Biologics and Biosimilars

Regulatory and Dispensing Requirements Impacting Pharmacy and Its Systems
Disclosures

- Thomas Felix is an employee of and shareholder in Amgen. The conflict of interest was resolved by peer review of the slide content. He declares no other conflicts of interest or financial interest in any product or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

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Learning Objectives

Following this presentation, attendees should be able to:

1. Compare and contrast biologics and biosimilars to small molecule therapies.

2. Describe the impact of current biologic and biosimilar legislation and regulations (biosimilar naming, state substitution, reporting) on your organization, institution and/or product.

3. Discuss framework of what needs to be done by stakeholders to capture to support specific product identification, ensure precise product tracking and allow for accurate, efficient reporting and tracing of adverse events associated with biologics.
Speaker Introduction

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Agenda

• Biologics and Biosimilars: An Overview
• Current FDA Activity around Biologics and Biosimilars
• State Regulatory Activity – Biologic and Biosimilar Substitution Communication
  • Components of Legislation
  • Standardization efforts for electronic communication
• Recommendations for Pharmacies and pharmacy systems
# Why Are Biologics so Important?

**Biologic Medicines in Development—by Therapeutic Category**

Some medicines are listed in more than one category.

<table>
<thead>
<tr>
<th>Therapeutic Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune Disorders</td>
<td>71</td>
</tr>
<tr>
<td>Blood Disorders</td>
<td>43</td>
</tr>
<tr>
<td>Cancer/Related Conditions</td>
<td>58</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>338</td>
</tr>
<tr>
<td>Diabetes/Related Conditions</td>
<td>28</td>
</tr>
<tr>
<td>Digestive Disorders</td>
<td>26</td>
</tr>
<tr>
<td>Eye Conditions</td>
<td>25</td>
</tr>
<tr>
<td>Genetic Disorders</td>
<td>30</td>
</tr>
<tr>
<td>Infectious Diseases</td>
<td>176</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td>34</td>
</tr>
<tr>
<td>Neurologic Disorders</td>
<td>39</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td>38</td>
</tr>
<tr>
<td>Skin Diseases</td>
<td>30</td>
</tr>
<tr>
<td>Transplantation</td>
<td>13</td>
</tr>
<tr>
<td>Other</td>
<td>58</td>
</tr>
</tbody>
</table>

Source: IMS Health Global Trends in Medicine.

Greater access to therapies: Biologics hold great promise for providing a lower cost treatment option for chronic diseases.
What is a Biologic Medicine?

• A biologic is a substance that is made from a living organism or its products.¹

• Biologics are developed in living systems, including bacterial², yeast³,⁴, and mammalian⁵,⁶ cells.

Biologics are Larger and Structurally More Complex than Small Molecule Drugs

**Small molecules**
(chemically based drugs)\(^1\)

- Acetyl salicylic acid
  - 21 atoms
  - MW = 180 Da

**Biologics**
(protein-based drugs)\(^1\)

- Biologic (monoclonal antibody)
  - ~ 25,000 atoms
  - MW = ~ 150,000 Da

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# Differences Between Small Molecules and Biologics

<table>
<thead>
<tr>
<th>Properties</th>
<th>Small Molecules</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example</strong></td>
<td>Acetyl salicylic acid(^1)</td>
<td>Biologic - monoclonal antibody</td>
</tr>
<tr>
<td></td>
<td>29 atoms; MW = 180 Da</td>
<td>~25,000 atoms; MW = ~ 150,000 Da(^6)</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Small(^2)</td>
<td>Large(^2) – ~600x larger</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Simple(^3) and well defined(^2,4)</td>
<td>Complex with many options for post-translational modification(^7)</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Predictable chemical process; Identical copy can be made(^2)</td>
<td>Each manufactured in a unique living cell line(^2)</td>
</tr>
<tr>
<td><strong>Characterizations</strong></td>
<td>Easy to fully characterize(^5)</td>
<td>Difficult to characterize fully due to a mixture of related molecules(^2)</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>Relatively stable(^2)</td>
<td>Sensitive to storage and handling conditions(^2)</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Lower potential(^2)</td>
<td>Higher potential(^2)</td>
</tr>
</tbody>
</table>

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\(^1\) Acetyl salicylic acid comprehensive prescribing information. [www.fda.gov/ohrms/dockets/ac/03/briefing/4012B1_03_Appd%201Professional%20Labeling.pdf](http://www.fda.gov/ohrms/dockets/ac/03/briefing/4012B1_03_Appd%201Professional%20Labeling.pdf). Accessed January 24, 2013;  
\(^3\) Prugnaud JL. *Br J Clin Pharmacol*. 2007;65:619-620;  
\(^5\) Gottlieb S. *Am J Health Syst Pharm*. 2008;65(suppl 6):S2-S8;  
\(^7\) Roger SD. *Nephrology*. 2006;11:341-346.
What are Biosimilars?

- Biosimilars are highly similar, but not identical to, existing biological products.¹
- The Public Health Service Act defines biosimilar or biosimilarity as:
  - “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,”² and
  - “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”²

2. Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the Public Health Service Act.
FDA Perspective: A “Totality of the Evidence” Approach will be Applied to Assess Biosimilarity

**Generics**
- Establish same active ingredient
- Demonstration of bioequivalence

**Biosimilars**
- Extensive structural and functional characterization
- Consider need for animal data to assess toxicity
- Clinical studies to compare PK/PD, safety/efficacy, and immunogenicity
  - Sufficient to demonstrate that the product is “highly similar” to the reference product and safe, pure, and potent for one or more approved conditions of use
  - FDA has discretion to determine that certain studies not required

Biosimilar Interchangeability Designation Requires Evidence Beyond That Needed to Demonstrate Biosimilarity

- **Highly similar** notwithstanding minor differences in clinically inactive components
- No clinically meaningful differences in **safety, purity, and potency**

Approved as a biosimilar **AND**:
- Expectation of **same clinical result** in any given patient and...
- For a product that is administered more than once, **no additional risk to safety or efficacy** as a result of alternating or switching

Patient Protection and Affordable Care Act.  
FDA Determines Biosimilar Interchangeability, While Automatic Substitution Is Governed by States

- FDA policy on approval standards for biosimilars does not address automatic substitution
- There is ongoing legislative activity in multiple states with regard to automatic substitution of interchangeable biologics for the reference product

Summary of guidance:

• Biosimilarity requirements are met first
• Totality of evidence will be considered
• Data and information showing product can be expected to produce the same clinical result as the RP* in ALL of the RP’s licensed conditions of use expected
• Seeking licensure for ALL RP’s licensed conditions of use recommended
• Extrapolation is acceptable when justified
• Switching studies generally expected
• Presentation/s generally limited to those of the RP
• Post marketing safety monitoring may be required but is itself not sufficient

* RP = Reference Product
32 States Have Enacted Laws Related to Interchangeable Biosimilar Substitution and Biologics Tracking

32 US States and Puerto Rico

- Indiana
- Delaware
- Massachusetts
- North Dakota
- Florida
- Virginia
- Oregon
- California
- Colorado
- Illinois
- Idaho
- Louisiana
- New Jersey
- North Carolina
- Tennessee
- Texas
- Utah
- Kentucky
- Arizona
- Missouri
- Rhode Island
- Hawaii
- Pennsylvania
- Washington
- Georgia
- Puerto Rico
- Ohio
- Montana
- Iowa
- New Mexico
- Kansas
- South Carolina
- Nebraska

## Key Provisions of State Biosimilar Legislation

<table>
<thead>
<tr>
<th>Principle</th>
<th>Prevailing Generic Requirements</th>
<th>Suggested Biosimilar Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substitution based on an FDA determination</td>
<td>Yes-therapeutic equivalence</td>
<td>Yes-interchangeable</td>
</tr>
<tr>
<td>The prescribing physician should be able to specify ‘dispense as written’</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>The patient should be informed of the substitution</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pharmacy records should be maintained</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Only after dispensing, the patient’s medical record should be updated</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>(e.g., through direct entry into a shared electronic record, communication via fax)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sample State Legislative/Regulatory Language

• **FDA Certified Interchangeability**
  - Arizona: “Allows a pharmacist to substitute a biological product if the FDA has determined that the biological product is interchangeable with the prescribed biological product”

• **Electronic Communication**
  - Idaho: “Communication shall occur via an entry in an interoperable electronic medical records system, an electronic prescribing technology, a pharmacy benefit management system or a pharmacy record that can be accessed electronically by the prescriber.”

• **Patient Notification**
  - Florida: "The pharmacist must notify the patient or person at the counter of the substitution”

• **Prescriber’s “Brand Medically Necessary” Blocks Substitution**
  - California: “Authorizes a pharmacist to select an alternative biological product when filling a prescription order for a prescribed biological product if the alternative biological product is designated interchangeable by the FDA and the prescriber does not personally indicate that a substitution is not to be made.”
Sample State Legislative/Regulatory Language

• **Pharmacy Records Must Be Retained**
  - Delaware: “Maintain a three year record of such substitutions”

• **Posted List of Interchangeables**
  - Hawaii: “Requires pharmacists to inform consumers of [interchangeable biological products from the Hawaii list](#) when filling a prescription order and to communicate the product name and manufacturer to the practitioner after dispensing the product.”

• **Price Related Provisions**
  - Georgia: “Pharmacist shall dispense the lowest retail priced interchangeable biological product which in in stock”
  - Arizona: “Requirement that the pharmacy notify the patient of any price difference.”

• **Other Provisions**
  - Delaware: “Provide liability protections for pharmacists who substitute biosimilars.”
  - Missouri: “Requires notification to patients and within 5 days communicate with prescriber”
NCPDP Standards Work Around Electronic Communication of Biologic Substitution

- NCPDP Biologics and Biosimilars Task Group Formed Sept, 2016
- **Goal**: Evaluate existing NCPDP standards including RxFill and Medication History (MedHx) on viability for use as electronic communications from pharmacy to provider for biologic and biosimilar substitution

- **DERF passed at NCPDP meeting, May 2017**
  - Will allow electronic communication of biologic and biosimilar substitution using RxFill
    - Adds a message type of “Biosimilar Substitution” to RxFill message type
    - Will allow providers to filter on and receive these types of RxFill messages only
Biologics Will Be Named Differently

Pharmacy laws do not require a shared nonproprietary name. Current FDA naming convention promotes traceability and could be suitable for use after interchangeable designations. Minor label update could take place to specifically state that a molecule is interchangeable. Molecules would not have to be renamed after receiving interchangeability designation.

Interchangeable biosimilars - maintain unique, manufacturer specific suffixes

Recommendations for Pharmacies

• Understand State Regulations surrounding communication of biologic and biosimilar substitution
• Ensure pharmacy and pharmacists followed correct process for communication in states where legislative mandate exists
• Work with Pharmacy vendors to implement RxFill messages to allow for electronic communication of substitution
Questions

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