Biologics and Biosimilars — Regulatory Requirements Impacting EHRs and Pharmacy Systems Used by IDNs
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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
- Impact of Regulatory Activity on IDNs, EHR Vendors and Pharmacy System Vendors
- Recommendations for EHRs and pharmacy systems
  - Describe best practices by IDNs to capture and support specific product identification, ensure precise product tracking within their EHRs and allow for accurate, efficient reporting and tracing of adverse events associated with biologics.
Why Are Biologics so Important?

Greater access to therapies: Biologics hold great promise for providing a lower cost treatment option for chronic diseases

Source: IMS Health Global Trends in Medicine.
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

Biologics (protein-based drugs)$^{1}$

Acetyl salicylic acid$^{2}$
- 21 atoms
- MW = 180 Da

Biologic (monoclonal antibody)$^{3}$
- ~ 25,000 atoms
- MW = ~ 150,000 Da

Example

## Differences Between Small Molecules and Biologics

<table>
<thead>
<tr>
<th>Properties</th>
<th>Small Molecules</th>
<th>Biologics</th>
</tr>
</thead>
</table>
| **Example**   | Acetyl salicylic acid<sup>1</sup>  
29 atoms; MW = 180 Da | Biologic - monoclonal antibody  
~25,000 atoms; MW = ~ 150,000 Da<sup>6</sup> |
| **Size**      | Small<sup>2</sup> | Large<sup>2</sup> – ~600x larger |
| **Structure** | Simple<sup>3</sup> and well defined<sup>2,4</sup> | Complex with many options for post-translational modification<sup>7</sup> |
| **Characterizations** | Easy to fully characterize<sup>5</sup> | Each manufactured in a unique living cell line<sup>2</sup> |
| **Stability** | Relatively stable<sup>2</sup> | Similar but not identical copy can be made<sup>2</sup> |
| **Immunogenicity** | Lower potential<sup>2</sup> | Higher potential<sup>2</sup> |

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Images are for illustrative purposes and are not to scale.

5. Gottlieb S. *Am J Health Syst Pharm*. 2008;65(suppl 6):S2-S8;  
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

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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

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Biosimilar Interchangeability Designation Requires Evidence Beyond That Needed to Demonstrate Biosimilarity

Biosimilarity

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

Interchangeability

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

Scientific Judgment

Interchangeable biologic

Biosimilar

FDA designation

State jurisdiction

Physician Prescription Required
(Substitution of biosimilar with reference product is not recommended by FDA)

Pharmacy Practice

Substitution Without Physician Involvement permitted
(Substitute to state laws, pharmacist may substitute interchangeable 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


- 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

Partnering with IDNs: BioPharma Strategy Summit; August 16-17 • Philadelphia, PA
## 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 with HCP (e.g., through direct entry into a shared electronic record, communication via fax)</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Sample State Legislative/Regulatory Language

<table>
<thead>
<tr>
<th>FDA Certified Interchangeability</th>
<th>Patient Notification</th>
</tr>
</thead>
<tbody>
<tr>
<td>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”</td>
<td>Florida: &quot;The pharmacist must notify the patient or person at the counter of the substitution”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electronic Communication</th>
<th>Prescriber’s “Brand Medically Necessary” Blocks Substitution</th>
</tr>
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<tbody>
<tr>
<td>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.”</td>
<td>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.”</td>
</tr>
</tbody>
</table>
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 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”
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

The EHR market continues to expand as most HCPs have integrated the technology into their practices.

EHR systems are becoming the digital platforms where doctors practice: >85% of physicians are ePrescribing and >80% of office-based physicians are using EHRs.

HCPs spend an average of **3.3 hours per day using EHR systems**, twice as long as on all other digital resources combined.

Opportunities exist to integrate utilization management tools within EHRs and ePrescribing workflow for **both specialty and non-specialty medications**.

References: CMI Media; Decision Resource Group; GHG
Impact of Naming Convention and Interchangeability Indication

Biosimilar must be available in EHRs to be prescribed

Product Naming should consider how product will be listed in ePrescribing systems

- HCPs will need to be able to identify a biosimilar and easily distinguish it from the reference biologic
- EHR Vendors will need to clearly distinguish when a biosimilar is interchangeable

IDN order sets will need to be updated when existing biologic name change occurs
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
Dispensing, Administration & Reporting Scenarios

Dispensing Entity: Hospital Pharmacy, LTPAC Pharmacy, Specialty Pharmacy, Physician’s Practice, Retail Pharmacy, Mail Pharmacy

Place of Administration: Hospital, LTPAC Facility, Infusion Center, Physician’s Practice, Patient’s Home (self-administer)

Many Adverse Drug Event Reporting Scenarios
- Reported by hospital staff or hospital pharmacy staff ✱
- Detected by facility staff. Reported by facility or LTPAC pharmacy staff ✱
- Detected during administration and reported by infusion center or specialty pharmacy staff ✱
- Detected during administration and reported by clinic staff ✱
- Detected by patient and...
  (a) self-reported
  (b) discussed with and reported by clinic staff
  (c) discussed with and reported by infusion center staff
  (d) discussed with / reported by pharmacy staff

ADE reporting occurs at different times and places. All systems need dispensed medication details.

OR... Adverse reaction is detected and reported later ... by the patient or at subsequent provider visit.
Importance of capturing product information for ADE reporting

**Typical information gaps / challenges:**

- **Hospital EHR and admin system:** Lacks dependable NDC, mfr., lot #
- **Hospital pharmacy:** Lot # not integrated into dispensing system
- **Facility EHR and admin system:** Lacks dependable NDC, mfr., lot #
- **LTPAC pharmacy:** Lot # not integrated into dispensing system
- **Physician’s EHR:** Contains no dispensed med details (no mfr./lot)
- **Infusion center med admin system:** Lacks NDC, mfr., lot #
- **Specialty pharmacy:** Lot # not integrated into dispensing system
- **Physician’s EHR:** Contains no dispensed med details (no mfr./lot)
- **Specialty, retail pharmacy:** Lot # not integrated to dispensing system
- **Physician’s EHR:** Contains no dispensed med details (no mfr./lot)
- **Pharmacy:** Lot # not integrated into dispensing system
- **Patient’s medication package:** Lacks mfr., lot #

**Decreasing med details conveyed / captured electronically**

- Manufacturer, NDC, Lot # carried to inventory system
- Lot # is not integrated into dispensing system
- Dispensed med ID may not be actual dispensed NDC. No mfr., lot #
- Dispensed med data not transmitted electronically

**Supply Med to the Dispensing Entity**

- Hospital pharmacy
  - Inventory ➔ Dispensing
- LTPAC pharmacy
  - Inventory ➔ Dispensing
- Specialty pharmacy
  - Inventory ➔ Dispensing
- Retail pharmacy
  - Inventory ➔ Dispensing
- Mail pharmacy
  - Inventory ➔ Dispensing

**Dispense Med to the Place of Administration**

- Hospital
- LTPAC Facility
- Infusion Center
- Physician’s Practice
- Patient’s Home (self-administer)

**Report Adverse Drug Event**

- **Hospital EHR and admin system:** Lacks dependable NDC, mfr., lot #
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Partnering with IDNs: BioPharma Strategy Summit; August 16-17 • Philadelphia, PA
Recommendations for working with IDNs

- Ensure product is being displayed accurately in EHR
  - New Names with suffix
  - Name changes
  - Interchangeability indicator
- Understand Federal and State Regulations surrounding biologics and biosimilars and ensure pharmacies have process in place for communication of substitution
- Understand IDNs ability to capture required product information for adverse event event reporting
Questions

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