The Emerging Role of Biosimilars

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This webinar is intended to be a primer for Update on Biologics and the Emerging Classifications of Biosimilars, a 2-hour live session on Friday, March 27, 2015, 3:30PM-5:30PM PT, at the APhA Annual Meeting and Exposition.

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The Emerging Role of Biologics
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Biologic Pharmacovigilance: Key Considerations for Pharmacists
Attendance Code

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Disclosures

- James G. Stevenson, PharmD, FASHP declares that he has served as a consultant for Amgen, as a board member and on advisory panels for Baxter, Daiichi-Sankyo, and Sanofi-Aventis, and is president of Visante, Inc.
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Learning Objectives

- Describe the importance of biosimilars and their development.
- Discuss the impact of biosimilars for patient care and disease management.
- Identify key elements of the FDA's draft guidance for developing biosimilars.
- Identify potential implications of biosimilars for pharmacists working in various practice settings.

Assessment Question 1
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 biological product and is manufactured in an identical manner

Assessment Question 2
Which of the following statements regarding biosimilars is true?

a. The Public Health Service Act defines an abbreviated pathway for approval of biosimilars
b. The FDA recognizes only one category of biosimilar drugs
c. There are over 20 biosimilar products currently on the market in Europe
d. None of the biosimilar products that have been approved by the EMA have been removed from the market through regulatory action
Assessment Question 3
Which of the following statements regarding potential substitution of biosimilars is false?

a. The “Purple Book” will provide information on interchangeable biosimilar products
b. Several states have passed legislation placing limits on the substitution of biosimilar products
c. The FDA has created a category of “interchangeable biosimilars” that would be able to be substituted similar to traditional generic drugs
d. Substitution of biosimilars has been a widespread practice throughout the countries in Europe

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

Relative Size and Complexity of Small Molecule Drugs and Biologics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Molecular Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>151 daltons</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>558 daltons</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>6063 daltons</td>
</tr>
<tr>
<td>Rituximab</td>
<td>145,000 daltons</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>158,800 daltons</td>
</tr>
<tr>
<td>Coagulation Factor VIII</td>
<td>264,400 daltons</td>
</tr>
</tbody>
</table>


Manufacturing Process for Biologics

- Extract DNA sequence producing desired protein from source
- Clone into DNA vector
- Transfer vector into host cell for expression
- Cell expansion in bioreactors
- Recovery of desired protein through filtration or centrifugation
- Purification and formulation of drug product


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

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

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

What Is a Biosimilar?

- Approved via an abbreviated pathway
- Exhibits “highly similar” efficacy and safety compared with reference product
- “Totality of the evidence” approach
- Interchangeable biosimilar
  - Can switch back and forth between biosimilar and reference with no clinical consequences
  - Appropriate for substitution without consulting the prescriber
Manufacturing Process for Biosimilars

<table>
<thead>
<tr>
<th>Manufacturing Step</th>
<th>Potential Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extract DNA sequence producing desired protein</td>
<td>Possibly same gene sequence</td>
</tr>
<tr>
<td>from source</td>
<td></td>
</tr>
<tr>
<td>Clone into DNA vector</td>
<td>Probably different vector</td>
</tr>
<tr>
<td>Transfer vector into host cell for expression</td>
<td>Different cell expression system</td>
</tr>
<tr>
<td>Cell expansion in bioreactors</td>
<td>Different cell line, bioreactor conditions</td>
</tr>
<tr>
<td>Recovery of desired protein through filtration</td>
<td>Different operating conditions</td>
</tr>
<tr>
<td>or centrifugation</td>
<td></td>
</tr>
<tr>
<td>Purification and formulation of drug product</td>
<td>Different binding and elution conditions, different reagents and reference standards</td>
</tr>
</tbody>
</table>

Potential Differences vs. Reference

- Primary amino acid sequence
- Modification of amino acids (e.g., glycosylation)
- Higher-order structure
  - Folding
  - Quaternary structure
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 molecular complexity and differences in manufacturing processes
- Therefore, an assessment of biosimilarity is much more complex than the assessment of “bioequivalence” for small-molecule generic drugs

The Issue of “Manufacturing Drift”

- Biologic drugs are sensitive to changes in manufacturing
- Similarity is established at approval, but there is no obligation to demonstrate similarity after approval
- Over time, changes in manufacturing may make products “less similar”
- Hence, there is a “drift” in similarity between the biosimilar and the branded product
- Drift also occurs **within** a branded biologic drug

Why are Biologics Important?
Many Top Drugs by Clinic Expenditure

1. Pegfilgrastim
2. Epoetin alfa
3. Infliximab
4. Rituximab
5. Bevacizumab
6. Ranibizumab
7. Trastuzumab
11. Denosumab
14. Bortezomib
15. Cetuximab

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### Growing Role of Biologics in Pipeline

<table>
<thead>
<tr>
<th>In Market</th>
<th>In Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>89%</td>
<td>61%</td>
</tr>
</tbody>
</table>


### Projected U.S. 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>Palifermin</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>


### Prescription Benefit Implications in U.S.

- Biologics and specialty pharmaceuticals are the fastest growing pharmaceutical expense in the US
- Biosimilars bring savings opportunities
  - Estimate of $250 billion in US over next 10 years from just 11 biosimilar products (American Consumer Institute Center for Citizen Research)
  - 2008 Congressional Budget Office (CBO) estimated a $25 billion reduction in U.S. expenditures on biologics by 2018
- There will be significant pressure to utilize biosimilars to control health care costs
Prescription Benefit Implications in U.S.

- Expect pharmacy benefit plans to use established formulary review processes to review each drug on its own merit.
- If two drugs are considered “therapeutically equivalent,” then the plan will decide where on its benefit tier each drug should reside or if it should be covered at all.
- Plans likely to use patient financial incentives to drive the use of biosimilars:
  - For example, a 20% copayment for a biologic on its fourth tier, and a biosimilar on the third tier may mean the difference between $50 per month and $200 or more.

Pharmacy Practice Implications

- Biosimilars present opportunities and responsibilities for pharmacists:
  - Current generic substitution practices are not appropriate for biosimilars, but therapeutic equivalence could be considered in select settings.
  - Pharmacists will need to be aware of federal and state requirements around biosimilar substitution.
  - Pharmacists should lead the objective evaluation of biosimilars using the formulary process.
  - Pharmacists will be key sources of information on biosimilars for patients and providers.
  - Pharmacists will need to assist in assuring a robust pharmacovigilance approach.

European Union Biosimilar Experience

- Biosimilars are high-quality products with strict regulations in manufacturing and scientific development.
- Similar vs. identical debate is not unique to biosimilars (applies to each biologic for lot-to-lot comparability – “manufacturing drift”).
- Safety data is required pre-approval (including immunogenicity).
- Postmarketing surveillance (mandatory) seeks to identify residual concerns; not unique to biosimilars.
- Be aware of indication differences and extrapolate if appropriate.
- Interchange practices highly variable between EU countries.
Substitution/Prescribing Policies in Several EU Countries (2014)

- Substitution possible only for patients starting treatment
- Biological substitution prohibited by law
- Biologicals/biosimilars not considered substitutable (or not on national substitution list)
- Substitution only for otherbiosimilars
- All substitution (including SM generics) prohibited
- No guidance, but substitution happening (no official figures)

Use of Biosimilars in EU

- Market uptake has been somewhat slow with 11% of total EU biologic sales (5%–20%), but growing at a rate greater than other market segments
- Costs generally 15%–30% below reference products
- EU biosimilars have enhanced market competition and helped stabilize health care costs – even without high uptake
- EMA has not identified any specific safety issues for approved and marketed biosimilar products – even with relatively robust pharmacovigilance programs

Practice Issues and Considerations

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: Formulary Consideration**
- Product and manufacturer evaluation
- Range of indications (on-label and off-label) for use
- Indication extrapolation
- Therapeutic interchange +/- guided-use policies
- Transitions of care or health system considerations
- Payer policies and patient adherence issues

**Considerations for Formulary Selection of Biosimilars**

<table>
<thead>
<tr>
<th>Efficacy/Safety</th>
<th>Manufacturing Considerations</th>
<th>Product Considerations</th>
<th>Hospital, Payer, and Patient Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical data</td>
<td>Product packaging and labeling</td>
<td>Economic considerations</td>
</tr>
<tr>
<td></td>
<td>Range of indications</td>
<td>Bedside bar coding</td>
<td>Hospital</td>
</tr>
<tr>
<td></td>
<td>Immunogenicity concerns</td>
<td>Compatibility with CSTDs, bar codes</td>
<td>Payer</td>
</tr>
<tr>
<td></td>
<td>Potential for therapeutic interchange</td>
<td>Product preparation and administration</td>
<td>Patient</td>
</tr>
<tr>
<td></td>
<td>Number of similar agents on formulary</td>
<td>Storage requirements</td>
<td>Payer policies</td>
</tr>
<tr>
<td></td>
<td>Pharmacovigilance requirements</td>
<td></td>
<td>Transitions of care</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IT and medication system changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Educational requirements</td>
</tr>
</tbody>
</table>

**Major Challenges for P&T Committees with Biosimilars**
- If approved for a specific indication, will use be allowed for other indications?
- Decisions surrounding product naming critical to provide clarity when ordering, prevent errors, ensure traceability, and facilitate 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
Major Challenges for P&T Committees with Biosimilars

- 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?

Operational Challenges: Information Systems

- Differentiate between similar biologics in electronic systems
  - Pharmacy information systems
  - CPOE and ePrescribing systems
  - Dispensing systems and automation
  - eMAR
- Order sets, protocols
- Medication reconciliation
- Patient’s own medicine


Operational Challenges: Inventory Management

- Purchaser needs adequate information (NDC, etc.)
- Will multiple products be stocked?
  - Reference and biosimilar
  - Multiple biosimilars
- Product storage, placement on shelf, etc.
- Inventory costs
- Wrong product dispensing errors

Operational Challenges: Financial Analysis
- Pricing information comparison (provider, payer)
  - Portfolio pricing
- Reimbursement implications for healthcare provider
- Patient assistance and out-of-pocket expenses
- Determine financial impact from various perspectives


Operational Challenges: Education
- Education of all providers (clinical information, policies, appropriate use, etc.) to avoid confusion
- Patient education
- Managing transitions of care


Product Substitution
- State legislation to clarify pharmacist authority to substitute
- FDA “Purple Book”
- Challenges
  - Care transitions
  - Medication reconciliation
  - Differences in federal and state regulations
State Legislative Activity

- As FDA continues work on implementing BPCI Act, states have been considering proposals to restrict substitution of biologic medications
- Supporters of state proposals believe the ultimate decision on substitution should be left to the patient’s prescribing physician
- Opponents believe state proposals are restrictive/inconsistent with forthcoming national standards, and will increase the cost of healthcare unnecessarily

State Biosimilar Legislation

- 8 states have enacted statutes
  - Oregon, Utah, North Dakota, Florida, Indiana, Virginia, Delaware, Massachusetts
- 1 state passed but vetoed
  - California
- 10 states did not pass
  - Washington, Nevada, Arizona, Colorado, Texas, Arkansas, Mississippi, Georgia, Maryland, Vermont
- 4 states pending
  - Michigan, Illinois, Pennsylvania, New Jersey

Common Elements in State Bills

- Prescriber preference
- Patient choice: notification of patient/prescriber if substitution occurs
- Labeling
- Recordkeeping (years required vary by state)
- Pricing (not more than product originally prescribed)
- List of substitutable products (State Board of Pharmacy)
How Can Pharmacists Prepare?

- Familiarize yourself with applicable laws
- Some laws are being adopted with sunset clauses and may expire in whole or in part before applications/determinations occur
- Closely follow your State Board of Pharmacy’s guidance
- Pharmacy/healthcare organizations are a good resource for updates

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

Nomenclature Issues

- Naming should allow the practitioner to quickly understand the relationship between the biosimilar and reference product
- Major responsibility for pharmacists and practicing clinicians to identify and report potential safety/immunogenicity concerns
- Naming convention for biosimilars is a concern for effective reporting (must be able to trace adverse effects to a specific product)
- Importance of configuring IT systems to be able to track specific products
- Can the use of codes help pharmacovigilance efforts?

Post-Marketing Surveillance

- Pharmacovigilance activities essential to further assess ongoing safety and immunogenicity
- Major responsibility for pharmacists and practicing clinicians to identify and report potential safety/immunogenicity concerns
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Recommendations for Biosimilars for Pharmacists

- 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 and state regulatory guidance
- Prepare IT systems to facilitate effective pharmacovigilance programs
- Meet educational needs of patients and providers

Resources for Pharmacists

- ASHP Resource Center on Biosimilars
- American Journal of Managed Care Resource Center
Conclusion

- Biosimilars present significant opportunities and challenges for pharmacists managing formularies and providing patient care
- A framework for biosimilar introduction has existed in Europe and is being defined in the U.S.
- European biosimilar experience has been good
- Pharmacists must educate themselves to be prepared to play leadership roles in the safe and appropriate introduction of biosimilars

Conclusion

- Integration of biosimilar agents into clinical practice presents 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

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