New Drug Updates: Biosimilars

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Objectives

- Describe current information concerning approval of biosimilar projects
- List currently available biosimilar products
- Examine factors that should be considered for a biosimilar's inclusion into your institution's medication-use process
- Identify potential differences in available biosimilars and reference products that may affect the medication use process (technicians)
Christopher Allen reports that he has no financial relationships with any commercial supporters or providers.

Products not yet approved by the Food & Drug Administration may be discussed during this presentation.
Drug Expenditures in 2015

- In 2015, biological products represented (in terms of overall expenditures)...
  - Eight of the top 25 drugs overall (~$40 billion) – 7 with + growth
  - Nineteen of the top 25 drugs in clinics, including the top 9 (~$26.5 billion) – 17 with + growth
  - Fifteen of the top 25 drugs in nonfederal hospitals, including the top 6 (~$8.7 billion) – 11 with + growth
- Antineoplastic agents and biologicals rank #1 and #5, respectively, by expenditures in nonfederal hospitals
- Projected increases of ~12%, ~16%, and ~11%, respectively
How did we get to this point?

- **1984**
  - Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act)

- **2010**
  - Biologics Price Competition and Innovation (BPCI) Act
    - 351(k) Biosimilar application

## Potential Growth in Biosimilars?

<table>
<thead>
<tr>
<th>Product</th>
<th>U.S. Patent Expiration Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira®)</td>
<td>December 2016</td>
</tr>
<tr>
<td>Etanercept (Enbrel®)</td>
<td>2012/2028</td>
</tr>
<tr>
<td>Infliximab (Remicade®)</td>
<td>2018</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta®)</td>
<td>Expired</td>
</tr>
<tr>
<td>Interferon beta-1a (Avonex® / Rebif®)</td>
<td>Expired</td>
</tr>
<tr>
<td>Rituximab (Rituxan®)</td>
<td>September 2016</td>
</tr>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>2019</td>
</tr>
<tr>
<td>Epoetin alfa (Epogen® / Procrit®)</td>
<td>Expired</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin®)</td>
<td>2019</td>
</tr>
</tbody>
</table>


Regulatory Definition of a Biosimilar

- Food and Drug Administration (U.S)
  - A biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components and for which there are no clinically meaningful differences in terms of safety, purity and potency.

Biosimilar Manufacturing – An Impossible Copycat Process

Cloning and Protein Expression

- Cloning into DNA Vector
  - Source DNA
  - Target DNA
- Transfer into Host Cell Expression
  - Screening/Selection
  - Possibly same gene sequence
  - Probably different vector
  - Different cell expression system

Protein Production, Purification and Validation

- Cell Expansion
  - Different cell line, growth media, method of expansion
- Cell Production in Bioreactors
  - Different cell line, growth media, bioreactor conditions
- Recovery through filtration or centrifugation
- Purification through chromatography
- Characterization and Stability
  - Different binding and elution conditions
  - Different methods, reagents, reference standards
  - Purified Bulk Drug

FDA Guidelines for Demonstrating Biosimilarity – A Stepwise Approach

- Comparative process, not a demonstration of therapeutic equivalence!
  - Structure
  - Function
  - Animal Toxicity
  - Human Pharmacokinetics / Pharmacodynamics
  - Clinical Immunogenicity
  - Clinical Safety and Effectiveness

- The FDA reserves the right to determine if more data is needed (or less in some cases!)

- *Totality-of-the-evidence* approach

Totality of the Evidence – What’s the Difference?

Totality of Scientific Evidence to Characterize the Biosimilar

- Phase III Clinical Studies
- Phase II Clinical Studies
- Phase I Clinical Studies
- Nonclinical Studies
- Molecule Characterization

Comparability & Biosimilarity Design 351(k)

- Clinical Studies
- PK / PD (behavioral)
- Nonclinical Studies
- Functional (biologic) Characterization
- Physicochemical Characterization

Size of pyramid = “quantity” of effort

“High regulatory emphasis”
“Lower regulatory emphasis”

[Image of pyramid diagram]

### FDA 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</td>
<td>May obtain licensure for fewer than all indications for which reference product is licensed</td>
</tr>
<tr>
<td>Strength</td>
<td>Must be the same</td>
</tr>
</tbody>
</table>

Naming of a Biosimilar

- **WHO & FDA**
  - Biosimilar identified by international nonproprietary name (INN) + four letter suffix

- **EMA**
  - Biosimilar & reference product share INN

- **JMCP 2016**
  - Pharmacists prefer INN + suffix for biosimilars, but would be more confident in substituting interchangeable products if INN shared
Which of the following details MUST be identical when comparing a biosimilar product to its reference product?

a. Labeled indications
b. Routes of administration
c. Strength
d. Formulation
THE CURRENT BIOSIMILAR PRODUCT LANDSCAPE
Filgrastim-sndz (Zarxio®)

- FDA approval: March 6, 2015
- “Key” differences:
  - Approved for 5 of the 6 indications that Neupogen® carries
    - Not labeled to increase survival in patients acutely exposed to myelosuppressive doses of radiation
  - Available only as prefilled syringes
Filgrastim-sndz (Zarxio®) – Approval Data

- Supported by evaluations of analytical similarity and animal studies of pharmacodynamics and toxicity
- Preclinical study - Sörgel F, et al.
  - Protein structure and bioactivity “highly similar”
  - Pharmacokinetic and pharmacodynamics parameters bioequivalent
  - No observed differences in safety or immunogenicity

Filgrastim-sndz (Zarxio®) – Approval Data

- Clinical study – Blackwell K, et al.
  - Conducted in 218 women with breast cancer receiving TAC x 6 cycles (docetaxel, doxorubicin, cyclophosphamide)
  - Randomized 1:1:1:1
    - Biosimilar, Reference, Biosimilar-Reference or Reference-Biosimilar (alternating with each cycle)
  - Hospitalization due to febrile neutropenia, incidence of infections, depth of/time to ANC nadir, and time to ANC recover equivalent; higher number of patients with FN with biosimilar (but within expected variability)
  - No observed differences in safety profile

Currently, there are 8 branded biosimilar filgrastim products approved for use in the European Union

2010 EORTC Guidelines for the Use of G-CSF

- Filgrastim biosimilars are an acceptable treatment option (Grade A recommendation)
- Recommends that clinicians identify products by brand name to ensure there are no changes in treatment without informing the physician and patient

Pooled data from 5 post-approval studies of Zarxio®

- Among 1,302 patient, rates of febrile neutropenia (2.2%) and severe neutropenia (8.5%) were comparable to previous studies of reference filgrastim
Infliximab-dyyb (Inflectra®)

- FDA approval: April 5, 2016
- “Key” differences:
  - Approved for 7 of the 8 indications that Remicade® carries
    - Not labeled for pediatric ulcerative colitis due to orphan drug exclusivity
- Initial application (2014) rejected due to “residual uncertainty” regarding differences in bioactivity and immunogenicity, which were addressed in the follow-up application

**Infliximab-dyyb (Inflectra®) – Approval Data**

- Supported by evaluations of analytical similarity and animal studies of pharmacodynamics and toxicity
- Preclinical study – Park W, et al.
  - Pharmacokinetic parameters bioequivalent
  - No observed differences in safety
- Additional PK/PD data reported as “highly similar” in larger clinical studies comparing biosimilar infliximab to the E.U. reference product; safety profiles and immunogenicity were comparable

Clinical study – Yoo DH, et al.

- Conducted in 606 patients with active rheumatoid arthritis despite methotrexate therapy
- Randomized 1:1
  - Biosimilar infliximab or E.U. reference product – 3 mg/kg at weeks 0, 2, 6, and then every 8 weeks
  - ACR20 responses at week 30, secondary endpoints - comparable
- Results at 54 weeks, and at 2 years (after switching to biosimilar) - comparable
Infliximab-dyyb (Inflectra®) – Approval Data – Ankylosing Spondylitis

- Clinical study – Park W, et al.
  - Conducted in 250 patients with active ankylosing spondylitis
  - Randomized 1:1
    - Biosimilar infliximab or E.U. reference product – 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks
  - Primary endpoint was PK evaluation
    - ASAS20/ASAS40 responses at week 30, other secondary endpoints – comparable
- Results at 54 weeks - comparable

Infliximab-dyyb (Inflectra®) – Barriers to Market Availability?

FDA approves biosimilar version of infliximab

FDA and Pfizer Inc. on April 5 announced the approval of Inflectra, or infliximab-dyyb, a biosimilar version of Janssen Biotech Inc.’s Remicade.

The new product is the second FDA-approved biosimilar and the first approved biosimilar monoclonal antibody product.

Pfizer, through its acquisition of Hospira Inc. last year, holds U.S. marketing rights for Inflectra, which is manufactured in the Republic of Korea by Celltrion Inc. of Incheon. Pfizer stated that it is preparing to launch the monoclonal antibody product this year in the United States, but the precise date will depend on “marketplace dynamics and intellectual property considerations.”

But the labeling for infliximab-dyyb includes no comparative data for the biosimilar and Remicade—and Christl, FDA’s associate director for therapeutic biologics, stated that the omission is intentional.

 “[W]e generally do not recommend that comparative data supporting the demonstration of biosimilarity be included in biosimilar product labeling,” Christl stated. “Ultimately, the comparative data are useful for the FDA to make a decision about biosimilarity, but are not likely to be relevant to a health care provider’s prescribing considerations.”

A Rocky Start for Biosimilar Inflectra?

— Infliximab biosimilar approved, but...

J&J braces for biosim attack after losing last-ditch Remicade patent fight

Newly Approved Biosimilar Inflectra™ Market Launch Held Up in Court

Biosimilars Walking a Fine Line?

ASH Clinical News™
FDA Declines Approval of Biosimilar Pegfilgrastim

Bloomberg
BNA
FDA Response Delays Pfizer's Release of Epogen Biosimilar

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### What’s in the Pipeline?

<table>
<thead>
<tr>
<th>Reference Product</th>
<th>Biosimilar Developer</th>
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<tbody>
<tr>
<td>Adalimumab (Humira®)</td>
<td>Sandoz/Novartis, Amgen, Pfizer, Biogen, Samsung Bioepis/Merck</td>
</tr>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>Amgen, Pfizer, Samsung Bioepis/Merck</td>
</tr>
<tr>
<td>Cetuximab (Erbitux®)</td>
<td>Amgen</td>
</tr>
<tr>
<td>Epoetin alfa (Procrit®, Epogen®)</td>
<td>Sandoz/Novartis</td>
</tr>
<tr>
<td>Infliximab (Remicade®)</td>
<td>Sandoz/Novartis, Amgen, Samsung Bioepis/Merck</td>
</tr>
<tr>
<td>Rituximab (Rituxan®)</td>
<td>Sandoz/Novartis, Amgen, Pfizer</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin®)</td>
<td>Amgen, Pfizer, Samsung Bioepis/Merck</td>
</tr>
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- **Others in development…**
  - Tocilizumab, golimumab, abatacept…
  - What about “biosimilar” insulins? – insulin glargine (Basaglar®, MK-1293)

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What’s in the Pipeline?

Source: IMS Health, IMS Institute for Healthcare Informatics, Jan 2016

KEY CONSIDERATIONS IN BIOSIMILAR REVIEW
What to Consider When Reviewing Biosimilars for Formulary Inclusion

**Safety & Efficacy**
- Product characteristics
- Clinical data
- Immunogenicity
- Pharmacovigilance for safety concerns

**Manufacturer Considerations**
- Medication availability
- History of shortages or recalls
- Handling practices
- Supply chain security
- Anti-counterfeit protection

**Hospital & Patient Factors**
- Packaging and labeling
- Product storage
- Product administration
- Interchangeability
- Variety (extrapolation) of indications
- Product naming
- Information technology support
- Economic considerations
- Patient education

Key Questions

Does the clinical data (pre-approval, post-approval, international) available support the indications for which the biosimilar has been approved and is being considered for formulary inclusion? What about use of the biosimilar in off-label indications?

How will your health system address pharmacovigilance concerns regarding potential differences in immunogenicity and other adverse effects?

Manufacturer Considerations

Key Questions

Will the manufacturer be able to maintain a reliable supply and adequate production of the biosimilar to meet demand for its anticipated usage?

Does the manufacturer have a recent history of shortages or recalls that would decrease your health system’s confidence in the biosimilar’s availability?

# Hospital & Patient Factors

## Key Questions

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<thead>
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<tbody>
<tr>
<td>Are there any differences in packaging, shelf life, storage requirements or routes of administration between the biosimilar and reference product?</td>
</tr>
<tr>
<td>How should interchangeability of the biosimilar be addressed?</td>
</tr>
<tr>
<td>Will the biosimilar being reviewed be included on formulary for all indications for which the reference product is approved, if different?</td>
</tr>
<tr>
<td>How will the naming of the biosimilar affect adverse event reporting/tracking and its inclusion in your health system’s IT systems?</td>
</tr>
<tr>
<td>What cost factors, besides acquisition cost, should be considered?</td>
</tr>
</tbody>
</table>

The biological product is **biosimilar** to the reference product, can be expected to produce the **same clinical result** as the reference product in any given patient, and...the **risk** in terms of safety or diminished efficacy of **alternating or switching** between use of the biological product and the reference product is **not greater than the risk of using the reference product without such alternation or switch**.

**Impact of state substitution laws?**


Interchangeability

Legislation on Biologics and Biosimilar Substitution, 2013-2016

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See NCSL reports for details at www.ncsl.org

Interchangeability – The Shift is On

- CVS Health’s 2017 formulary management strategy
  - Filgrastim-sndz (Zarxio®) replacing filgrastim (Neupogen®)
  - Insulin glargine (Basaglar®) replacing insulin glargine (Lantus®)
- Chingcuanco F, et al.
  - Systematic review of clinical data for biosimilar and reference TNF-α inhibitors
  - Biosimilarity supported by pharmacokinetic and adverse effect variable as well as major clinical efficacy endpoints
  - “Despite the paucity of studies, the existing evidence supports the biosimilarity and interchangeability of these newly developed TNF-α inhibitor products, especially for the treatment of patients with RA.

Resources for Pharmacists

- FDA’s Purple Book

- FDA Website – Information on Biosimilars

- ASHP Resource Center on Biosimilars

  - Partnership between 8 pharmacy-related associations

Audience Response Question #2

Filgrastim-sndz (Zarxio®) is considered interchangeable by the Food & Drug Administration.

a. True

b. False
References


References

References


References


References


Additional Resources


