Exploring Biosimilars & Barriers to Adoption

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- The speakers do not have any relevant financial relationships during the past 12 months to disclose.
- The speakers do not intend to discuss indications for non-FDA approved medications.

Learning Objectives

At the end of this presentation, each participant will be able to:

- Explain the history of biosimilars in the United States.
- Describe barriers of biosimilar adoption.
- Predict biologic usage based on availability of biosimilars and interchangeable biosimilars.
Audience Participation
Please rate your current knowledge of biosimilars.

a. I have only heard of biosimilars
b. I can define a biosimilar
c. I can define a biosimilar and list all available biosimilars
d. I consider myself an expert on biosimilars

Biosimilars
Why the hype?

First U.S. Biosimilar Approved
The impact of the FDA’s approval of the first ‘biosimilar’ drug...
Biologic Defined

A biologic is a therapeutic protein, such as a monoclonal antibody, that is manufactured from natural sources, including living “host” systems, such as human and animal cells, yeast, and bacteria.


Put Size Into Perspective

Biosimilar Defined

A biosimilar is a type of biological product that is licensed by the FDA because it is highly similar to an already FDA-approved biological product, known as the reference product and has been shown to have no clinically meaningful differences from the reference product.

### FDA Specifications

<table>
<thead>
<tr>
<th>Specification</th>
<th>Comparison with Reference</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 for which reference product is licensed</td>
</tr>
<tr>
<td>Strength</td>
<td>Must be the same</td>
</tr>
</tbody>
</table>

### Interchangeability

- No Automatic Substitution

#### Interchangeable Biosimilars

- Automatic Substitution Allowed

### State Legislation

- Legislation on Biosimilars and Interchangeability, 2011-2016

### References:
Global Sales of Biologics ($ millions)

References: Deloitte, Generic & Biologics Institute, IMS Health

Top Line Data

2017 AWP Cost Comparison

$367.15 (300mcg/ml) Neupogen®

$330.79 (300mcg/0.5ml) Zarxio®

Difference = $36.36/300mcg (~10% Savings)


Biosimilar History
The 351(k) pathway and other pertinent regulations...
Indications

<table>
<thead>
<tr>
<th>Indication (*Extrapolated Indication)</th>
<th>Neupogen® (filgrastim)</th>
<th>Granix® (tbo-filgrastim)</th>
<th>Zarxio® (filgrastim-sndz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer patients receiving myelosuppressive chemotherapy</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
</tr>
<tr>
<td>Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy</td>
<td>Yes</td>
<td>Yes*</td>
<td>No</td>
</tr>
<tr>
<td>Patients receiving bone marrow transplant</td>
<td>Yes</td>
<td>Yes*</td>
<td>No</td>
</tr>
<tr>
<td>Patients undergoing peripheral blood progenitor cell collection and bone marrow transplant</td>
<td>Yes</td>
<td>Yes*</td>
<td>No</td>
</tr>
<tr>
<td>Patients with severe chronic neutropenia</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Patients acutely exposed to myelosuppressive doses of radiation</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Pregnancy category

FDA Naming Convention

- Core name with an added four-letter suffix for all biologics
- Suffix will be:
  - Unique/devoid of meaning
  - Four lowercase letters of which at least three are distinct
  - Non-proprietary
  - Free of legal barriers that would restrict its usage
- Manufacturer can suggest up to 10 suffixes
- Example:
  - Sandoz’s Zarxio (filgrastim-sndz) \(\rightarrow\) filgrastim-bflm
  - Amgen’s Neupogen (filgrastim) \(\rightarrow\) filgrastim-jcwp

FDA Naming

Benefits

- Can differentiate
- Groups similar biologics together in electronic systems
- Brand and generic receiving a suffix, reduces inferiority perception

Concerns

- Different suffixes may inhibit interchange
- Meaningless suffixes potential for error
- More complex and may actually harm pharmacovigilance
- Retrospective renaming of existing biologics
**Purple Book**

- List of all biological products
  - Biosimilar products
  - Interchangeable biosimilar products
- Similar to the FDA Orange Book

**Emerging Biosimilars**

FDA-approved and pipeline biosimilars...

**Infliximab**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Remicade®</th>
<th>Inflectra™ (infliximab-dyyb)</th>
<th>Renflexis™ (infliximab-abda)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial FDA</td>
<td>August 1998</td>
<td>April 2016</td>
<td>April 2017</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Psoriatic Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis</td>
<td>Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Psoriatic Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis</td>
<td>Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Psoriatic Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis</td>
</tr>
<tr>
<td>AWP/56 days*</td>
<td>$7006</td>
<td>$5677</td>
<td>N/A</td>
</tr>
<tr>
<td>Marked</td>
<td>Yes</td>
<td>Yes</td>
<td>No (180 days from approval)</td>
</tr>
</tbody>
</table>

*Source assumes an 80kg individual dosed at 5mg/kg
Adalimumab

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Abbvie</th>
<th>Amgen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial FDA Approval</td>
<td>December 31, 2002</td>
<td>September 30, 2016</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Rheumatoid Arthritis, Axial Spondyloarthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis, Uveitis, Pediatric Crohn’s Disease</td>
<td>Rheumatoid Arthritis, Axial Spondyloarthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis, Ulcerative Colitis, Pediatric Crohn’s Disease</td>
</tr>
<tr>
<td>AWP/28 days</td>
<td>$9,949 (adalimumab)</td>
<td>n/a</td>
</tr>
<tr>
<td>Marketed</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>


Etanercept

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Amgen</th>
<th>Sandoz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial FDA Approval</td>
<td>November 1998</td>
<td>August 2016</td>
</tr>
<tr>
<td>FDA Indications</td>
<td>Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis</td>
<td>Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis</td>
</tr>
<tr>
<td>AWP/28 days</td>
<td>$5330</td>
<td>n/a</td>
</tr>
<tr>
<td>Marketed</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>


Pipeline Snapshot

- Epoetin alfa
- Interferon (alpha)
- Insulin & analogs
- Neupogen (filgrastim)
- Rituxan (rituximab)
- Somatropins
- Herceptin (trastuzumab)
- Remicade (infliximab)
- Neulasta (pegfilgrastim)
- Erelzi (etanercept)
- Lantus (insulin glargine)
- Interferons (beta)
- Enbrel (etanercept)
- Avastin (bevacizumab)
- Humira (adalimumab)
- Interferons (alpha)
- Epoetin alfa
- Insulin & analogs
- Neupogen (filgrastim)
- Remicade (rituximab)
- Herceptin (trastuzumab)
- Interferon (beta)
- Neulasta (pegfilgrastim)
- Entremed (sulfamethoxazole)
- Lantus (insulin glargine)
2017 Pipeline Snapshot

**Neulasta® (pegfilgrastim)**
- Amgen & Coherus
  - PDUFA est. 6/09/17
- Mylan
  - PDUFA 6/06/17

**Herceptin® (trastuzumab)**
- Mylan
  - PDUFA 9/07/17

**Avastin® (bevacizumab)**
- Allergan
  - PDUFA 6/09/17
- Mylan
  - PDUFA 10/09/17


Stakeholder Perceptions
Potential barriers for patients, prescribers, and payors...

Existing Biologic Barriers

Access    Administration
Adverse Events    Adherence
International Survey of Patients

- US and EU; 3,198 respondents
- ≥ 18 years, literate, no minimum education

<table>
<thead>
<tr>
<th></th>
<th>Diagnosed</th>
<th>Diagnosed Advocacy</th>
<th>Caregiver</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afflicted by applicable disease(s)</td>
<td>• Afflicted and participated in support groups</td>
<td>• Afflicted and participated in support groups</td>
<td>• Involved in care of a loved one w/disease</td>
<td>• Not falling in another category</td>
</tr>
</tbody>
</table>

Patient Awareness of Biologics

<table>
<thead>
<tr>
<th>US, %</th>
<th>General Population n = 250</th>
<th>Diagnosed n = 635</th>
<th>Advocacy n = 245</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awareness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General impression</td>
<td>11</td>
<td>39</td>
<td>47</td>
</tr>
<tr>
<td>Just know the name</td>
<td>15</td>
<td>19</td>
<td>31</td>
</tr>
<tr>
<td>Not sure</td>
<td>17</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>Never heard of it</td>
<td>50</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>Currently use</td>
<td>N/A</td>
<td>18</td>
<td>29</td>
</tr>
</tbody>
</table>

Patient Awareness of Biosimilars

<table>
<thead>
<tr>
<th>US, %</th>
<th>General Population n = 250</th>
<th>Diagnosed n = 635</th>
<th>Advocacy n = 245</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awareness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General impression</td>
<td>6</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Just know the name</td>
<td>10</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Not sure</td>
<td>14</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Never heard of it</td>
<td>76</td>
<td>54</td>
<td>31</td>
</tr>
<tr>
<td>Currently use</td>
<td>N/A</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

* p < 0.05 for the column proportions test in comparison to the general population group in the same region.
** p < 0.05 for the column proportions test in comparison to the diagnosed group in the same region.
*** p < 0.05 for the column proportions test in comparison to the diagnosed advocacy group in the same region.
Impact of Biosimilar Awareness

<table>
<thead>
<tr>
<th>Safety, efficacy, access perceptions</th>
<th>Aware of Biosimilars (n = 270)</th>
<th>Perception Gap</th>
<th>Unaware of Biosimilars (n = 610)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comfortable switching to this medication</td>
<td>48%</td>
<td>-17</td>
<td>54%</td>
</tr>
<tr>
<td>Is safe</td>
<td>41%</td>
<td>-7</td>
<td>30%</td>
</tr>
<tr>
<td>Has minimal side effects</td>
<td>34%</td>
<td>-13</td>
<td>22%</td>
</tr>
<tr>
<td>Best option to treat condition</td>
<td>43%</td>
<td>-10</td>
<td>23%</td>
</tr>
<tr>
<td>Effectively treats condition</td>
<td>53%</td>
<td>+13</td>
<td>31%</td>
</tr>
<tr>
<td>Is affordable</td>
<td>37%</td>
<td>-8</td>
<td>13%</td>
</tr>
<tr>
<td>Effective care at reasonable cost</td>
<td>40%</td>
<td>+8</td>
<td>24%</td>
</tr>
</tbody>
</table>

Biologic vs. Biosimilar Perceptions

<table>
<thead>
<tr>
<th>Safety, efficacy, access perceptions</th>
<th>Biologic Perceptions (n = 258)</th>
<th>Perception Gap</th>
<th>Biosimilar Perceptions (n = 258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has minimal side effects</td>
<td>60%</td>
<td>-7</td>
<td>33%</td>
</tr>
<tr>
<td>Comfortable switching to this medication</td>
<td>55%</td>
<td>-5</td>
<td>48%</td>
</tr>
<tr>
<td>Is safe</td>
<td>52%</td>
<td>-4</td>
<td>53%</td>
</tr>
<tr>
<td>Best option to treat condition</td>
<td>61%</td>
<td>-10</td>
<td>45%</td>
</tr>
<tr>
<td>Effectively treats condition</td>
<td>66%</td>
<td>-10</td>
<td>40%</td>
</tr>
<tr>
<td>Is affordable</td>
<td>35%</td>
<td>+11</td>
<td>52%</td>
</tr>
<tr>
<td>Effective care at reasonable cost</td>
<td>38%</td>
<td>+3</td>
<td>41%</td>
</tr>
</tbody>
</table>

The Pharmacist’s Role

- Biosimilar awareness
- Safety & efficacy education
- Access support
- Formulary navigation

Physician Biosimilar Survey
- Developed by the Biosimilars Forum
- 19-question survey
- 1,201 US specialists
- Must be biologic prescribers


Prescriber Knowledge Gaps
- Defining terms
- Approval process
- Comparable safety
- Extrapolation
- Interchangeability


Defining Terms

Correct Identification of Biologics Used by Specialty

- Dermatologists
- Gastroenterologists
- Rheumatologists
- Nephrologists
- Hematology-Oncologists
- Medical Oncologists

Correct Incorrect or Don't Know
Approval Process

What Criteria is Required for FDA Approval of a Biosimilar?

- 14% don't know.
- 9% of the above.
- A mutual recognition based on the biosimilar being already rigorously evaluated and approved in Europe.
- Data from at least one clinical study conducted in a patient population that is sensitive to detect potential differences.
- Data from one or more clinical studies evaluating the safety and efficacy of a biosimilar in every indication of use for which it is approved.
- A comparison of PK/PD data for the biosimilar and its originator brand counterpart.
- A comparison of analytical characteristics between the biosimilar and its originator brand counterpart.

Comparable Safety

Biosimilars will be safe and appropriate for use in naïve and existing patients.

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Agree</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>55.2%</td>
<td>44.8%</td>
</tr>
<tr>
<td>Hematology-Oncology</td>
<td>49.6%</td>
<td>50.4%</td>
</tr>
<tr>
<td>Medical Oncology</td>
<td>49.5%</td>
<td>50.5%</td>
</tr>
<tr>
<td>Nephrology</td>
<td>54.5%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>68.0%</td>
<td>32.0%</td>
</tr>
<tr>
<td>Dermatology</td>
<td>62.6%</td>
<td>37.4%</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>55.5%</td>
<td>44.5%</td>
</tr>
</tbody>
</table>

Extrapolation & Interchangeability

The biosimilar will always be approved for all of the indications of use of the originator brand counterpart.

- 28.7% incorrectly agreed

A pharmacist will be allowed to substitute a biosimilar for the originator brand counterpart without asking the prescriber.

- 20.5% incorrectly agreed
Access
With originator biologic medicines, I have concerns about my patients' compliance and/or access to treatment options.

<table>
<thead>
<tr>
<th>Speciality</th>
<th>Agree or strongly agree</th>
<th>Disagree or strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>58%</td>
<td>42%</td>
</tr>
<tr>
<td>Rheumatology/Oncology</td>
<td>61%</td>
<td>39%</td>
</tr>
<tr>
<td>Medical Oncology</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Nephrology</td>
<td>59%</td>
<td>41%</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>61%</td>
<td>39%</td>
</tr>
<tr>
<td>Dermatology</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>58%</td>
<td>42%</td>
</tr>
</tbody>
</table>


The Pharmacist’s Role
- Biosimilar education
- Biosimilar availability
- Interchangeability
- Impact on patient access

Payors
- 70-80% will review like new drugs
- Unlikely to exclude reference drugs early on
- Formulary changes will vary by therapeutic area

Biosimilar Payor Mandates

Percentage of cost-savings required to mandate biosimilar use by patient type

- New Start Patients
- Existing Patients

The Pharmacist’s Role

- Formulary adherence
- Facilitating therapy transitions

What Will We Dispense?
Reference product, biosimilar, interchangeable...
Not a Generic!

Written for: Brand-only medication, Brand with generic equivalents, Biologic with biosimilar

Dispense?:

Biosimilar Scenarios (1 of 2)

Written for: Reference product with any number of biosimilars not interchangeable, Reference product with one interchangeable biosimilar, Reference product with multiple interchangeable biosimilars

Dispense?:

Biosimilar Scenarios (2 of 2)

Written for: Biosimilar is not interchangeable with reference product, Biosimilar is interchangeable with reference product, Reference product w/ interchangeable biosimilar(s), DAW included

Dispense?:

Dispense?: 
Summary

BIOSIMILARS

Net Generics

New Approved Pathway

Lower Cost

Varied State Laws

Rich Pipeline

Patient Acceptance

Prescriber Awareness

Payer Formulary Placement

Questions?

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