Biosimilars in Oncology:
Implementation for Future Therapies in Oncology

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Financial Disclosure(s)

• I currently have or have had the following relevant financial relations to disclose:
  
  • Speaker’s Bureau: Takeda
  • Consultant: Hospira, Sandoz
  • Contracted Research: Sanofi
Off-Label Use Disclosure(s)

• I do not intend to discuss an off-label use of a product during this activity.
Objectives

1. Describe the regulatory process for biosimilar products for approval
2. Develop a plan for implementing biosimilars into practice, considering issues related to the medication use process, pharmacovigilance, and reimbursement
3. Interpret how the current status and issues related to the FDA guidance documents on biosimilar naming and labeling will affect practice
4. Discuss the concepts of interchangeability, including the current status of the FDA guidance document
## Lexicon of Biosimilar Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic</td>
<td>An approved product composed of proteins, nucleic acids, or combinations of these, or living entities such as cells and tissues, which is isolated from natural sources (including humans, animals, and microorganisms) and produced by biotechnology methods and other cutting-edge technologies</td>
</tr>
<tr>
<td>Biosimilar</td>
<td>A biological product developed such that there are “no clinically meaningful differences between the biological product and the reference [originator] product in terms of safety, purity, and potency” and “demonstrates similarity to the [originator] in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise”</td>
</tr>
<tr>
<td>Generic drug</td>
<td>Small (single molecule) or low molecular weight chemically synthesized compounds consisting of a simple, well defined structure that is independent of the manufacturing process and easy to characterize completely</td>
</tr>
<tr>
<td>Extrapolation</td>
<td>A core concept for approval of biosimilars, extrapolation allows for the approval of a biosimilar for use in an indication held by the originator not directly studied in clinical trials of the biosimilar. It is based on sufficient scientific justification and the totality of the evidence</td>
</tr>
<tr>
<td>Interchangeable biosimilar</td>
<td>The product is approved as a biosimilar; the biosimilar can be expected to produce the same clinical effects as the originator in any given patient, and the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its originator is not greater than the risk of using the originator without such alternation or switch</td>
</tr>
<tr>
<td>Intended copy</td>
<td>Copies of an originator biologic that have not been evaluated using the stringent, specifically defined criteria of the EMA, FDA, or WHO guidelines for biosimilars</td>
</tr>
</tbody>
</table>
# Current Biologics on the Market

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human insulin</td>
<td>Several</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Interferons: (\alpha, \beta, \gamma)</td>
<td>Several</td>
<td>Several</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Procrit®, Epogen®, Aranesp®</td>
<td>Anemias</td>
</tr>
<tr>
<td>Darbepoetin alfa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Neupogen®, Neulasta®, Leukine®</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sargramostim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin®</td>
<td>Her2Neu cancers</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Rituxan®</td>
<td>Lymphomas, NHL</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erbitux®, Avastin®</td>
<td>EGFR-expressing cancers</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Biologic Production

- Process important for biologics production
- Production process for biologics has more steps and is more complex than process for traditional drugs

http://biosimilarsource.com/biosimilars.htm
Biologic Manufacturing
## Annual Sales of Biologic Agents

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Avastin</td>
<td>bevacizumab</td>
<td>Genentech</td>
<td>02/06/2004</td>
<td>06/18/2019</td>
<td>$2,662,842</td>
<td>$292,912.62</td>
</tr>
<tr>
<td>EpoGen</td>
<td>epoetin alfa</td>
<td>Amgen</td>
<td>06/01/1989</td>
<td>05/26/2015</td>
<td>$2,254,245</td>
<td>$247,966.95</td>
</tr>
<tr>
<td>Herceptin</td>
<td>trastuzumab</td>
<td>Genentech</td>
<td>09/25/1998</td>
<td>08/27/2019</td>
<td>$1,837,693</td>
<td>$202,146.23</td>
</tr>
<tr>
<td>Humira</td>
<td>adalimumab</td>
<td>AbbVie</td>
<td>12/31/2002</td>
<td>12/31/2016</td>
<td>$4,505,380</td>
<td>$495,591.80</td>
</tr>
<tr>
<td>IntronA</td>
<td>Interferon alfa-2a</td>
<td>Merck</td>
<td>06/04/1986</td>
<td>08/26/2020</td>
<td>$ 94,009</td>
<td>$ 10,340.99</td>
</tr>
<tr>
<td>Neulasta</td>
<td>pegfilgrastim</td>
<td>Amgen</td>
<td>01/31/2002</td>
<td>10/20/2015</td>
<td>$3,472,988</td>
<td>$382,028.68</td>
</tr>
<tr>
<td>Neupogen</td>
<td>filgrastim</td>
<td>Amgen</td>
<td>02/20/1991</td>
<td>11/10/2013</td>
<td>$1,007,172</td>
<td>$110,788.92</td>
</tr>
<tr>
<td>PEG-Intron</td>
<td>Peginterferon alfa-2b</td>
<td>Merck</td>
<td>01/19/2001</td>
<td>08/26/2020</td>
<td>$ 121,828</td>
<td>$ 13,401.08</td>
</tr>
<tr>
<td>Procrit</td>
<td>epoetin alfa</td>
<td>Janssen Products</td>
<td>06/01/1989</td>
<td>05/26/2015</td>
<td>$1,127,024</td>
<td>$123,972.64</td>
</tr>
<tr>
<td>Remicade</td>
<td>infliximab</td>
<td>Janssen Biotech</td>
<td>08/24/1998</td>
<td>09/04/2018</td>
<td>$3,796,422</td>
<td>$417,606.42</td>
</tr>
<tr>
<td>Rituxan</td>
<td>rituximab</td>
<td>Genentech</td>
<td>11/26/1997</td>
<td>07/05/2015</td>
<td>$3,183,625</td>
<td>$350,198.75</td>
</tr>
</tbody>
</table>

7-5-2016 US Federal Court (Amgen vs Apotex) requires biosimilar manufacturer to give notice to reference manufacturer and wait 180 days before bringing the drug to market.

<table>
<thead>
<tr>
<th>Drug (examples)</th>
<th>Patent Expires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovenox</td>
<td>2012</td>
</tr>
<tr>
<td>Neupogen</td>
<td>2013</td>
</tr>
<tr>
<td>Epogen</td>
<td>2013</td>
</tr>
<tr>
<td>Lantus</td>
<td>2014</td>
</tr>
<tr>
<td>Interferon beta 1-a</td>
<td>2015</td>
</tr>
<tr>
<td>Neulasta</td>
<td>2015</td>
</tr>
<tr>
<td>Synagis</td>
<td>2015</td>
</tr>
<tr>
<td>Humira</td>
<td>2016</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2016</td>
</tr>
<tr>
<td>Erbitux</td>
<td>2016</td>
</tr>
<tr>
<td>Remicade</td>
<td>2018</td>
</tr>
<tr>
<td>Avastin</td>
<td>2019</td>
</tr>
<tr>
<td>Herceptin</td>
<td>2019</td>
</tr>
<tr>
<td>Aranesp</td>
<td>2024</td>
</tr>
</tbody>
</table>

*Etanercept (Enbrel) approved 9-2016, delayed market release to 3-2017*
Biosimilar Cost Reduction in US Market

$250 Billion of Projected Savings – From Just 11 Biosimilars

PROJECTED U.S. SPEND ON BIOLOGICS

Projected U.S. Spend on 11 Specific Biologics (in 000's)

<table>
<thead>
<tr>
<th>Year</th>
<th>Without Biosimilars</th>
<th>With Biosimilars</th>
<th>Savings Projection with Biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>$50,000,000</td>
<td>$20,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2013</td>
<td>$60,000,000</td>
<td>$30,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2014</td>
<td>$70,000,000</td>
<td>$40,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2015</td>
<td>$80,000,000</td>
<td>$50,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2016</td>
<td>$90,000,000</td>
<td>$60,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2017</td>
<td>$100,000,000</td>
<td>$70,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2018</td>
<td>$110,000,000</td>
<td>$80,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2019</td>
<td>$120,000,000</td>
<td>$90,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2020</td>
<td>$130,000,000</td>
<td>$100,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2021</td>
<td>$140,000,000</td>
<td>$110,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2022</td>
<td>$150,000,000</td>
<td>$120,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2023</td>
<td>$160,000,000</td>
<td>$130,000,000</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>2024</td>
<td>$170,000,000</td>
<td>$140,000,000</td>
<td>$30,000,000</td>
</tr>
</tbody>
</table>

Price change since introduction in biosimilar accessible market:
- Germany: -55%
- France: -39%
- Italy: -14%
- Spain: -13%
- UK: -24%
- Spain: -18%

Source: IMS Health, The Impact of Biosimilar Competition, Nov 2015

Note: Analysis based on publicly available prices
Regulatory Pathways for Drugs and Biologics

Small Molecules—Approved via FDCA

- Small Molecules
  - New Drug Applications 505(b)(1) and 505(b)(2)
    - Full report of safety and efficacy investigations
    - Two pathways (505(b)(1) and 505(b)(2)) based on right of reference

Generics

- Abbreviated New Drug Applications 505(i)
  - Identical to an already approved product
  - No safety/efficacy data required (only bioequivalence)

Biologics—Approved via PHSA

- Biologics
  - Biologics License Applications 351(a)
    - Full report of safety and efficacy investigation
  - Biosimilar Biologics License Applications 351(k)
    - Highly similar to a 351(a) product
    - Applicant has right of reference to essential investigations
    - Data showing absence of clinically meaningful difference

Interchangeable biologics are approved under the biosimilar pathway but must meet higher standards.

Note: For historical reasons, a few biological products are currently approved under the FDCA. However, under the BPCI Act, all biological products will be approved under the PHSA beginning in 2020.


Biosimilar Development Approach

Develop highly similar biologic
- Analytical methods for structure/function
- Cell lines
- In vitro/vivo models
- Substance pilot and final scale
- Formulation and final drug product

Test and confirm biosimilarity
- Human clinical trials
- Consideration of clinically sensitive endpoints
- Clinically sensitive patient population
- Immunogenicity
- Efficacy and safety

FDA Approval

Postmarketing Monitoring
- Assessment of rare but serious adverse effects
- Active and/or passive surveillance methods
- Follows previous guidance

Test and confirm interchangeability
- No explicit FDA guidance
- Will be “difficult” to do in the initial 351(k) application

Biosimilar and Biologic Development

Totality of the Evidence

351(a)

No “one size fits all” assessment:

FDA scientists will evaluate the applicant’s integration of various types of information to provide advice on scope and extent of develop plan and, ultimately, an overall assessment that a biological product is (or is not) biosimilar to an approved reference product.

351(k)

Biosimilar

Highly Similar

Four Assessments of Analytical Characterization

Studies of Structure and Function:
Residual Uncertainty

- Low
  - Highly similar with fingerprint-like similarity
    - Very high confidence; appropriate for more targeted clinical studies
  - Highly similar
    - High confidence; appropriate for targeted clinical studies
  - Similar
    - Additional information needed: analytical, comparative PK/PD, etc.
  - Not similar
    - No further development through 351(k)

Human Pharmacokinetics and Pharmacodynamics

• “Fundamental” for demonstrating biosimilarity
• Both PK and PD will be necessary
  • PK: patient population considerations
  • PD should study measures that
    • Are relevant to clinical outcomes
    • Can be quickly assessed with precision
    • Have the sensitivity to detect clinically meaningful difference
• Ideally correlate exposure to clinical outcomes
• Use crossover and parallel designs

Comparative Clinical Studies

• Efficacy and safety: specific clinical trial design will depend on what residual questions remain
  • Clinical studies should be designed to demonstrate neither decreased nor increased activity
  • Use clinically relevant and sensitive endpoints in the right population
  • Biosimilar sponsor to justify comparability delta

Indication Extrapolation Framework

Patient Factors
- Similarity of biologic disposition: PK/PD
- Organ function
- Age, ethnicity, etc.

Disease Factors
- Clear MOA?
- Similarity of disease (e.g., histology, stage, pathophysiology, etc.)
- Single vs. combo therapy
- Clinical manifestation

Endpoint Factors
- Efficacy and toxicity
- Short-term vs. long-term
- Sensitivity of surrogate outcomes

Quantitative Evidence of Biosimilarity
In vitro, preclinical, epidemiological studies, diagnostic studies, clinical trials, and observational studies

Indication Extrapolation Determination
No extrapolation; extrapolation to some indications; extrapolation to all indications


Source of Names and Numbers

- Originator Manufacturer
  - Reference Product (Trade Name)
- United States Adopted Names (USAN)
  - The generic name (Reference Name)
  - Provided by AMA
  - Generally adopted by FDA
- United States Pharmacopeia (USP)
  - Monographs and consistency concerns
- Institute for Safe Medication Practices (ISMP)
  - Consults on Naming Clarity and Safety concerns
  - Advocates for Labeling standards
- Food and Drug Administration (FDA)
  - Ultimately approves product name
  - Assigns National Drug Code (NDC)
- Centers for Medicare & Medicaid Services (CMS)
  - Assigns HCPCS codes
  - Codes usually the same between biosimilars & originator

HCPCS=Healthcare Common Procedure Coding System
Biosimilar Naming

FDA Proposed Suffix

- Unique
- Devoid of meaning
- Four lowercase letters of which at least three are distinct
- Nonproprietary
- Attached to the core name with a hyphen
- Free of legal barriers that would restrict its usage

FDA Proposed Suffix

- Be false or misleading
- Include numerals and other symbols aside from the hyphen attaching the suffix to the core name
- Include abbreviations commonly used in clinical practice in a manner that may lead the suffix to be misinterpreted as another element on the prescription or order
- Contain or suggest any drug substance name or core name
- Look similar to or be capable of being mistaken for the name of a currently marketed product
- Look similar to or otherwise connote the name of the license holder
- Be too similar to any other FDA-designated nonproprietary name suffix
FDA Draft Guidance on Naming

• Goal: facilitate pharmacovigilance and prevent inadvertent substitution

• INN with an added random four-letter suffix for all biologics (including reference products)
  • replicamab-cznm
  • replicamab-hixf

• Benefits
  • Common INN will group similar biologics in electronic systems
  • Having suffix for all products reduces perception that biosimilar is inferior to reference product

# The Dilemma of Biosimilar Naming

**Biosimilars should have the exact same INN as the reference product**

**Pros**
- Communicate that these products are “highly similar”
- Facilitate adoption and substitution of interchangeable biologics

**Cons**
- Hard to trace for pharmacovigilance

**Biosimilars should have a distinct INN to differentiate from reference and other biosimilars**

**Pros**
- Improved pharmacovigilance
- Recognize as distinct products

**Cons**
- Confusion about whether they are “interchangeable”
- May impede adoption
- Issues with substitution

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Biosimilar Product Labeling: Basic Principles

• Reference biologic is found to be safe and effective as per the originator’s registration trials
• Biosimilar manufacturer demonstrates that the biosimilar is “highly similar” to the reference, with no clinically meaningful differences
• What about:
  • Minor differences in inactive components?
  • Differences in stability or storage?
  • Differences in conditions of use?

FDA Draft Guidance on Biosimilar Labeling

• Clearly identifies the product as a biosimilar
• Incorporates relevant data and information from the reference
  • Clinical trial data
  • Adverse effects
• With appropriate product-specific modifications
  • Conditions of use
  • Administration, preparation, storage
  • Safety information that does not preclude demonstration of biosimilarity

FDA Draft Guidance on Biosimilar Labeling

• Approaches to product identification
  • Biosimilar product name
  • Reference product name
  • Core name

• May include information from studies for specific indications for which the biosimilar is not seeking approval

Biosimilar Implementation
Biosimilar Pharmacovigilance

Risk Identification and Characterization

Pharmacovigilance
- Practical to encourage healthcare provider reporting
- Real-time data
- Ensure traceability

Risk minimization
- Healthcare provider communication
- Recalls and alerts
- FDA REMS?

FDA Approval

Healthcare Provider Responsibility for Reporting
- Correct attribution of safety event
- Maintenance of electronic medical record
- Bar code administration
- Medication reconciliation
- Consideration of transitions of care

Biologic Manufacturing Process Changes

- Despite these differences, when the products are within a prespecified acceptable range, the products are marketed with no change in label.
- If large alterations occur, analytical studies (and possibly additional clinical studies) are required to compare post-change product with existing pre-change product.

One Change in the Formulation of an Established Biopharmaceutical Led to Unpredicted Immunogenicity

![Graph showing PRCA cases associated with epoetin alfa](image)

- **Substitute polysorbate 80 for HSA**
- **Coated rubber syringe stoppers**


FDA: Interchangeability

• The biological product is **biosimilar** to the reference product
• It can be expected to produce the **same clinical result** as the reference product **in any given patient**
• For a product that is administered more than once to an individual, the **risk** in terms of safety or diminished efficacy of alternating or switching between use of the product and its reference product is **not greater than the risk of using the reference product without such alteration or switch**
• A product with an interchangeable designation may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
Biosimilar Substitution State Legislation

- **H 2310**
- Signed 5/17/2016 as Act No. 293
- Allows a pharmacist to substitute a biological product for a prescribed biological if certain conditions are met, including a requirement that the pharmacy inform the patient of the substitution and a requirement that the pharmacy retain a record, requires notification of any price difference,
Biosimilars in Oncology

• Hematology/Oncology
  • Rituximab
  • Bevacizumab
  • Trastuzumab

• Supportive Care
  • Filgrastim

First MabThera biosimilar to launch in EU for cancer
Frequency of publications of reported named proposed biosimilars and ICs in oncology.
Biosimilar Development Pipeline

[Diagram showing the development pipeline for various biosimilars, including Etanercept, Infliximab, Adalimumab, and Rituximab.]


# Summary of Oncology Biosimilars

<table>
<thead>
<tr>
<th>Biologic Originator</th>
<th>Biosimilar (name[s]; company)</th>
<th>Comparator studies</th>
<th>Post-marketing/observational studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Analytical studies</td>
<td>Nonclinical studies</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>ABP 215 (Amgen, USA)</td>
<td>★★★★★</td>
<td>★★★★★</td>
</tr>
<tr>
<td></td>
<td>BCD-021 (Biocad, Russia)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>PF-06439535 (Pfizer, USA)</td>
<td>★ or ★★</td>
<td>★★★★</td>
</tr>
<tr>
<td></td>
<td>RPH-001 (Alphapharm, China/R-Pharm, Russia)</td>
<td>NA</td>
<td>★</td>
</tr>
<tr>
<td>Rituximab</td>
<td>BCD-020 (AcelisBiT™; Biocad, Russia)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>GP2013 (Sandoz, Switzerland)</td>
<td>★★★★★</td>
<td>★★★★★</td>
</tr>
<tr>
<td></td>
<td>PF-05280586 (Pfizer, USA)</td>
<td>★★ or ★★★</td>
<td>★★★★</td>
</tr>
<tr>
<td></td>
<td>RTXMS3 (mAbScience, Switzerland)</td>
<td>★</td>
<td>★★★★</td>
</tr>
<tr>
<td></td>
<td>SAlT101 (Samsung, South Korea)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>IB8 (Center of Molecular Immunology, Cuba)</td>
<td>NA</td>
<td>★</td>
</tr>
<tr>
<td>Intended Copies of</td>
<td>Kikunthera® (Probiomed, Mexico)</td>
<td>★★ or ★★★</td>
<td>★★★★</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Reditin™ (Dr. Reddy’s Laboratories, India)</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>BCD-022 (Biocad, Russia)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>CT-P6 (Celltrion, South Korea)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>FTMB (ABP 980; Allergen, USA/Amgen, USA/Synthon, the Netherlands)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>PF-05280014 (Pfizer, USA)</td>
<td>★★ or ★★★</td>
<td>★★★★</td>
</tr>
</tbody>
</table>
Rituximab

• Rituximab is a chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B cells

• Rituximab destroys B cells and is therefore used to treat diseases that are characterized by excessive number of B cells, overactive B cells, or dysfunctional B cells

• This includes many lymphomas, leukemias, transplant rejections, and autoimmune disorders

• The originator product, Roche’s MabThera/Rituxan (rituximab), was approved by the US Food and Drug Administration (FDA) in November 1997 and by the European Medicines Agency (EMA) in June 1998
Extrapolation in Rituximab

• From “Biosimilars: what clinicians should know”
  • “Extrapolation of efficacy and safety data to other indications of the reference product that have not been investigated during the clinical development of the biosimilar always requires convincing scientific justification, which should address the mechanism of action, toxicities, and immunogenicity in each indication of use.”

• With a rituximab biosimilar can we extrapolate:
  • From non-malignant use (e.g. RA) to lymphoma?
  • From use in lymphoma to autoimmune disease?
  • From single agent to combination?
  • From combination to single agent?

Zelenetz A. Presentation to New York Academy of Sciences (NYAS); March 2012.
European Experience – Example Zarzio®

• Biosimilars of filgrastim based on the originator product Neupogen®, have been available since 2008 and are now in widespread clinical use in Europe and elsewhere.

• To assess whether biosimilars are effective in the real-world clinical practice setting, a pooled analysis of five post-approval studies of biosimilar G-CSF (Zarzio®) that included 1,302 adult patients who received at least one cycle of chemotherapy with G-CSF support for the prevention of neutropenia was conducted.

• The occurrence of severe or febrile neutropenia was within the range of that observed in previous studies of originator G-CSF.

• Since the launch of Zarzio® in 2009, the estimated exposure to this biosimilar is approximately 4.5 million patient days (as of June 2013 Sandoz data on file).
Biosimilar: Filgrastim

• First application under the new biosimilar pathway brought to an FDA advisory committee

• On January 7, 2015, the FDA Oncologic Drugs Advisory Committee unanimously voted that Sandoz’s EP2006 (Zarxio) should be licensed as biosimilar to the reference product, Neupogen
  • Includes all 5 indications for which Neupogen is approved

• FDA did not announce when they will make the final decision about the licensing application for Sandoz’s filgrastim product
The P&T Committee Will Be Integral to the Biosimilar Implementation Process

• The review process will be different than that used for a generic small-molecule drug
• P&T Committees will likely establish institutional policies around therapeutic substitution

Considerations for Formulary Selection of Biosimilars

**Efficacy/Safety**
- Clinical data
- Range of indications
- Immunogenicity concerns
- Potential for therapeutic interchange
- Number of similar agents on formulary
- Pharmaco-vigilance requirements

**Manufacturer Considerations**
- Supply reliability
- History of drug shortages
- Supply chain security
- Anti-counterfeit measures
- Patient assistance programs
- Reimbursement support

**Product Considerations**
- Product packaging and labeling
- Bar coding
- Compatibility with CSTDs,* robotics
- Product preparation and administration
- Storage requirements

**Hospital and Patient Factors**
- Economic considerations
  - ✓ Hospital
  - ✓ Payer
  - ✓ Patient
- Payer policies
- Transitions of care
- IT and medication system changes
- Educational requirements

*CSTDs = closed system transfer devices

Formulary Selection Considerations: Efficacy and Safety

• Clinical data and populations studied in FDA approval
• Range of indications
• Presence of biomarker to assess efficacy and safety
• Experienced vs. de novo patients
  • Immunogenicity concerns due to switching

Formulary Selection Considerations: Manufacturer Considerations

- Expertise manufacturing biologics
- Supply reliability
- Supply security and anti-counterfeit measures
- Patient assistance programs
- Reimbursement support programs

Pharmacy & Therapeutics Committee Membership and Functions

Committee Chair (Chief of Pharmaceutical Services)

Member secretary

Pharmacy & Therapeutics Committee

Committee members

Clinical
- Physicians
- Nurses and physician assistants

Pharmacy
- Pharmacists

Hospital administration
- Dean
- Hospital director

Formulary Selection Considerations: Product Considerations

- Product packaging and labeling from safety perspective
- Bar coding
- Compatibility with closed system transfer devices (if NIOSH hazardous drug)
- Preparation and administration considerations
- Storage requirements
- Dosage forms meet needs of patient populations

Formulary Selection Considerations: Payer, Provider, and Patient Factors

• Economic considerations
  • Payer
  • Provider
  • Patient out-of-pocket cost – impact on adherence

• Management of transitions of care
  • How many products in “preferred” status
  • Consistency of product provided
CMS Billing Guidance, April 2015

• CMS Payment
  • Utilize same HCPCS code as Reference Drug
  • Initial: 106% AWP
  • Then: Biosimilar ASP + 6% Reference ASP
  • Reference Product: ASP + 2.3% (varies)

• CMS release:
  • “…unique opportunity to achieve measurable cost savings and greater beneficiary access to expensive therapeutic treatments for chronic conditions.”
  • “CMS is considering policy options for coding of additional biosimilars and will release further guidance in the future”
  • Expects price to be 15 – 30% lower than reference product

CMS Biosimilar Modifiers

• Biosimilars will share the same HCPCS code, but with a modifier that identifies the manufacturer of the specific biosimilar product

<table>
<thead>
<tr>
<th>Biosimilar HCPCS Code</th>
<th>Product Brand names</th>
<th>Corresponding Required Modifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q5101 Injection, Filgrastim (G-CSF), Biosimilar, 1 microgram</td>
<td>Zarxio</td>
<td>ZA - Novartis/Sandoz</td>
</tr>
<tr>
<td>Q5102 Injection, infliximab, biosimilar, 10 mg</td>
<td>Inflectra</td>
<td>ZB - Pfizer/Hospira</td>
</tr>
</tbody>
</table>

https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/Part-B-Biosimilar-Biological-Product-Payment.html
Patient / Co-Pay Assistance?

- Most originator drugs have PAP
- Most “biosimilar drugs” are produced by companies that have PAP programs
- To be competitive, providers should insist on at least the same level of support as with the originator drug.
Summary

• New biosimilar therapies are expected to hit the market over the next five years within multiple treatment areas currently progressing through phase I and phase III studies.

• The role of these new biologics will become important in addressing the clinical studies for each indication, but understanding the extrapolation of the content for other indications will be increasingly important to review.

• Addressing the intent of therapy, supportive care versus therapeutic intent, will continue to be scrutinized and questioned in regards to treatment outcomes based on study will need to be reviewed.

• Biosimilar uptake continues to increase in Europe, and no specific safety issues have been identified for approved and marketed biosimilars.
Questions?

"Baseball is ninety percent mental. The other half is physical."

Yogi Berra