AstraZeneca.
Pre-Activity Questions 1–4
Pre-activity Question 1

Which of the following statements is false?

A. All biosimilars are interchangeable with their reference product and each other

B. The molecular composition of biologics are impossible to fully characterize

C. The manufacturing process for biologics significantly impacts stability, structure, and immunogenicity

D. A biosimilar is a “copy” of a originator product with determined similarity in physicochemical properties and is unlikely to have “clinically meaningful” differences with the originator product
Pre-activity Question 2

Which of the following statements regarding biosimilars is true?

A. The Public Health Service Act (PHSA) created an abbreviated FDA approval pathway for biosimilars
B. Like the EMA, the FDA has issued specific guidance on the development of biosimilar insulins
C. The EMA requires immunogenicity studies of at least 12 months for biosimilar insulins
D. The FDA recognizes only 1 category of biosimilar drugs
Pre-activity Question 3

Which of the following is **true** regarding biosimilar insulin?

A. All biosimilar insulins will be designated as being interchangeable to the originator insulin

B. It has been determined that post-marketing pharmacovigilance is optional

C. It has been decided that biosimilar insulins will have the same name as the originator product

D. Only FDA designated interchangeable insulins are appropriate to be substituted for the reference product without the intervention of the prescribing healthcare provider
Pre-activity Question 4

Your organization has decided to add a biosimilar to the formulary. Which of the following actions would be appropriate for you to take?

A. Ensure a process is in place to trace adverse events for the specific product

B. Ensure that automatic substitution is in place for the biosimilar

C. Ensure that the biosimilar is maximally used to improve pharmacy margins

D. None of the above
Differences Between Biopharmaceuticals, Biosimilars, and Generics
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”
### Differences Between Chemical Drugs and Biologics

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

Relative Size and Complexity of Small Molecule Drugs and Biologics

Acetaminophen
151 daltons

Atorvastatin
558 daltons

Insulin Glargine
6063 daltons

Filgrastim
158,880 daltons

Rituximab
145,000 daltons

Coagulation Factor VIII
264,400 daltons

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

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
Why Biosimilars?
# Biologics Expenditures

## Top 15 Drugs by Expenditures in Clinics in 2012

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegfilgrastim</td>
<td>2,411,397</td>
<td>11.4</td>
<td>1,919,238</td>
<td>7.2</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>3,119,524</td>
<td>-16.5</td>
<td>1,870,309</td>
<td>-21.2</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2,255,393</td>
<td>3.2</td>
<td>1,865,160</td>
<td>8.5</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2,119,656</td>
<td>7.6</td>
<td>1,633,746</td>
<td>5.2</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2,092,741</td>
<td>-14.8</td>
<td>1,533,918</td>
<td>-2.1</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>1,592,326</td>
<td>23.3</td>
<td>1,101,816</td>
<td>-6.1</td>
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<tr>
<td>Trastuzumab</td>
<td>1,328,336</td>
<td>6.8</td>
<td>1,082,530</td>
<td>11.1</td>
</tr>
<tr>
<td>Oxaliplatin c</td>
<td>840,706</td>
<td>26.3</td>
<td>862,309</td>
<td>6.9</td>
</tr>
<tr>
<td>Varicella vaccine</td>
<td>771,031</td>
<td>10.1</td>
<td>652,645</td>
<td>28.9</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>804,033</td>
<td>5.5</td>
<td>639,058</td>
<td>7.5</td>
</tr>
<tr>
<td>Denosumab</td>
<td>382,903</td>
<td>1873.0</td>
<td>525,098</td>
<td>119.0</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>758,485</td>
<td>-9.3</td>
<td>512,328</td>
<td>-11.0</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>637,880</td>
<td>-2.6</td>
<td>443,686</td>
<td>-9.1</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>526,431</td>
<td>17.6</td>
<td>400,255</td>
<td>3.9</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>455,628</td>
<td>4.0</td>
<td>390,627</td>
<td>16.6</td>
</tr>
<tr>
<td>All others</td>
<td>18,715,804</td>
<td>9.0</td>
<td>14,187,464</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38,812,274</strong></td>
<td><strong>5.7</strong></td>
<td><strong>29,620,187</strong></td>
<td><strong>3.4</strong></td>
</tr>
</tbody>
</table>

a. Based on data collected between January 1 and September 30, 2012.  
   b. Percent change compared with same period in 2011 (data not shown in table).  
   c. Available from one or more manufacturers, distributors, or repackers by generic name.

## Projected US Patent Expirations for Major Biologicals

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

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 for development of biosimilars**
Biosimilar Legislation

• Biologics Price Competition and Innovation Act (BPCI) of 2009 created an abbreviated FDA approval pathway for biosimilars

• Before BPCI, there was no abbreviated pathway for FDA approval of copies of biologics

• FDA approval pathway for chemical drugs and biologics differ
Pathways for Approval in the USA

Chemical Drugs
- Small molecules
- Approved via FDCA
  - New Drug Application (NDA)
    - Safety and Efficacy must be demonstrated
  - Abbreviated New Drug Application (ANDA)
    - Bioequivalence must be demonstrated

Biologics
- Proteins
- Approved via PHSA
  - Biologics License Application (BLA)
    - Safety and Efficacy must be demonstrated
  - Biosimilar Biologics License Application
    - Must demonstrate that it is highly similar to reference
      - Interchangeable biosimilars require more data

FDCA = Federal Food Drug and Cosmetic Act; PHSA = Public Health Service Act.


• Requirements can vary for abbreviated approval process

• 12 years of exclusivity for innovator biologic products (6 month pediatric indication extension)

• Three categories for biosimilar
  – Biosimilar (non-interchangeable)
  – Interchangeable biosimilar
  – Full BPCI-approved biologic (BLA)

BLA = biologic licensing application.
A similar biological medicinal product, also known as “biosimilar”, is a product that is similar to a biological medicine that has already been authorized, the so-called “reference medicinal product”. The active substance of a biosimilar medicine is a known biological active substance and similar to the reference medicinal product. A biosimilar medicine and its reference medicinal product are expected to have the same safety and efficacy profile and are generally used to treat the same conditions.

EMA Approval Process

• FDA modeled guidance after EMA with few exceptions
  – EMA does not have an “interchangeable biosimilar” category. This is left to national agencies
  – EMA has biosimilar pathway for heparins, while FDA approved enoxaparin through ANDA (only PK evidence)
  – EMA has pharmacovigilance requirements for ALL biologics (each has an EU Risk Management Plan)

• EMA does not permit extrapolation to all indications, unlike small molecule generics
  – Working Party on Similar Biologic Medicinal Products currently considering guidelines for extrapolation (MOA, safety profile, ability to monitor)

• Until now, insulins have been approved as new drugs – one application for insulin glargine biosimilar currently under consideration

MOA = mechanism of action.
EMA: Specific Guidance on Biosimilar Insulin Development

- First adopted in 2006 and revised in December 2012
- Outlines non-clinical and clinical requirements for biosimilar recombinant insulin products
- Non-clinical studies
  - In vitro pharmacodynamic and toxicological studies
- Clinical studies
  - Time-concentration and time-action profiles
  - Immunogenicity studies of at least 12 months
    - Impact on glycemic control, insulin requirements, local and systemic hypersensitivity reactions
- Requires pharmacovigilance plan
- Extrapolation of indications if similar PK, PD, and immunogenicity demonstrated

FDA: Development of Biosimilar Insulins

• Unlike the EMA, the FDA currently has no specific guidance for the development of biosimilar insulins

• No requirement for 12 month immunogenicity studies
  – Increases uncertainty

The Development of Biosimilars
Demonstrating Biosimilarity: General Principles

• 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

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 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**

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Demonstrating Biosimilarity: A Stepwise Approach

- Compare proposed biosimilar with reference in terms of:
  - Structure
  - Function
  - Animal data
  - Human pharmacokinetics (PK) and pharmacodynamics (PD)
  - Clinical immunogenicity
  - Clinical safety and effectiveness

- FDA intends to use 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

Four Assessments of Analytical Characterization

Studies of Structure and Function: Residual Uncertainty

- **High:**
  - Not similar → No further development through 351(k)
  - Similar → Additional information needed: analytical, comparative PK/PD, etc.
  - Highly similar → High confidence; appropriate for targeted clinical studies
  - Highly similar with fingerprint-like similarity → Very high confidence; appropriate for more targeted clinical studies

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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.**

Pharmacokinetics:
- At least 1 clinical study on the relative PK properties of biosimilar insulin vs reference after subcutaneous administration
- Single-dose, crossover design preferably in patients with type 1 diabetes
- Primary endpoint: AUC
- Secondary endpoints: Cmax, Tmax, half-life

Pharmacodynamics:
- Euglycemic glucose dose clamp
- Double-blind, crossover with collection of PK
- No specifics regarding study population

These may be sufficient for market approval (efficacy)

PK and PD Profiles of Failed Biosimiliar Insulins

**Pharmacokinetics**

- Humulin R (S)
- Marvel Rapid

**Pharmacodynamics**

- Humulin R (S)
- Marvel Rapid

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
Biologic Development

- Animal data
- Function
- Structure

Physiochemical characterization

Biological characterization

Preclinical studies

Human PK/PD

Clinical Trials

FDA approval

Other indications

Post-market monitoring

- Efficacy/safety
- Immunogenicity
- PK/PD

Biosimilar Development

- Physiochemical characterization
- Biological characterization
- Preclinical studies
- Human PK/PD
- Clinical Trials

Interchangeability

Biosimilarity

Post-market monitoring

- Efficacy/safety
- Immunogenicity
- PK/PD

- Animal data
- Function
- Structure

Biosimilar Development Approach

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

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

FDA Approval

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

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

# FDA Specifications for Biosimilars

<table>
<thead>
<tr>
<th>Biosimilar Product Specification</th>
<th>Comparison with Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>May be different</td>
</tr>
<tr>
<td>Delivery device/container</td>
<td>May be different</td>
</tr>
<tr>
<td>Routes of administration</td>
<td>May obtain licensure for fewer than all routes of administration for which reference product is licensed</td>
</tr>
<tr>
<td>Conditions of use</td>
<td>May obtain licensure for fewer than all conditions of use for which reference product is licensed</td>
</tr>
<tr>
<td>Strength</td>
<td>Must be the same</td>
</tr>
</tbody>
</table>

Safety and Efficacy of Biosimilars
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 the chance of immunogenicity
- Scientific tools for detecting immunogenicity exist, but they are not precise

Manufacturing Process for Biologics

Cloning into DNA Vector

Transfer into Host Cell
Expression
Screening / Selection

Cell Production
in Bioreactors

Recovery through Filtration or Centrifugation

Purification through Chromatography

Characterization and Stability

Purified Bulk Drug

Manufacturing Process for Biosimilars

Cloning into DNA Vector

Transfer into Host Cell Expression Screening / Selection

Possibly same gene sequence

Probably different vector

Different cell expression system

Cell Expansion

Cell Production in Bioreactors

Recovery through Filtration or Centrifugation

Purification through Chromatography

Characterization and Stability

Different cell line, growth media, method of expansion

Different cell line, growth media, bioreactor conditions

Different operating conditions

Different binding and elution conditions

Different methods, reagents, reference standards

Differences 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

Impurity Profiles Vary Based on Manufacturing Process

**Basalog®** - biosimilar insulin glargine expressed in the yeast *Pichia pastrois*

AU = absorption units.
Potential Differences vs Reference

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

# Biosimilar vs Reference Product

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Comparison with Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stability</strong></td>
<td>May be different</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Unlikely to have clinically meaningful differences</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Unlikely to have clinically meaningful differences</td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
<td>Not exactly the same</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Different process</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>May be different</td>
</tr>
</tbody>
</table>

Concern over antibodies to human insulin

- Antibodies to human insulin occur frequently but often without major clinical consequences
- Possible loss of efficacy, altered pharmacokinetics, lipoatrophy, allergy, etc...

Study design

- Longitudinal (6–12 months)
- Primary endpoint: incidence of antibodies to biosimilar insulin and reference insulin
- Allow for the analysis and correlation of immunogenicity with clinical data

References:

Post-Market 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:

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Risk Management Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Detection</td>
<td>Identify risk</td>
<td>Pharmacovigilance</td>
</tr>
<tr>
<td>2. Assessment</td>
<td>Understand/monitor risk</td>
<td></td>
</tr>
<tr>
<td>3. Communication</td>
<td>HCP education</td>
<td>Risk minimization</td>
</tr>
<tr>
<td>4. Minimization</td>
<td>Act to reduce risk</td>
<td></td>
</tr>
</tbody>
</table>

FDA Guidance: Post-Marketing Monitoring (for Safety)

• Important to assure safety
  – 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 PV guidances by FDA

PV = pharmacovigilance.
Pharmacovigilance: Challenges in the U.S.

- Traceability and attribution
  - Naming
  - Codes: NDC vs. HCPCS

- Data
  - Prospective registries
  - Administrative claims
  - Electronic health record
  - Linked databases

- Health care provider awareness: Correct attribution of safety signal
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”

Interchangeability Study Design

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

- What is switching?

  \[
  \begin{align*}
  &R \rightarrow B &B \rightarrow R \rightarrow B \\
  &B \rightarrow R &R \rightarrow B \rightarrow R \\
  &R \rightarrow R \\
  &B \rightarrow B
  \end{align*}
  \]

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

Biosimilar Naming

- Two positions: same vs. unique non-proprietary name
  - Unique: improved PV and patient safety
  - Same: facilitate substitution of interchangeable biologics

- ASHP position:
  - “…it is essential that biosimilars be given the same root name following standards for nonproprietary names”

- Ongoing discussions
  - FTC Follow-On Biologics Workshop
  - World Health Organization INN discussions

Biosimilars Are Coming
When Will the First Biosimilar Be Approved in the USA?

• March 6, 2015 - FDA approved Zarxio (filgrastim-sndz), the first biosimilar product approved in the United States.

• Biosimilar insulin glargine from Eli Lilly has tentative FDA approval, but final approval is not likely until mid-2016 due to ongoing patent litigation.

sndz=Sandoz a Novartis Company

The Purple Book

Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations

The "Purple Book" lists biological products, including any biosimilar and interchangeable biological products licensed by FDA under the Public Health Service Act (the PHS Act). The lists include the date a biological product was licensed under 351(a) of the PHS Act and whether FDA evaluated the biological product for reference product exclusivity under subsection 351(k) of the PHS Act. The Purple Book will also enable a user to see whether a biological product licensed under section 351(k) of the PHS Act has been determined by FDA to be biosimilar to or interchangeable with a reference biological product (an already-licensed FDA biological product). Biosimilar and interchangeable biological products licensed under section 351(k) of the PHS Act will be listed under the reference product to which biosimilarity or interchangeability was demonstrated.

Separate lists for those biological products regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) will be updated periodically.

Issues and Considerations for Biosimilar Insulins: 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 impact clinical evaluation and application
Clinical Issues for Biosimilar Insulin Use

Lack of Published Data

- EMA Guidance: clinical PK/PD data may be enough for market approval
  - Profound lack of scientific publications on biosimilar insulins
  - Practically no results of clinical studies with biosimilar insulins have been published; most data are with the original insulin formulations
  - Glucose clamp studies are the basis for PK/PD data but no glucose clamp study performed in the EU or USA as part of an application for biosimilar insulin approval has been published

Clinical Issues for Biosimilar Insulins

Immunogenicity

• Differences in sourcing and manufacturing
  – May result in differences in stability and impurities
  – Batch-to-batch variability not systemically investigated
  – Immunogenicity differences, may not be well studied prior to approval, post-market pharmacovigilance needed for further elucidation

Clinical Issues for Biosimilar Insulins

*Delivery Devices*

- If available, insulin pen used to administer biosimilar insulin likely different than originator
  - Patients switching will require education

Issues of Pharmacist Substitution

• State legislation to clarify pharmacist authority to substitute
  – Criteria for substitution: FDA interchangeability designation
  – DAW
  – Health systems to have own process?
  – Patient/prescriber notification/communication
  – Record keeping
  – Expanded scope of practice considerations

• Challenges
  – Agents with narrow therapeutic window (i.e., insulins)
  – Care transitions throughout health system
  – Medication reconciliation

DAW = dispense as written.
Practical Issues for Biosimilar Use

• Formulary analysis
  – Limited available data; indication extrapolation; therapeutic interchange

• Order management and information systems
  – Difficulty differentiating between all the insulins (biosimilar vs originator)
  – Incorrect attribution of ADE reporting

• Inventory management
  – Cost of stocking both biosimilar and originator, product storage, shelf placement

• Financial analysis
  – Dollars saved/earned worth the staff management time

• Education
  – Providers and patients need to be educated on biosimilars

ADE = adverse drug event.

Summary

• Unlike generic drugs, biosimilars are not identical copies of a originator product due to its origin of a living source, complex manufacturing process and molecular structure.

• The FDA has established an abbreviated pathway for the approval of biosimilars in the U.S. but unlike the EMA, there is currently no specific guidance for development of biosimilar insulins.

• Differences in immunogenicity is an area of concern with biosimilars as differences in sourcing and manufacturing can affect product stability, impurities, and immunogenicity.
Summary

• Biosimilar naming is yet to be resolved and will impact adverse event attribution and traceability.

• Biosimilar substitution is permissible if biosimilar deemed “interchangeable” by FDA but biosimilar substitution of narrow therapeutic window products are associated with increased risks as may be the case with insulin.

• Integration of biosimilar insulins into clinical practice presents many clinical and practical challenges.

• Pharmacists should take an active role in pharmacovigilance and implementation of a strategy for successful operational/clinical use of biosimilars.
Post-Activity Questions 1–4
Which of the following statements is **false**?

A. All biosimilars are interchangeable with their reference product and each other

B. The molecular composition of biologics are impossible to fully characterize

C. The manufacturing process for biologics significantly impacts stability, structure, and immunogenicity

D. A biosimilar is a “copy” of a originator product with determined similarity in physicochemical properties and is unlikely to have “clinically meaningful” differences with the originator product
Which of the following statements regarding biosimilars is **true**?

A. The Public Health Service Act (PHSA) created an abbreviated FDA approval pathway for biosimilars

B. Like the EMA, the FDA has issued specific guidance on the development of biosimilar insulins

C. The EMA requires immunogenicity studies of at least 12 months for biosimilar insulins

D. The FDA recognizes only 1 category of biosimilar drugs
Which of the following is true regarding biosimilar insulin?

A. All biosimilar insulins will be designated as being interchangeable to the originator insulin

B. It has been determined that post-marketing pharmacovigilance is optional

C. It has been decided that biosimilar insulins will have the same name as the originator product

D. Only FDA designated interchangeable insulins are appropriate to be substituted for the reference product without the intervention of the prescribing healthcare provider
Post-activity Question 4

Your organization has decided to add a biosimilar to the formulary. Which of the following actions would be appropriate for you to take?

A. Ensure a process is in place to trace adverse events for the specific product

B. Ensure that automatic substitution is in place for the biosimilar

C. Ensure that the biosimilar is maximally used to improve pharmacy margins

D. None of the above
Questions and Answers