Biosimilar Drug Overviews

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Disclosures

- Nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject of this presentation

Learning Objectives

- Define biosimilars and how it differs from a generic drug
- Review FDA approval process for biosimilars in comparison to novel drug development
- Identify practical prescribing and dispensing implications for biosimilars
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What is a biologic?

- Innovative medicines that are grown in living cells
- Complex molecules
  - Monoclonal antibodies
  - Blood derivatives
  - Vaccines
  - Recombinant or purified proteins
  - Cytokines
  - Thrombolytic agents
  - Enzymes

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### Comparison of Small Molecule Drugs and Biological Drugs

<table>
<thead>
<tr>
<th></th>
<th>Small Molecule Drugs</th>
<th>Biological Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>Small (&lt;1000 Daltons)</td>
<td>Large (&gt;10,000 Daltons)</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Chemical synthesis</td>
<td>Cultures of living cells</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Simple, well defined, independent of manufacturing process</td>
<td>Complex (heterogeneous), defined by the exact manufacturing process</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Single entry, high chemical purity, identical copy can be made</td>
<td>Produced in living cell culture, difficult to control from starting material to final active pharmaceutical ingredient</td>
</tr>
<tr>
<td><strong>Characterization</strong></td>
<td>Easy to characterize</td>
<td>Cannot be characterized completely</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>

What is a biosimilar?

- Highly similar to FDA-approved biologic, known as the reference product
  - Only minor differences in clinically inactive components
- No clinically meaningful differences in terms of safety, purity, potency
- Not generic biologics
- All biosimilars are biologics, but not all biologics are biosimilars


Biosimilar Manufacturing

Cloning and Protein Expression

- Different DNA sequences
- Different cell lines
- Different operating conditions
- Different manufacturing processes
- Different testing and evaluation methods

Manufacturing Challenges

- Large molecular structures, increased molecular weight
- Complex three-dimensional structure
- Utilize cell-based systems for drug production
- Potential variations among biologic products
  - Minor changes can occur during cell production


True or False

- In order for a product to be FDA approved as a biosimilar it must have the same indication, MOA, route of administration, dosage form, and strength as its reference product.

Biosimilar Specifications

<table>
<thead>
<tr>
<th>Biosimilar Product Specification</th>
<th>Comparison with Reference Product</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>Indications for 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>


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True or False

- Biosimilars have no clinically meaningful differences in safety and effectiveness from the reference product.

Growth Potential for Biosimilars

- When biosimilars hit the market, health care system is estimated to save $108 billion

Biosimilars ON THE MARKET

- First U.S. approved biosimilar
  - Filgrastim-sndz (Zarxio®; Sandoz)
- Applications before FDA
  - Infliximab (Celltrion) – PDUFA date, June 2015
  - Pegfilgrastim (Apotex) – PDUFA date, September 2015
  - Filgrastim (Hospira) – PDUFA date, October 2015
  - Epoetin (Apotex) – PDUFA date, October 2015
- Likely be less costly, but still expensive

*PDUFA – prescription drug user fee act
Comparison of Approval Pathways

### Small Molecule Drugs—Approved via FDCA

- **Application**
  - FDA application
  - FDA approval
- **Demonstrated safety and efficacy**
- **Labeling**
  - USP/DIN/NCI-based on site of reference

### Biologics—Approved via PHSA

- **Application**
  - Biologics license application
  - Biologics license approval
- **Demonstrated safety and efficacy**
- **Labeling**
  - USP/DIN/NCI-based on site of reference


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**Biosimilars**

**FDA-approval pathway**

- **Biologics Price Competition and Innovation Act of 2009 (BPCI Act)**
  - Creates an abbreviated licensure pathway for biologics
  - Increase competition with biologics
  - Prices or innovation
- **Can only be approved by FDA if it has:**
  1. Same mechanism(s) of action (MOA), route(s) of administration, dosage form(s), and strength(s)
  2. Same indication(s) and condition(s)
  3. Manufacturer facilities meet FDA’s standards
- Can be approved for fewer than all the indications and routes approved for reference product

Pharmacist Letter. FAQs About Biosimilars. October 2015.

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**Biosimilars**

**FDA-approval pathway**

- **Goal:** demonstrate biosimilarity or interchangeability with reference product
  - NOT to independently establish safety and efficacy
- **Different than “stand alone” development where goal is to demonstrate that the proposed product is safe and efficacious**
  - Drug development starts with preclinical research, moves to Phase 1, 2 and culminates in Phase 3 “pivotal” trials to show safety and efficacy
Stepwise Evidence Development

Totality of the Evidence

No “one size fits all” assessment:

PSA scientists will evaluate the applicant’s integration of various types of information to provide advice on scope and extent of development plan and, ultimately, an overall assessment that a biosimilar is similar to an approved reference product.

Sherman RE. Biosimilar Biological Products. 2012.

Biosimilars Development Approach


True or False

➢ If a product is classified as biosimilar, it may be substituted for the reference product by a pharmacist without intervention of the prescriber.
General Requirements: 351(k) Application

- Must include, among other things, information demonstrating biosimilarity based upon data from:
  - Analytical studies demonstrating biologic is "highly similar", except for minor differences in clinically inactive compounds
  - Animal studies (including assessment of toxicity)
  - Clinical study or studies (including assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use
- Additional requirements for interchangeable biologics


Definition: Interchangeability

- Biosimilar that meets additional standards for interchangeability:
  - Expected to produce same clinical result as reference product in any given patient, and
  - For a product that will be administered more than once to an individual, the risk in terms of safety or diminished effectiveness of alternating/switching between proposed interchangeable product and reference product is not greater than the risk of using reference product without alternative or switching.
- Note: Federal regulations allow interchangeable biologic to be substituted for reference product by a pharmacist without the intervention of the prescriber
  - State pharmacy boards may have different regulations

Pharmacist Letter. FAQs About Biosimilars. October 2015

Indication Extrapolation

- Potential exists for a biosimilar product to be approved for one or more conditions of use for which reference product is licensed
- Extending information and conclusions from one population to make inferences in another target population
- Data extrapolated to demonstrate biosimilarity in one condition of use
- Sufficient scientific justification is necessary
- Purpose
  - Avoid unnecessary studies or reduce the number of studies
  - Limited feasibility in studying the target population
  - Industry/regulator extrapolation to reference's labeled indications

**Extrapolation Considerations**

- FDA guidance outlines considerations when providing scientific justification for extrapolation including, for example*,
  - MOA(s) in each condition of use
  - PK and bio-distribution in different patient populations
  - Immunogenicity differences in expected toxicities in each condition of use and patient population
  - Differences between conditions of use do not necessarily preclude extrapolation

*This list is a subset of the issues outlined in the FDA guidance document

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**True or False**

- The Orange book serves as a resource to determine if a biological product has been listed as biosimilar or interchangeable by the FDA.
A pharmacist's role...

- A pharmacist may only dispense a substitute biological product for the prescribed biological product if:
  - A. U.S. FDA determined that substitute biological product is biosimilar to and interchangeable for the prescribed biological product
  - B. Prescribing health care provider does not express a preference against substitution in writing, verbally, or electronically
  - C. The pharmacist notifies the person presenting the prescription of the substitution
  - D. Pharmacist retains written or electronic record of substitution for at least 2 years

Pharmacist Letter, FAQs About Biosimilars. October 2015

The Purple Book

- Lists licensed biological products
  - Any biosimilar and interchangeable biological licensed by FDA
- Lists date of approval and approval pathway
- Designated with “B” if biosimilar or “I” if also interchangeable
- Defines exclusivity period
- Separate lists for biological products regulated by Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) will be updated periodically

FDA Purple Book. October 2015

Legislation on Substitution

Enacted by the Legislature of the State of Florida

Section 1. Subsection (6) of section 465.019, Florida Statutes, is amended to read:

(6) In a Class II institutional pharmacy, an institutional formulary system may be adopted with approval of the medical staff for the purpose of identifying those medicinal drugs, and proprietary preparations, biologics, biosimilars, and biosimilar interchangeables that may be dispensed by the pharmacists employed in such institution. The institutional formulary system for the development of the system in accordance with the joint standards of the American Hospital Association and American Society of Hospital Pharmacists for the utilization of a hospital formulary system.

Section 2. Section 465.025, Florida Statutes, is created to read:

Substitution of interchangeable biosimilar products.—

(2) A pharmacist may only dispense a substitute biological product for the prescribed biological product if:

(a) The U.S. FDA has determined that the substitute biological product is biosimilar to and interchangeable for the prescribed biological product.

(b) The prescribing health care provider does not express a preference against substitution in writing, verbally, or electronically.

(c) The pharmacist notifies the person presenting the prescription of the substitution in the same manner as provided in s. 465.025(3)(a).

(d) The pharmacist retains a written or electronic record of the substitution for at least 2 years.

(3) A pharmacist who practices in a class II or modified class II institutional pharmacy shall comply with the notification provisions of paragraph (2)(c) by entering the substitution in the institution’s written medical record system or electronic medical record system.

Naming Biologics

FDA issued draft guidance on how biologics marketed in the U.S. should be named

Proposed all biologic names have a four-letter suffix, perhaps derived from the name of the license-holder

- Filgrastim-sndz; “sndz” represents Sandoz, manufacturer of Zarxio

Not decided if interchangeable biologics will have unique suffix, or will have same suffix as reference product


Importance of Naming Strategy

Goal:
- Identify relationship between the biosimilar and reference/originator
- Differentiate products
  - Support pharmacovigilance
  - Intended product administered
  - Outcomes and ADEs attributed to correct product
- Avoid “sound alike” and “look alike” errors
Immunogenicity Concerns

- All biologics hold a risk of immunogenicity
- Neutralizing antibody formation and cytokine release
- Changes to protein structure increase variation in immunogenicity
  - Lot-to-lot and between manufacturers
  - Variations in manufacturing must be minimized
- Variable clinical consequences
  - Loss or diminished safety or efficacy
  - Rare but serious autoimmune responses can be life-threatening
- Immunogenicity of biologic drugs is unpredictable, unforeseeable

Pharmacovigilance

- Important to assure safety
  - Consider risks seen in reference product
  - Any new safety concerns?
    - Immunogenicity differences
    - Rare events
    - Population-based assessments gives larger n to identify rare safety concerns
    - May be mandatory for some products
- How will products be differentiated for pharmacovigilance purposes

Pharmacovigilance (Biosimilar Pharmacovigilance)
Pharmacovigilance: Pharmacist’s Role

- Monitor and report
  - Adverse events: FDA MedWatch
  - Medication errors
- Correct attribution of safety events
  - Drug ordered vs. drug received?
    - Maintenance of EMR
    - Bar code administration
  - Medication reconciliation
    - Consider transitions of care

Summary

- Biologics are complex drugs that should not be considered “generic”
- Incorporation of biosimilars into clinical practice offers opportunities for cost savings and increased patient access to biologic therapies
- Interchangeability designation requires data that switching between the biosimilar and reference is appropriate

Summary

- Purple book a great resource for list of biosimilar/interchangeable products
- Key issues to be resolved include naming, interchangeability criteria and requirements, and pharmacovigilance requirements
- Pharmacovigilance is necessary to verify safety and identify rare but serious adverse effects
References

- Li E. Biosimilars Overview and Reflections on the Use of Biosimilars to Date Presentation. December 2015.
- McIlhaun D. FAQs About Biosimilars, October 2015.

Questions

- Q1
- Q2
- Q3