Biosimilar Check-up: Availability and Clinical/Financial Issues

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Learning Objectives

1. Discuss the approval pathway for biosimilars and the “totality of the evidence” needed to demonstrate biosimilarity

2. Identify currently available biosimilars and those in development

3. Describe how the availability of biosimilars may help to control medication expenditures
Background on Drugs & Biologics

• Drugs are approved under Section 505 of the FDCA
  • NDA: Section 505(b)(2); ANDA: Section 505(j)

• Biologics are approved under the PHSA
  • Originator/reference/follow-on: 351(a); Biosimilar: 351(k)

• The Biologics Price Competition and Innovation Act was enacted to increase competition with biological medications
  • Decreased prices (or overall expenditures)
  • Increased innovation

• Several older biologics (e.g., insulins) were approved under Section 505
  • BPCI allows a transition period to allow approval under Section 505 before 2020

Biologics: More Complex than Traditional Small Molecule Drugs

**Human EPO**
- 165 amino acids
- MW ~ 34,000 Da

**Cisplatin**
- (NH₃)₂PtCl₂
- MW ~ 300 Da

**Biologics**
- Produced by living systems
- High molecular weight
- Complex & heterogeneous
- Impossible to fully characterize
- Sensitive to external conditions & manufacturing changes
- Relatively higher immunogenicity

**Small-molecule drugs**
- Produced by chemical reactions
- Relatively low molecular weight
- Final structure independent of process
- Able to be characterized fully
- Stable
- Mostly non-immunogenic

Illustration courtesy of Ogun Guvench, M.D., Ph.D., University of New England College of Pharmacy.
Biosimilars are NOT Exact Copies of Existing Biologics

- Generic drugs can be produced as exact copies of existing drugs and therefore regulatory approval requires data showing pharmacokinetic similarity (bioequivalence)
- Biosimilars are much larger and more complex than a generic copy of a small molecule
- Biologics are made up of amino acids:
  - Forming unique folds and variable glycosylation patterns
- Combined with the complicated manufacturing process, an exact copy of a biologic cannot be made
- Therefore, the regulatory requirements are more rigorous than generics to ensure that the molecules are highly similar and that there are no clinically meaningful differences
- The regulatory exercise requires extensive chemical and pharmacological characterization as well as some clinical studies to demonstrate this

Generics: Exact Copies

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 reference

- Generics
  - Abbreviated New Drug Applications 505(j)
    - Identical to an already approved product

Biosimilars: Highly Similar

Biologics—Approved via PHSA

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

- Biosimilars
  - Biosimilar Biologics Applications 351(k)
    - Highly similar to a 351(a) product

Interchangeable biologics are approved under the biosimilars pathway, but must meet higher standards

FDCA: Food, Drug, and Cosmetics Act; PHSA: Public Health Service Act

Manufacturing Biosimilars: Sources of Variation

Cloning and Protein Expression

Target DNA

Cloning into DNA vector

Transfer into host cell
Expression screening/selection

Source DNA

Possibly same gene sequence

Possibly 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

Different operating conditions

Purification through chromatography

Different binding and elution conditions

Characterization and stability

Purified bulk drug

Different methods, reagents, reference standards

Originator Manufacturing Process Changes

- Small modifications may result in gradual changes

Darbepoetin alfa

- 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

Regulatory Definitions of a Biosimilar

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

• European Medicines Agency – Europe
  • ... structurally highly similar versions of an already authorized biological medicinal product (the reference product) with demonstrated similarity in physicochemical characteristics, efficacy, and safety based on a comprehensive comparability exercise

General Principles for Demonstrating Biosimilarity

• Biosimilars approved via an abbreviated pathway
• Demonstration of biosimilarity is a comparability exercise and not a therapeutic equivalence study
• Goal of the biosimilarity exercise is to establish that the candidate biosimilar is not significantly different from the reference product and is unlikely to have any clinically significant differences
  • Smaller-scale direct comparisons and extrapolation are used

Biosimilar Development Approach

**Develop highly similar biologic**
- Cell lines, in vitro/vivo models
- Analytical methods for quality attributes (structure/function)
- Substance pilot and final scale
- Formulation and final drug product

**Test and confirm biosimilarity**
- Human clinical trials
- Consideration of clinically sensitive endpoints & patient population
- PK/PD, immunogenicity, efficacy and safety

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

**Test and confirm Interchangeability**
- Generally requires switching studies
- Data package and study design/endpoints depends on type of biological molecule and analytic similarity
- Post-marketing safety data may be required for complex molecules with rare adverse effects
- Similar product presentation (design and user interface) compared to the reference

Biosimilar Pathway Represents a Paradigm Shift From Standard Originator Registration Pathway

**Biosimilar Development Program Objective:**

*Establish Biosimilarity* Based Upon Totality of Evidence, *Not Re-Establish Benefit*

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**Originator Pathway [§ 351(a)]**

- Analytical
- Preclinical
- Clinical pharmacology
- Clinical Studies

**Biosimilar Pathway [§ 351(k)]**

- Analytical
- Preclinical
- Clinical pharmacology
  - PK/PD
  - Clinical Studies

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Conducted in sensitive patient population with sensitive endpoints; Designed to detect a difference, if there is one

PD = pharmacodynamics.


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THE 2017 COMMUNITY ONCOLOGY CONFERENCE FUELING THE CANCER MOONSHOT
Structure and Function

• Serve as the “foundation” of biosimilar development
• Useful in determining what future studies are necessary

• Structure
  • Amino acid sequence, higher-order structures, glycosylation, pegylation, etc.
  • Analyze lot-to-lot variability

• Function
  • Evaluate pharmacologic activity via in vitro or in vivo experiments
  • Functional evaluation that compares candidate to reference

Analytical Characterization: Fingerprinting

Four Assessments of Analytical Characterization

Residual uncertainty after comparison of quality attributes:

High Uncertainty

- Insufficient analytical similarity → No further development through 351(k)
- Analytical similarity with residual uncertainty → Additional information needed: analytical, comparative PK/PD, etc.
- Tentative analytical similarity → High confidence; appropriate for targeted clinical studies
- Fingerprint-like analytical similarity

Low Uncertainty

- "Very high confidence; appropriate for more targeted clinical studies"

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

Clinical Trial Design: Equivalence

- Establish the equivalence margin (δ) via the 95-95 method
- 95% CI should fall between -δ and +δ for equivalence

However, non-inferiority studies may be appropriate if it is well-established that the biologic saturates the receptors at the clinical dose

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

The totality of evidence supports no differences in efficacy or safety.

Reference

<table>
<thead>
<tr>
<th>Structural attributes</th>
<th>HIGHLY SIMILAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological functions</td>
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<td>Nonclinical/tox</td>
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<td>Human PK/PD</td>
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<td>Sensitive indication</td>
<td>HIGHLY SIMILAR</td>
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<tr>
<td>Less sensitive indications</td>
<td>JUSTIFIED</td>
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</table>

“SIMILARITY SPACE”
Immunogenicity Concerns

• All biologics confer a risk of immunogenicity
  • Formation of antidrug antibodies (ADA)
  • Related to patient, disease, and product factors
  • Scientific tools for detecting ADA exist, but they do not always translate to clinical outcomes

• Changes to the structure of the protein increase variation in immunogenicity
  • Lot-to-lot and between manufacturers
  • Variations in manufacturing must be minimized

Immunogenicity concerns

• Clinical consequences:
  
  - Loss of efficacy
  - Immune effects: allergy, serum sickness, anaphylaxis
  - Neutralization of endogenous protein

• Clinical immunogenicity assessment for biosimilars
  
  - Goal is to evaluate potential differences in incidence and severity of immune responses using endpoints such as antibody formation (binding, neutralizing), cytokine levels, etc.
  - FDA recommends a comparative parallel study

Biosimilar Pharmacovigilance

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

Risk Identification and Characterization

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

Interchangeability

• Appropriate to be “substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product”

• Additional and different data standards than establishing biosimilarity only

• Regulatory requirement for determining interchangeability:
  • Must be a biosimilar
  • Produces same clinical result as the reference in any given patient
  • Risk of harm or diminished efficacy due to alternating or switching between biosimilar and reference is no more than using the reference product with no switching

Interchangeable FDA Designation Requires Additional Data

- **Interchangeable** is an FDA designation
  - Dedicated switching study and postmarketing monitoring
  - Study endpoints to evaluate PK/PD, immunogenicity, and safety (efficacy is not adequately sensitive at therapeutic doses)
  - The actual data package of study design and endpoints depends on the complexity of the molecule and degree of analytical similarity
  - The product presentation and user interface must be similar to the reference.

- **Product with an interchangeable designation may be substituted without intervention of prescribing provider**
  - State substitution laws will impact practice
  - Any biological product under consideration for substitution must first be approved by FDA as "interchangeable"

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
Biosimilar Pathway: Key Points

• There is a robust approval pathway for biosimilars
• Based on the totality of the evidence
• Comparative clinical studies vs. Phase 3 RCTs
• Extrapolation to other indications will be scientifically justified
• Pharmacovigilance will ensure safety after real-world utilization
Available Biosimilars and those in Development
FDA-approved Biosimilars

Cancer (active treatment)

Cancer (supportive care)

Inflammation
- Adalimumab-atto
- Etanercept-szss
- Infliximab-dyyb

Filgrastim-sndz
# Biosimilar Applications to the FDA

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Manufacturer</th>
<th>Filed on</th>
<th>Status</th>
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<tr>
<td>Filgrastim</td>
<td>Sandoz</td>
<td>May 2014</td>
<td>Approved March 2015</td>
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<tr>
<td>Infliximab</td>
<td>Celltrion/Pfizer</td>
<td>August 2014</td>
<td>Approved April 2016</td>
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<tr>
<td>Pegfilgrastim</td>
<td>Apotex</td>
<td>October 2014</td>
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<tr>
<td>Filgrastim</td>
<td>Apotex</td>
<td>December 2014</td>
<td></td>
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<tr>
<td>Epoetin</td>
<td>Hospira</td>
<td>December 2014</td>
<td>Complete response letter – October 2015</td>
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<tr>
<td>Etanercept</td>
<td>Sandoz</td>
<td>September 2015</td>
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<tr>
<td>Adalimumab</td>
<td>Amgen</td>
<td>November 2015</td>
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<tr>
<td>Pegfilgrastim</td>
<td>Sandoz</td>
<td>November 2015</td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Samsung Bioepis</td>
<td>May 2016</td>
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</table>

BsUFA Workload and Volume: Interim Report.
## Future Oncology Biosimilars (Sample – not complete or comprehensive)

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Current development phase or key clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Recruiting for phase 3 non-squamous NSCLC (NCT02754882)</td>
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<tr>
<td>Bevacizumab</td>
<td>PK in mCRC (NCT02069704)</td>
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<tr>
<td>Rituximab</td>
<td>PK/PD in RA (PMID: 26909489); recruiting for phase 3 first-line FL (NCT02213263);</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Phase 3 in DLBCL (with CHOP) completed (NCT02268045)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Completed phase 3 in early/locally advanced breast cancer (NCT02149524)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Completed phase 3 in early breast cancer (NCT01901146)</td>
</tr>
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# Oncology Biosimilar Applications to the FDA

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Manufacturer</th>
<th>Filed on</th>
<th>BsUFA Date</th>
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<td><strong>Active Treatment</strong></td>
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<tr>
<td>Trastuzumab</td>
<td>Mylan/Biocon</td>
<td>Nov 8, 2016</td>
<td>Sep 3, 2017</td>
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<tr>
<td>Bevacizumab</td>
<td>Amgen/Allergan</td>
<td>Nov 15, 2016</td>
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<td>Rituximab</td>
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<td><strong>Supportive Care</strong></td>
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<td>Pegfilgrastim</td>
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<td>Dec 17, 2014</td>
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<td>Pegfilgrastim</td>
<td>Coherus</td>
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<td>Mylan/Biocon</td>
<td>Feb 16, 2017</td>
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<td>Epoetin</td>
<td>Hospira/Pfizer</td>
<td>Dec 16, 2014</td>
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</table>

https://biosimilarsrr.com/us-biosimilar-filings/
Biosimilar Trastuzumab Comparative Clinical Trial

- Multicenter, double-blind, randomized, equivalence study
- 500 patients

### Biosimilar Trastuzumab

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Biosimilar + taxane</th>
<th>Reference + taxane</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response type (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1.3</td>
<td>0</td>
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<tr>
<td>PR</td>
<td>68.3</td>
<td>64</td>
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<tr>
<td>SD</td>
<td>20.9</td>
<td>21.5</td>
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</tr>
<tr>
<td>PD</td>
<td>3.9</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>69.6</td>
<td>64</td>
<td>1.09</td>
</tr>
<tr>
<td>90% CI</td>
<td>64.57 to 74.56</td>
<td>58.81 to 69.26</td>
<td>0.974 to 1.211</td>
</tr>
</tbody>
</table>

- Rates of adverse effects (neutropenia, peripheral neuropathy, diarrhea) were similar between cohorts

Biosimilars in Development: Key Points

- Currently no biosimilars approved for the active treatment of cancer
- Biosimilar trastuzumab, rituximab, and bevacizumab are in development
  - Biosimilar trastuzumab comparative clinical trial has been published
- Pegfilgrastim biosimilar is expected in 2017
Biosimilars: Cost Implications
Cancer: Top Expenditure Drugs

Rituximab, bevacizumab, and trastuzumab are consistently within the top 10 of expenditures within US clinics and hospitals:
- Accounted for $8.9 billion in expenditures in 2015
- A 30% discount with these 3 agents alone would save $2.7 billion annually

Pegfilgrastim is ranked #2-3 in clinic and hospital expenditures, with $3.7 billion


### Table 4. Top 25 Drugs by Expenditures in Clinics in 2015

<table>
<thead>
<tr>
<th>Drug</th>
<th>2015 Expenditures ($ Thousands)</th>
<th>Percent Change From 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>3,280,663</td>
<td>11.2</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>2,976,527</td>
<td>9.7</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2,462,831</td>
<td>3.6</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>2,456,606</td>
<td>-9.7</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2,382,695</td>
<td>7.0</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>1,923,290</td>
<td>12.8</td>
</tr>
</tbody>
</table>

### Table 5. Top 25 Drugs by Expenditures in Nonfederal Hospitals in 2015

<table>
<thead>
<tr>
<th>Drug</th>
<th>2015 Expenditures ($ Thousands)</th>
<th>Percent Change From 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>1,044,624</td>
<td>8.1</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1,007,033</td>
<td>8.1</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>846,688</td>
<td>-1.2</td>
</tr>
<tr>
<td>Immune globulin</td>
<td>825,446</td>
<td>-1.2</td>
</tr>
<tr>
<td>Alteplase</td>
<td>731,292</td>
<td>20.8</td>
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<tr>
<td>Natalizumab</td>
<td>698,851</td>
<td>20.6</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>644,964</td>
<td>-6.1</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>619,684</td>
<td>14.0</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>619,468</td>
<td>90.1</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>509,862</td>
<td>22.8</td>
</tr>
</tbody>
</table>
Forecasting Immuno-oncology

- Estimated major-market sales are expected to grow to $7 billion by 2020 (33% annual growth)

- Robust pipeline with 14 agents in Phase I through III development

## Trends in Oncology Drug Expenditures: 2010-2014

<table>
<thead>
<tr>
<th>Year Period</th>
<th>Total Expenditures (US$ - thousands)</th>
<th>Percentage Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-2011</td>
<td>9,000,000</td>
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<tr>
<td>2011-2012</td>
<td>9,400,000</td>
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</tr>
<tr>
<td>2012-2013</td>
<td>9,600,000</td>
<td></td>
</tr>
<tr>
<td>2013-2014</td>
<td>11,200,000</td>
<td></td>
</tr>
</tbody>
</table>

*Novel Mabs*

**Generic gemcitabine**

**Generic docetaxel**

**Generic oxaliplatin**

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Cumulative Cost Savings in Hospitals: tbo-Filgrastim vs Filgrastim (Nov 2013 - Aug 2014)

IMS Health National Sales Perspectives database, data on file.

- Estimated GCSF units sold (480-mcg) was higher in 2015 vs. 2014
- Total GCSF expenditures was lower in 2015 ($915 million) vs. 2014 ($947 million)


IMS Health National Sales Perspectives database, data on file.
The Cost Savings Potential of Biosimilars in the United States

$44.2 billion over 10 years
(Range: $13 to $66 billion)

Rand analysis used a framework that incorporated the following drivers that determine the magnitude of savings:

1. Safety and efficacy
2. Payment
3. Acceptability
4. Competition

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.
Cost: Key Points

• Loss of exclusivity of generics have helped to moderate oncology medication expenditures
• Experience with increased competition with GCSF has resulted in cost savings
• Biosimilars for “top 3” biologics and pegfilgrastim can result in large savings
Presentation Summary

• There is a rigorous regulatory framework for the approval of biosimilars in the United States

• While biosimilars have been approved for inflammatory conditions, those for oncologic diseases may be approved in 2017

• Increased competition with biosimilars is poised to save the healthcare system a significant amount