Introducing Biosimilars: Opportunities and Challenges

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Disclosures

Steven Lucio is an employee of Vizient, Inc.
James Stevenson has served on advisory boards for Pfizer and has spoken in a program sponsored by AbbVie. He owns stock in and receives a salary from Visante, Inc.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Learning Objectives

1. Discuss the current status of biosimilars in the United States, including recent FDA activities and guidance.
2. Identify potential implications of biosimilars for pharmacists working in various practice settings, including issues of product substitution and interchangeability, as well as transitions of care.
3. Identify unresolved and emerging issues that complicate formulary decision-making for biosimilar products.
4. Describe challenges in the safe introduction of biosimilars into electronic ordering, dispensing, and administration systems based on the proposed naming convention, and potential strategies to support pharmacovigilance.

• Target Audience: Pharmacists and Pharmacy Technicians
• ACPE#: 0202-0000-17-013-L04-P/T
• Activity Type: Knowledge-based
Compared to the reference biological product, a biosimilar should be:

- Identical
- Highly similar
- Functionally similar
- Similar structure and function, but less immunogenic

According to the FDA, which type of product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product?

- Identical
- Biosimilar
- Interchangeable biologic
- Biobetter

None of the above may be substituted without the intervention of the prescriber.

Which of the following is correct about biosimilar clinical trial data?

- The range of indications for which the biosimilar is approved and for which the reference product is used must be considered.
- The dosage forms of the biosimilar need not be considered, since they will be identical to the reference product.
- The price, reimbursement, and patient out-of-pocket costs associated with the biosimilar and the reference product must be evaluated.
- A plan needs to be developed regarding how patients will be managed at the transitions of care (e.g., moving between outpatient and inpatient sites of care).

According to the FDA guidance, which of the following regarding the naming of biosimilars is FALSE?

- All biologics, including the reference product, should be named with an INN plus a 4-character suffix devoid of meaning.
- An INN plus a 4-character suffix devoid of meaning is required for biosimilars, but not for reference products.
- The reference product and any biosimilars should have distinct US Adopted Names (USAN) in order to foster pharmacovigilance.
- Use of a common INN plus a suffix for biosimilars will allow similar products to be grouped together in electronic ordering, dispensing and administration systems.

Integrating Biosimilars in Clinical Practice

- Approval of multiple biosimilars in the past 18 months and many more expected over the next several years.
- Some guidance from FDA just recently finalized or proposed (naming, interchangeability designation).
- State practice acts may not reflect biosimilars and/or new legislation is being adopted.
- A variety of practical questions and challenges are encountered when considering the implementation of biosimilars in the healthcare system.

Application Scenario

- Your organization supports large rheumatoid arthritis and gastroenterology practices and incurs a significant expense for the purchase of the biologic DMARDs. Concerned about this expense, your CFO asks you to start purchasing biosimilar versions of infliximab, etanercept, and adalimumab immediately as he saw in an e-mail that all of these products have been approved. How do you respond?
  A. Limit your CFO’s access to e-mail.
  B. Notify your buyer of this request so they can change ordering patterns.
  C. Notify the CFO that you must first obtain P & T approval for this switch.
  D. Notify your CFO that while these products are all approved, they are not all immediately available due to patent disputes and current regulatory interpretations.
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Why Are Biosimilars Not Immediately Launched Upon Approval?

- Issues:
  - Ongoing Litigation
    - Amgen vs. Sandoz (filgrastim)
    - Janssen vs. Celltrion (infliximab)
    - Amgen vs. Hospira (epotin alfa)
    - Amgen vs. Sandoz (etanercept)
    - Amgen vs. Sandoz (pegfilgrastim)
    - AbbVie vs. Amgen (adalimumab)
  - Supreme Court will review the Amgen vs. Sandoz case
    - April 2017 hearing (possible June 2017 ruling)

Biosimilars Currently Approved in the US

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Date Approved</th>
<th>Date Launched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim-sznd (Zarxio; Sandoz)</td>
<td>March 6, 2015</td>
<td>Launched September 3, 2015</td>
</tr>
<tr>
<td>Infliximab-dyyb (Inflectra; Celltrion/Pfizer)</td>
<td>April 5, 2016</td>
<td>Late November 2016</td>
</tr>
<tr>
<td>Etanercept-szsd (Enbrel; Sandoz)</td>
<td>August 30, 2016</td>
<td>?????</td>
</tr>
<tr>
<td>Adalimumab-atto (Amjevita; Amgen)</td>
<td>September 23, 2016</td>
<td>?????</td>
</tr>
</tbody>
</table>

Application Scenario

- The chair of P & T asks your opinion on biosimilar infliximab. He wants to wait to evaluate the product until phase III clinical trial data in all indications of the originator are available. Which of the following is the best response?

A. Agree since your organization primarily uses infliximab in inflammatory bowel disease patients and the approval of infliximab-dyyb did not include a study in these patients.
B. Agree with him since you hope the originator just lowers their price and you do not have to make a conversion.
C. Explain that data from the EU suggest that biosimilar infliximab is safe.
D. Explain that the rigor of the biosimilar approval pathway is so strong, replication of all clinical data is unnecessary and would add further expense and lessen the value these products can bring to market.

Biosimilar development concepts

- Clinical data
  - Adequate PK and PD (if relevant) comparison
  - Clinical study evaluating immunogenicity
  - If residual uncertainties in any previous steps, a comparative clinical study is required

- Animal studies
  - Toxicity studies, PK/PD studies, immunogenicity studies
  - Comparison of key quality attributes

Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic
Biosimilar Approval and Extrapolation

<table>
<thead>
<tr>
<th>Name</th>
<th>Indications studied</th>
<th>Mean of Approvals</th>
<th>Adaptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
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</table>

Extrapolation of Indications

- Extrapolation of data from a clinical trial in one disease to support approval for additional indications
- Factors to be considered
  - Clinical experience with the reference product
  - Mechanism(s) of action in each indication
  - Target receptors
  - Product structure and target/receptor interactions
  - Pharmacokinetics in different patient populations
  - Differences in the safety/immunogenicity profile between indications

Application Scenario

A patient you see in your RA clinic asks about biosimilars as she saw some information on a rheumatoid arthritis web site that she did not understand. Which of her following concepts about biosimilars is correct?

A. Biosimilars are not the same as generics.
B. Biosimilars will always be less expensive for her than the originator branded biologic.
C. If she has tried and failed an originator biologic, a biosimilar of that same product, might still work since it is not an identical product.
D. A biosimilar will always come in the same dosage form as the branded version with which she is familiar.

Potential Topics for Patient Education on Biosimilars

- Use of biologic therapies in the specific disease
- Definition of a biosimilar
- Totality of evidence required of a biosimilar
- Efficacy and safety similar to originator biologic
- Clinical trials to support biosimilars
- Delivery/administration of the agent
- Device use (if applicable)
- Access to treatment
- Insurance coverage and out-of-pocket cost
- Services available to support the patient
- Manufacturer identify

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Comparison of Dosage Forms

<table>
<thead>
<tr>
<th>Product</th>
<th>Originator Formulations</th>
<th>Biosimilar Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>300 mcg/mL, single dose vial</td>
<td>300 mcg/0.5 mL prefilled syringe</td>
</tr>
<tr>
<td></td>
<td>480 mcg/1.6 mL, single dose vial</td>
<td>480 mcg/0.8 mL prefilled syringe</td>
</tr>
<tr>
<td>Infliximab</td>
<td>100 mg/20 mL, lyophilized vial</td>
<td>100 mg/20 mL, lyophilized vial</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>10 mg, 20 mg, 40 mg, 80 mg prefilled glass vial</td>
<td>20 mg, 40 mg prefilled glass vial</td>
</tr>
<tr>
<td></td>
<td>40 mg, 80 mg prefilled pen</td>
<td>40 mg prefilled autoinjector</td>
</tr>
<tr>
<td></td>
<td>40 mg single use glass vial</td>
<td></td>
</tr>
<tr>
<td>Elenacept</td>
<td>25 mg, 50 mg prefilled syringe</td>
<td>25 mg, 50 mg prefilled syringe</td>
</tr>
<tr>
<td></td>
<td>50 mg prefilled autoinjector</td>
<td>50 mg prefilled syringe</td>
</tr>
<tr>
<td></td>
<td>25 mg multiple dose vial</td>
<td></td>
</tr>
</tbody>
</table>

Application Scenario
A new biosimilar has been approved for a biologic that is used in both adults and children. The reference product is approved for use in 5 indications and the biosimilar has been approved for the same indications.

- There is some “off-label” use of the reference product for two indications, both of which are well-supported by the literature but haven’t gone through the FDA-approval process
- The dose of the product is standardized in adults, but it is weight based in children
- The reference product is available in both pre-filled syringes and vials. The biosimilar is available in pre-filled syringes only. The biosimilar is priced about 25% less than the reference product.

Application Scenario (continued)
In considering the formulary status of the biosimilar and reference product, which of the following is a valid concern?

A. The biosimilar does not have clinical studies supporting its use for the non-approved indications so the reference product should be reserved for these indications

B. The biosimilar is only available in pre-filled syringes so it will be difficult to use in pediatrics

C. The biosimilar is priced less than the reference product so there will be a reduced margin for the healthcare provider/organization if a biosimilar is used instead of the reference product

D. Given that the biosimilar is not “interchangeable”, there is no reason in the formulary system to use the biosimilar instead of the reference product.

Application Scenario (continued)
In considering the formulary status of the biosimilar and reference product, which of the following is a valid concern?

A. The biosimilar does not have clinical studies supporting its use for the non-approved indications so the reference product should be reserved for these indications

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Factors Impacting Selection and Use of Biosimilars

- Range of indications
- Price/Reimbursement
  - CMS reimbursement policy – ASP + % of ASP of the REFERENCE Product
  - Proposal to have a common J code for biosimilars in a category
- Position within prescription drug plans (patient out-of-pocket costs)
- Dosage forms available
- Supply reliability
- Transitions of care
- IT and medication system changes
- Educational requirements
Application Scenario

A reference biologic and multiple biosimilars are available on formularies and in pharmacies. What strategy should be considered to prevent wrong-product selection errors in electronic ordering, dispensing, and administration systems?

A. Always list the reference product first in any list of products available
B. Always list the biosimilars first in any list of products available
C. Consider listing both the INN+suffix PLUS the brand name
D. List only the INN+suffix

The Conundrum of Biosimilar Naming

Biosimilars should have exactly the same United States Adopted Name (USAN) as the reference product

Pros
• Communicate that these products are "highly similar"
• Facilitate adoption and substitution of interchangeable biologics

Cons
• Difficult to trace for pharmacovigilance

Biosimilars should have a distinct USAN to differentiate from reference and other biosimilars

Pros
• Improved pharmacovigilance
• Recognize as distinct products
• Confusion about whether they are "interchangeable"
• May impede adoption
• Issues with substitution

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Biosimilar Naming Precedent

• WHO proposed guidance
  • Biological qualifier: INN + 4-letter, randomly assigned suffix
• EMA – approved with identical INN; differentiated with brand names
• Biosimilars approved in the U.S.
  • filgrastim-szsb (Sandoz)
  • infliximab-dyyb (Infectra, Celltrion, Hospira/Pfizer)
  • etanercept-szs (Erelzi, Sandoz)
  • adalimumab-atto (Amjevita, Amgen)

FDA Guidance onNaming

• USAN with an added random four-letter suffix “devoid of meaning” for all biologics (including reference products)
  • replicamab-czmn
  • replicamab-hsf
• Benefits
  • Ability to differentiate products for pharmacovigilance purposes
  • Common INN will group similar biologics in electronic systems
  • Having suffix for all products reduces perception that biosimilar is inferior to reference product

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### Scenarios with the listing of multiple biologics in electronic systems

<table>
<thead>
<tr>
<th>Filgrastim-dest</th>
<th>Filgrastim-rmfz</th>
<th>Filgrastim-rtrb</th>
<th>Filgrastim-znc</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS</td>
<td>VS</td>
<td>VS</td>
<td>VS</td>
</tr>
</tbody>
</table>

Which scenario do you believe is less prone to wrong-selection errors by prescribers, pharmacists, nurses?

### Application Scenario

A patient approaches the pharmacist about switching to one of the new biosimilar products because their prescription benefit plan has a higher co-pay for the reference product, which they have been taking for some time. Which of the following is the most appropriate action by the pharmacist?

A. Switch the patient to the biosimilar since the FDA has approved the biosimilar for the patient’s indication
B. Inform the patient that the biosimilar will likely not provide the same efficacy and safety as the reference product
C. Switch the patient to the biosimilar product, informing the physician after the fact that this interchange occurred
D. Contact the physician to discuss the patient’s access concern and ask to change the prescription to the biosimilar

### Interchangeability

- The biological is **biosimilar** to the reference product and can be expected to produce the *same clinical result* as the reference product in any given patient, and the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its reference product is *not greater* than the risk of using the reference product without such alteration or switch
- State substitution laws will impact practice

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

- Designed to enable a user to determine if a biological product is biosimilar or interchangeable with a reference biological per FDA evaluation
- Cross-references biological products licensed under 351(k) with biosimilar or interchangeable products licensed under 351(k)

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### Legislation on Biologics and Biosimilar Substitution, 2013–2016

- **Legend**
  - Purple box: States that have enacted biosimilar substitution laws
  - Orange box: States that have implemented biosimilar substitution laws
  - Blue line: States with private insurance among the 36 states
  - Red box: States with public insurance programs

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Application Scenario

A physician contacts you because he has learned about the abbreviated approval process for biosimilars and is concerned that the process may not be robust and lacks adequate clinical trials. She asks your opinion on the comparability of biosimilars and reference biologics. Which of the following is an appropriate response?

A. The FDA will only approve a biosimilar for a specific indication if they have conducted safety and efficacy studies in that population.
B. The FDA takes advantage of significant experience in understanding the physicochemical structure, function, and quality attributes of biologics and uses sophisticated methods to characterize the activity at receptor sites. A comparability clinical study may use more near-term endpoints to assure that there are no meaningful differences in efficacy and safety.
C. The biosimilar comparability exercise duplicates the safety and efficacy clinical trials of the reference product so one can be sure that the biosimilar will act the same as the reference product.
D. The manufacturing process for the biosimilar is exactly the same as for the reference product, so it is unlikely that there will be any meaningful differences in efficacy and safety.

Manufacturing Changes Can Slightly Alter Physicochemical Characteristics

<table>
<thead>
<tr>
<th>Reference Product</th>
<th># of Changes After Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>37</td>
</tr>
<tr>
<td>Etanercept</td>
<td>21</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>18</td>
</tr>
<tr>
<td>Abatacept</td>
<td>7</td>
</tr>
<tr>
<td>Rituximab</td>
<td>6</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>4</td>
</tr>
</tbody>
</table>

Changes made to tighten specifications and controls on the process and to increase production capacity.


Biologic Manufacturing Changes—Demonstration of Comparability

“Structurally highly similar version of an already authorized biological product with demonstrated similarity in physicochemical characteristics, efficacy, and safety based on a comprehensive comparability exercise”

A Definition of A Biosimilar

“Comparison study does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.”

**Approval Pathways in the US**

- Small Molecule Drugs
  - New Drug Application (NDA)
  - Abbreviated New Drug Application (ANDA)
- Biologics
  - Biologics License Application (BLA)
  - BLA (351(k))
  - BLA (351(a))

**Biosimilar and Biologic Development**

- Totality of the Evidence
  - 351(a)
  - 351(k)

**General Principles for Demonstrating Biosimilarity**

- Biosimilars approved via an abbreviated pathway
- Demonstration of biosimilarity is a comparability exercise and not a therapeutic equivalence study
- 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

**Analytical Tools to Evaluate Proteins**

- Chromatography
- Mass spectrometry
- Oligosaccharides
- Peptide mapping
- Lectin affinity

**Comparative Clinical Studies**

- Efficacy and safety: specific clinical trial design will depend on which 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
- Example – comparison of biosimilar and reference trastuzumab in HER2-positive metastatic breast cancer
  - Primary outcome was 24 week overall response rate (ORR)
  - Secondary outcome measures: time to tumor progression, progression-free survival, and overall survival at 48 weeks; adverse events


**Protein Heterogeneity**

- Amino Acid Substitution
- N- and C-terminal mods
- Mismatched S-S bonds
- Folding
- Denaturation
- Disulfide
- Fatty acylation
- Oxidation

- Carbamylation
- Carboxylation
- Formylation
- Gamma-Carboxyglutamylaton
- O-linked Glycosylation
- N-linked Glycosylation
- Methylation
- Phosphorylation
- Sulphation
- Pegylation

[Image 65x346 to 268x453]

3/23/2017
Primary Outcomes in Trastuzumab Biosimilar Assessment

**Primary Outcome: Ratio and Difference in Overall Response Rate at Week 24 in Intent to Treat Population**

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Biosimilar + Taxane (n=228)</th>
<th>Reference Trastuzumab + Taxane (n=228)</th>
<th>Difference (%)</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>3 (1.3)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>157 (68.3)</td>
<td>140 (64.0)</td>
<td>19.5</td>
<td>1.09</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>48 (20.9)</td>
<td>49 (21.5)</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>9 (3.9)</td>
<td>20 (8.0)</td>
<td>41.1</td>
<td></td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>13 (5.7)</td>
<td>12 (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Response</td>
<td>160 (90.6)</td>
<td>146 (64.0)</td>
<td>1.09</td>
<td></td>
</tr>
</tbody>
</table>

95% Confidence Interval: 57.81 to 75.51

75.51 57.81 63.62 3.9 75.51 63.62 3.6

(Roig HS, et al. JAMA 2017; 317:37-47. Effect of a proposed trastuzumab biosimilar compared with trastuzumab on overall response rate in patients with HER2-positive metastatic breast cancer.)

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**Key Points**

- Biologics are complex drugs that are not considered "generic"; still waiting for FDA guidance on "interchangeable biosimilars".
- Incorporation of biosimilars into clinical practice offers cost savings and increased patient access, but there are some important practical considerations that must be considered.
- Federal and state regulatory actions, pricing, and reimbursement policies will play key roles in determining future use of biosimilars and product selection in the U.S.
- Key challenges yet to be resolved include naming, interchangeability criteria and substitution requirements at the state level.
- Pharmacists should assume leadership in planning a strategy for successful operational and clinical use of these agents.

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**Compared to the reference biological product, a biosimilar should be:**

- **Identical**
  - 500494
- **Highly similar**
  - 500495
- **Functionally similar**
  - 500496
- **Similar structure and function, but less immunogenic**
  - 500497

**According to the FDA, which type of product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product?**

- **Biosimilar**
  - 500494
- **Interchangeable biologic**
  - 500495
- **Biobetter**
  - 500496
- **None of the above may be substituted without the intervention of the prescriber**
  - 500497

**Which of the following is correct about biosimilar clinical trial data?**

- **The range of indications for which the biosimilar is approved and for which the reference product is used must be considered**
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- **The dosage forms of the biosimilar need not be considered, since they will be identical to the reference product**
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- **The price, reimbursement, and patient out-of-pocket costs associated with the biosimilar and the reference product must be evaluated**
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- **A plan needs to be developed regarding how patients will be managed after transitioning from one product to another (e.g., moving between outpatient and inpatient sites of care)**
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- **The reference product and any biosimilars should have distinct US Adopted Names (USAN) in order to foster pharmacovigilance**
  - 500496
- **Use of a common INN plus a suffix for biosimilars will allow similar products to be grouped together in electronic ordering, dispensing and administration systems**
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