Biosimilar vs. Generic, What’s the Difference?

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Disclosures

- The presenter has no financial relationships with any commercial interests pertinent to this presentation.

- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.
Pharmacist Learning Objectives

At the end of this session, participants should be able to:

- Describe the process for approval of biosimilar products
- Recall the differences between generic and biosimilar products
- Identify newly approved biosimilar products in the United States
Pharmacy Technician Learning Objectives

At the end of this session, participants should be able to:

- Determine the regulatory requirements for a biosimilar product to be approved

- Identify three biosimilars currently on the U.S. market
Overview

- Terminology Review
- History of Generic and Biosimilar Regulations
- Comparison of Generic vs. Biosimilar vs. Interchangeable
- Approval Process for Biosimilars
- Naming of Biosimilars
- Prescribing and Substitution of Biosimilar Products
Definitions

- **Generic product**
  - Medication created to be same as existing approved medication in dosage form, safety, strength, route of administration, quality and performance characteristics

- **Biological product (“biologic”)**
  - “Virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide) or analogous product used to diagnose, prevent, treat and cure diseases and medical conditions”

- **Reference product**
  - Single biological product against which a proposed biosimilar is compared

- **Biosimilar biological product (“biosimilar”)**
  - Highly similar to **AND** no clinically meaningful differences from reference product

Relevance of Biosimilar Products

- In 2016, the United States spent $3,337 billion on healthcare - 18% of the gross domestic product (GDP) or $329 billion spent on prescription drugs!

- Biological products represent ~40% of prescription drug spending - Accounted for 70% of growth in spending from 2010 to 2015

Conventional Drug vs. Biologic Sales, Worldwide

*Percentage of sales attributable to each

10 Best-selling Drugs Globally in 2017

1. Humira® (adalimumab)
2. Eylea® (aflibercept)
3. Revlimid® (lenalidomide)
4. Rituxan® (rituximab)
5. Enbrel® (etanercept)
6. Herceptin® (trastuzumab)
7. Eliquis® (apixaban)
8. Avastin® (bevacizumab)
9. Remicade® (infliximab)
10. Xarelto® (rivaroxaban)

### Top 10 Branded Drugs in U.S. for Invoice Spending & Prescriptions in 2016

<table>
<thead>
<tr>
<th>Rank</th>
<th>Medicine</th>
<th>2012 ($ in Billions)</th>
<th>2016 ($ in Billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Humira</em> (adalimumab, AbbVie)</td>
<td>4.5</td>
<td>13.6</td>
</tr>
<tr>
<td>2</td>
<td><em>Harvoni</em> (ledipasvir sofostuvir, Gilead)</td>
<td>0.0</td>
<td>10.0</td>
</tr>
<tr>
<td>3</td>
<td><em>Enbrel</em> (etanercept, Amgen)</td>
<td>4.2</td>
<td>7.4</td>
</tr>
<tr>
<td>4</td>
<td><em>Lantus Solostar</em> (insulin glargine injection, Sanofi)</td>
<td>2.3</td>
<td>5.7</td>
</tr>
<tr>
<td>5</td>
<td><em>Remicade</em> (infliximab, Janssen Biotech)</td>
<td>3.8</td>
<td>5.3</td>
</tr>
<tr>
<td>6</td>
<td><em>Jonuvis</em> (sitagliptin, Merck)</td>
<td>2.6</td>
<td>4.8</td>
</tr>
<tr>
<td>7</td>
<td><em>Advair Diskus</em> (fluticasone/salmeterol, GlaxoSmithKline)</td>
<td>4.6</td>
<td>4.7</td>
</tr>
<tr>
<td>8</td>
<td><em>Lyrica</em> (pregabalin, Pfizer)</td>
<td>1.9</td>
<td>4.4</td>
</tr>
<tr>
<td>9</td>
<td><em>Crestor</em> (rosuvastatin, AstraZeneca)</td>
<td>4.8</td>
<td>4.2</td>
</tr>
<tr>
<td>10</td>
<td><em>Neulasta</em> (pegfilgrastim, Amgen)</td>
<td>3.4</td>
<td>4.2</td>
</tr>
</tbody>
</table>

- 5 of top 10 prescription meds were biologic products

History of Generic Drugs

- **Drug Price Competition and Patent Term Restoration Act of 1984**
  - Also known as “Hatch-Waxman Act”
  - Two goals of this law:
    
    *Encourage greater public access to generic drugs*
    
    *Support new pharmaceutical research and development*

<table>
<thead>
<tr>
<th>Enable Generic Competition</th>
<th>Reward Technological Advance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established abbreviated new drug application</td>
<td>Patent term extension allowed- relative to regulatory review length</td>
</tr>
<tr>
<td>(ANDA)</td>
<td></td>
</tr>
<tr>
<td>Allows testing before brand patent expires</td>
<td>Non-patent exclusivity benefits (NDA data proprietary thru FDA, etc.)</td>
</tr>
<tr>
<td>Incentive 180 day exclusivity- for first</td>
<td>Established process for patent challenges</td>
</tr>
<tr>
<td>successful ANDA filer</td>
<td></td>
</tr>
</tbody>
</table>

Generic Drugs Today

Source: Image from https://cen.acs.org/articles/92/i39/30-Years-Generics.html
The “Orange Book”

- **Approved Drug Products with Therapeutic Equivalence Evaluations**
  - Official name of the publication
  - First distributed as a proposal in January 1979

- Identifies drug products approved by FDA
  - Lists therapeutic equivalence evaluations (AA, AB, etc.)

- Provides drug patent and exclusivity information
  - Updated as part of Hatch-Waxman Act


History of Biosimilar Products

- European Medicines Agency
  - Biosimilar regulatory framework in place since 2006

- Biologics Price Competition and Innovation (BPCI) Act of 2009
  - Part of Patient Protection and Affordable Care (PPAC) Act of 2010
  - Created abbreviated approval pathway for biological products that are:
    - “Highly similar” OR
    - “Interchangeable” to reference biological product

- Goal of legislation similar to Hatch-Waxman Act
  - Enhance competition and patient access, lower cost
  - History repeats itself...

Defining Biosimilar

“Highly similar”

- Structural and functional analysis of reference product and proposed biosimilar
- Comparison for purity, chemical identity, bioactivity
- Minor differences allowed, such as differences in stabilizer or buffer

No clinically meaningful differences

- Refers to differences in safety, purity and potency
- Demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, clinical immunogenicity assessment and if needed, additional clinical studies

# Biological Product vs. Small Molecule Drug

## BIOLOGICAL PRODUCT
- Larger, complex molecules
- Chemical structure less easily characterized
- Produced through biotechnology methods in a living system (microorganism, plant or animal cell)
  - Inherent variations from manufacturing process
- Can be immunogenic
- Approved under Public Health Services (PHS) Act

## SMALL MOLECULE DRUG
- Small molecule drug made from pure chemical substances
- Chemical structure easily identified and characterized
- Synthesized through predictable chemical process according to a reproducible “recipe”
- Usually not immunogenic
- Approved under Food, Drug, Cosmetic (FDC) Act

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Traditional Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herceptin (breast cancer)</td>
<td>Lipitor (hypercholesterolemia)</td>
</tr>
<tr>
<td>molecular weight = 185,000 daltons</td>
<td>molecular weight = 559 daltons</td>
</tr>
</tbody>
</table>

Biosimilar Product

- Biological product
- Variation due to manufacturing process
- Highly similar AND no clinically meaningful differences

Generic Drug Product

- Small molecule drug
- Same active ingredients as reference product
- Bioequivalence

Same mechanism, administration route, dosage form & strength as branded product
Abbreviated approval pathways

Approval Process for Biosimilars

Biosimilar Biologics License Application (351k application)

Stepwise Approach (Research, Clinical Trials)

“Totality of Evidence”

Biosimilar Approval!

Approval Process for Biosimilars—a CAVEAT

- The Agency has the discretion to determine that an element described above is "unnecessary in a 351(k) application"
  - Biosimilar application can rely on certain existing scientific knowledge about the safety, purity and potency of the reference product to support licensure

Stepwise Approach to Biosimilar Approval

- Analytical Studies (the foundation)
- Animal Studies
- Pharmacology
- Clinical
- More Studies

Stepwise Approach to Biosimilar Approval

1. **Structural Analysis & Functional Assays**
   - Characterize structural and mechanistic differences between proposed biosimilar and reference product

2. **Animal Studies**
   - Assess toxicity and potentially some immunogenicity

3. **Clinical Pharmacokinetic, Pharmacodynamic & Immunogenicity Studies**
   - Demonstrate safety, purity and potency in appropriate conditions

“Totality of Evidence”

- No single study will demonstrate biosimilarity!

- FDA will license proposed biological product if FDA “determines that the information submitted in the application... is sufficient to show that the biological product is biosimilar to the reference product”

- Risk-based approach to evaluate data and information

What About Interchangeable Products?

- Interchangeable expected to produce same clinical result as reference product *in any given patient*
  - Additional requirements for approval

- Switching studies for products administered more than once
  - Evaluate safety and efficacy risks for switching between interchangeable and reference product

- Why be more stringent with interchangeable approval?
  - Interchangeable product may be substituted for the reference product WITHOUT prescriber involvement

Naming Biosimilars

- Biosimilar naming rules not established with initial approval in 2015
  - Zarxio® (filgrastim-sndz) given placeholder nonproprietary name

- Final industry guidance issued in January 2017
  - **Core name + four letter distinguishing suffix**
  - Suffix must be lowercase, three of four letter distinct

- What about biosimilars which were approved before the guidance?
  - Changes in names of already approved biosimilar products
  - Example- Erelzi® (etanercept-szzs) will need suffix with three distinct letters

Outpatient Prescribing of Biosimilars

- Pharmacist substitution of biosimilars for reference biological product
  - Dependent on state law

- United States Overview
  - Most states require the biologic drug be deemed “interchangeable” for pharmacist substitution to occur
  - Some states have additional notification and record keeping requirements
    - Can require prescriber and/or patient notification about substitution
  - Some states have requirements for when substitution required (i.e., if public dollars are being used)

States With Regulations Surrounding Pharmacist Substitution of Biologics

Inpatient Prescribing of Biosimilars

- Pharmacist substitution of biosimilars for reference biological product
  - Dependent on hospital or health system policies
  - Refer also to state regulations

- Several clinical considerations for Pharmacy and Therapeutics Committees
  - Evaluation of efficacy, safety
  - Manufacturer and supply chain considerations
  - Financial considerations
  - Processes to facilitate or limit substitution
  - Etc.

Purple Book: “Lists of Licensed Biological Products”

- Similar to Orange Book
  - Specific to biological products

- Includes information about:
  - Reference product exclusivity period
    (original licensing date, exclusivity expiration date)
  - Biosimilar or interchangeable biological products

- Lists updated “periodically” when FDA licenses a biological product
  - As resources permit

The "Purple Book" lists biological products, including any biosimilar and interchangeable biological products, licensed by FDA, under the Public Health Service Act (the PHS Act).

The Purple Book includes the date a biological product was licensed under 35(i)(a) of the PHS Act and whether FDA evaluated the biological product for reference product exclusivity under section 35(i)(c)(7) of the PHS Act.

The Purple Book, in addition to the date licensed, also includes whether a biological product licensed under section 35(i)(a) of the PHS Act has been determined by FDA to be biosimilar to or interchangeable with a reference biological product (an already-licensed FDA biological product). The Patient Protection and Affordable Care Act (Affordable Care Act), signed into law by President Obama on March 23, 2010, amends the PHS Act to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. This pathway is provided in part of the Affordable Care Act known as the Biologics Price Competition and Innovation Act of 2009 (BPCIA). Biosimilar and interchangeable biological products licensed under section 35(i)(a) of the PHS Act will be listed under the reference product to which biosimilarity or interchangeability was demonstrated.

Healthcare providers can prescribe biosimilar and interchangeable biological products just as they would prescribe other medications. The BPCIA describes an interchangeable product as a product that may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product. In contrast, FDA expects that a biosimilar product will be specifically prescribed by the healthcare provider and cannot be substituted for a reference product at the pharmacy level.

Separate lists for those biological products regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) will be updated periodically.

## List of Licensed Biological Products with (1) Reference Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations to Date

<table>
<thead>
<tr>
<th>BLA STN</th>
<th>PRODUCT (PROPER) NAME</th>
<th>PROPRIETARY NAME</th>
<th>DATE OF LICENSURE (mo/day/yr)</th>
<th>DATE OF FIRST LICENSURE (mo/day/yr)</th>
<th>REFERENCE PRODUCT EXCLUSIVITY EXPIRY DATE (mo/day/yr)</th>
<th>INTERCHANGEABLE (I)/BIOSIMILAR (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>125118</td>
<td>abatacept</td>
<td>Orencia</td>
<td>12/23/05</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>103575</td>
<td>abciximab</td>
<td>ReoPro</td>
<td>12/22/94</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>125274</td>
<td>abobotulinumtoxinA</td>
<td>Dysport</td>
<td>04/29/09</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>125057</td>
<td>adalimumab</td>
<td>Humira</td>
<td>12/31/02</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>761071</td>
<td>adalimumab-adz</td>
<td>Hymrozo</td>
<td>10/30/18</td>
<td>NA</td>
<td>NA</td>
<td>B</td>
</tr>
<tr>
<td>761058</td>
<td>adalimumab-adbm</td>
<td>Cyltezo</td>
<td>08/25/17</td>
<td>NA</td>
<td>NA</td>
<td>B</td>
</tr>
<tr>
<td>761024</td>
<td>adalimumab-atto</td>
<td>Amjevita</td>
<td>09/23/16</td>
<td>NA</td>
<td>NA</td>
<td>B</td>
</tr>
<tr>
<td>125427</td>
<td>ado-trastuzumab emtansine</td>
<td>Kadcyla</td>
<td>02/22/13</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>125387</td>
<td>aflibercept</td>
<td>Eylea</td>
<td>11/18/11</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>103979</td>
<td>agalsidase beta</td>
<td>Fabrazyme</td>
<td>04/24/03</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>125431</td>
<td>albiglutide</td>
<td>Tanzeum</td>
<td>04/15/14</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

## FDA-approved Biosimilars in the U.S.

<table>
<thead>
<tr>
<th>Reference Product Name</th>
<th>Biosimilar Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira®)</td>
<td>Adalimumab-adaz (Hyrimoz®)</td>
</tr>
<tr>
<td></td>
<td>Adalimumab-adbm (Cyltezo®)</td>
</tr>
<tr>
<td></td>
<td>Adalimumab-atto (Amjetiva®)</td>
</tr>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>Bevacizumab-awwb (Mvasi®)</td>
</tr>
<tr>
<td>Epoetin alfa (Epogen®, Procrit®)</td>
<td>Epoetin alfa-epbx (Retacrit®)</td>
</tr>
<tr>
<td>Etanercept (Enbrel®)</td>
<td>Etanercept-szzs (Erelzi®)</td>
</tr>
<tr>
<td>Filgrastim (Neupogen®)</td>
<td>Filgrastim-aafi (Nivestym®)</td>
</tr>
<tr>
<td></td>
<td>Filgrastim-sndz (Zarxio®)</td>
</tr>
<tr>
<td>Infliximab (Remicade®)</td>
<td>Infliximab-abda (Renflexis®)</td>
</tr>
<tr>
<td></td>
<td>Infliximab-dyyb (Inflectra®)</td>
</tr>
<tr>
<td></td>
<td>Infliximab-qbtx (Ixifi®)</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta®)</td>
<td>Pegfilgrastim-cbqv (Udenyca®)</td>
</tr>
<tr>
<td></td>
<td>Pegfilgrastim-jmdb (Fulphila®)</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin®)</td>
<td>Trastuzumab-dkst (Ogivri®)</td>
</tr>
</tbody>
</table>
Zarxio® (filgrastim-sndz) approved March 6, 2015

Approved for same 5 indications as reference product (Neupogen®)

Studies conducted prior to approval
  - Structural and functional characterization
  - Animal study data
  - Human pharmacokinetic
  - Clinical immunogenicity data
  - Other clinical safety and efficacy- PIONEER, phase IV studies

A Comparison of Proposed Biosimilar and Originator Filgrastim for the Prevention of Neutropenia in Patients with Breast Cancer Receiving Myelosuppressive Adjuvant or Neoadjuvant Chemotherapy: Phase III, Randomized, Double-Blind Trial (The PIONEER study)

Kimberly Blackwell, Vladimir Semiglazov, Pedro Gascon, Roumen Nakov, Stefan Kramer, Arnd Schwebig, and Nadia Harbeck


- **Purpose**
  - Compare safety and efficacy of filgrastim versus biosimilar, EP2006, with respect to mean duration of severe neutropenia following Cycle 1 chemotherapy

- **Methods**
  - Randomized, double-blind, multi-center, non-inferiority trial
  - 4 treatment groups
    - Filgrastim alone
    - EP2006 alone
    - EP 2006 initially then cycle between filgrastim and EP2006
    - Filgrastim initially then cycle between filgrastim and EP2006
  - Included women > 18 years old with histologically-proven breast cancer eligible for neoadjuvant or adjuvant chemotherapy treatment
PIONEER Trial

- **Results**
  - 218 patients randomized
  - Mean DSN in Cycle 1: $1.17 \pm 1.11$ days (EP2006) vs. $1.20 \pm 1.02$ days (filgrastim)
    - *Mean difference in DSN = 0.04 days (97.5% CI, lower limit -0.26 days)*
  - Febrile neutropenia incidence over 6 cycles chemotherapy
    - *EP: 2/40, 5.0%, EPNEU: 5/45, 11.1%, NEUEP: 1/44, 2.3%, NEU: 0/46, 0.0%*
  - No obvious difference in treatment emergent adverse events
    - *EP: 5/53, 9.4% patients; EPNEU: 4/54, 7.4%; NEUEP: 1/55, 1.8%; NEU: 2/52, 3.8%*
  - No subjects developed anti-drug antibodies

- **Conclusion**
  - Biosimilar result met predefined non-inferiority criteria

Cost of Biosimilar Products

- Biosimilars expected to cost 10 to 40% less than reference product

- Insurance Coverage of Biosimilar Products
  - Varies by state and health plan
  - Center for Medicare and Medicaid Services (CMS) finalized proposal in April 2018 to allow biosimilars to be covered at generic copay level
  - Several state Medicaid programs placing biosimilar as “preferred” product
## Comparison of U.S. Biosimilar and Generic Drug Average Share of Sales and Price Discount
(Six Months After Launch)

<table>
<thead>
<tr>
<th></th>
<th>Share of sales vs. originator</th>
<th>Price discount vs. originator*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Drug Average</td>
<td>≥75%</td>
<td>≥40%</td>
</tr>
<tr>
<td>Zarxio (biosimilar Neupogen)</td>
<td>~10%</td>
<td>15%</td>
</tr>
<tr>
<td>Granix (quasi-biosimilar Neupogen)</td>
<td>5-10%</td>
<td>~11-23%</td>
</tr>
</tbody>
</table>

* Does not include rebates or other contracted reductions.

Figure 1: LOE and Biosimilar Entry Timeline as of January 2018

What About Biosimilar Insulin Products?

- Basaglar® (insulin glargine) and Admelog® (insulin lispro) **NOT** approved as biosimilars
  - FDA refers to it as a “follow-on” insulin
  - Some protein products licensed under Food, Drug and Cosmetic (FDC) Act rather than Public Health Services (PHS) Act
  - Insulin and human growth hormones, historically, approved under the FDC Act

- What about the future for biologic protein products?
  - In 2020, these applications for protein biological products will fall under PHS Act

Currently Approved “Follow-on” Insulin Products

<table>
<thead>
<tr>
<th>“Reference” Insulin Product</th>
<th>“Follow-On” Insulin Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lantus® (insulin glargine)</td>
<td>Basaglar® (insulin glargine)</td>
</tr>
<tr>
<td>Novolog® (insulin lispro)</td>
<td>Admelog® (insulin lispro)</td>
</tr>
</tbody>
</table>
Future Discussion About Biosimilar Products

- Prescribing and pharmacist substitution
- Efficacy studies and extrapolation
- Additions to hospital or health plan formularies
Helpful Resources

- Academy of Managed Care Pharmacy Biosimilars Resource Center
  - Laws and Regulations https://www.biosimilarsresourcecenter.org
  - FAQs Section, https://www.biosimilarsresourcecenter.org/faqs/

- U.S. Food and Drug Administration website

- State Board of Pharmacy websites
References

Biosimilar and interchangeable products. US Food and Drug Administration website.

Biosimilar development, review, and approval. US Food and Drug Administration website.

Biosimilars action plan: balancing innovation and competition. US Food and Drug Administration website.


Chhina MN. Biosimilar biological products. FDA Basics Webinar.

References


References


Q & A

To ask the presenter a question, simply type it into the “chat” box within the WebEx tool bar. Be sure that you select “Host” when submitting your question in chat.
Thank you!

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