Biosimilars: Issues and Concerns for their Adoption in Health Care?

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  - University of Twente, Health Technology and Services Research
  - Conceptual framework, analysis plan, interpretation of results for multi-criteria decision analysis (MCDA)
- Charles L. Bennett, MD, PhD
  - University of South Carolina College of Pharmacy
  - Post-marketing safety research in oncology
- University of New Mexico, College of Pharmacy
Conflict of Interests

• Funding sources for studies:
  – National Institutes of Health grants
    • National Cancer Institute: R01 CA102713-03A2
    • National Cancer Institute: R01 CA165609-01A1
  – Patient-Centered Outcomes Research Institute (PCORI): CER 1310-08323
  – Paclitaxel/Docetaxel Research funded by Abraxis, Inc. Funding ended in 2010
• No other conflicts to report

Learning Objectives

• Pharmacists
  – Describe basic principles regarding the approval of biosimilars
  – Contrast the key concerns regarding effectiveness, safety, and immunogenicity of biosimilars
  – Explain how biosimilars may lower costs of treatments
  – Describe the relative importance of post-marketing studies of efficacy, safety and immunogenicity of biosimilars
• Technicians
  – Explain what biosimilars and reference biologicals are
  – Describe differences in biosimilars compared to reference biological
  – Contrast how costs differ between biosimilars and reference biological
  – Describe safety concerns with biosimilars
Outline of Presentation

• Definitions
• Expanding role of biologicals in medicine, especially cancer treatments
• Safety and immunogenic concerns with biologicals
• The case for biosimilars
• Uptake of biosimilars

Definitions for this Presentation

• Biological medicinal product (AKA biopharmaceutical) - A macromolecule medicinal (proteins) or nucleic acid-based drug
  – Engineered from biological tissue (human, animal or micro-organism)
  – May be gene-based or cellular-derived
    • FDA definition - virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood derivative, allergenic product, protein
• Reference biological (AKA the Originator) – the original patented product receiving FDA approval as a new drug under a BLA
• Biosimilar - “Highly similar” to the reference product, approved by the FDA after patent expiration of the reference biological
  – Studies demonstrate no clinical differences in effectiveness or safety
  – Minor differences in inactive components
  – FDA developed specific regulations for biosimilars subsequent to passage of the Affordable Care Act
Expanding Role of Biologicals in Medicine

- Fastest growing portion of pharmaceutical market
- Marked advances in therapeutics and personalized medicine
  - Growth factors (epoetin, filgrastim, human growth hormone, etc)
  - Monoclonal antibodies for cancer and other chronic conditions (rituximab, adalimumab, brentuximab, trastuzumab etc)
  - Tyrosine kinase inhibitors for cancer (imatinib, gefitinib, erlotinib, etc)

- Achieve efficacy not possible from nonbiological small molecules
- Therapy for complex, life-threatening conditions
  - Complexity in structure and manufacturing process
- $170 Billion in 2012 in EU and USA
  - Monoclonal antibodies account for greatest spending
- Predicted: By 2016, 5 of the top 10 drug expenditures
- Market exclusivity extends beyond patent expiration
Safety Concerns with Biologicals

• Expanding use = potential for overuse and increased risk
  – Epoetin - increased risk of mortality and thrombosis in patients with higher hemoglobin levels

• Side effects among high risk patients
  – Hepatitis C reactivation with rituximab
  – Progressive multifocal leukoencephalopathy (PML) with rituximab, brentuximab
  – Pancreatitis with brentuximab

Immunogenic Reactions from Biologicals

• Pure red cell aplasia from epoetin
  – Cause = a manufacturing change causing an interaction between the excipients and the syringe stopper
Post-marketing Surveillance– Peganesitide

- An erythropoietin, less expensive than other marketed epoetins
- Approval required a REMS post-marketing study for cardiotoxicity
- Active surveillance study performed at adoption by a large dialysis organization (LDO) – 25,000 treatments
  - Ten sites out of 2100 in US used peginesatide conducted a 7 month trial, beginning July 2012
  - Then, expanded to 348 sites for 2 weeks

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**Figure 1:** Fatal, Life-Threatening, and Non-Life-Threatening Occurrences of Anaphylaxis and Hypotension in Patients Who Received a First Dose of Peginesatide. Deaths and life-threatening and non-life-threatening events were reported to the Food and Drug Administration.
Post-marketing Surveillance– Peganesitide

- In 2 months
  - 8 cases of anaphylaxis
  - 2 deaths, 3 grade IV events
- By February 12, 2013
  - 28 anaphylaxis events by active surveillance versus
  - 10 events in FDA MedWatch
  - Incidence = 1.4/1,000
- Withdrawn from market on 2/23/2013
- Active surveillance resulted in more rapid identification and more complete reporting

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Post-marketing Surveillance– Peganesitide

*The New England Journal of Medicine*

**Anaphylaxis and Hypotension after Administration of Peginesatide**

Biosimilars

The Case for Biosimilars\textsuperscript{9,10}

\begin{itemize}
\item Regulations intended to establish interchangeability (without prescriber contact)
  \begin{itemize}
  \item European Medicines Agency (EMA)
    \begin{itemize}
    \item As early as 10 years after approval of reference biological (RB)
    \end{itemize}
  \item FDA Biologics Price Competition and Innovation Act
    \begin{itemize}
    \item As early as 12 years after approval of RB
    \end{itemize}
  \end{itemize}
\item Development and production costs for biosimilars - much higher than small molecules
\item Cost savings – Likely to be 25% or more
\item Expanding markets make biosimilars lucrative
\end{itemize}
Naming of Biosimilars

- FDA guidance seeking comment (August 2015)
  - The reference product’s “original proper name, plus the designated suffix attached with a hyphen”
    - 4 lowercase (unique and meaningless) letters
    - Example: Filgrastim-abcd

Patent Expirations of Some Biologicals¹

<table>
<thead>
<tr>
<th>Biological</th>
<th>EU</th>
<th>US</th>
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<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>2018</td>
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<tr>
<td>Etanercept (Enbrel)</td>
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<td>2015</td>
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<td>Infliximab (Remicade)</td>
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<tr>
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<td>Glatiramer Acetate (Copaxone)</td>
<td>2016</td>
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<tr>
<td>Etanercept (Enbrel)</td>
<td>2015</td>
<td>2015</td>
</tr>
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</table>
Biosimilar Approval Requirements\textsuperscript{9,10}

- One (or more) equivalence (or non-inferiority) study compared to the originator biological, with or without a placebo arm
- Demonstrated equivalence (no clinically meaningful differences) in efficacy, safety, immunogenicity, pharmacokinetics, and pharmacodynamics.

Biosimilar Approval Requirements\textsuperscript{9,10}

- Fewer patients treated than for biologic license approval, but costs for development and approval remain high (est. $40M to $300M).
- Clinical study requirements vary by biological and effectiveness/safety experience with the RP plus:
  - Uncertainty of structural and functional differences
  - Pharmacology/pharmaceutical properties
  - Immunogenicity results
  - Sufficient dose exposure and duration, detection of safety signals, proof of noninferiority
3. Clinical Safety and Effectiveness Data

As a scientific matter, comparative safety and effectiveness data will be necessary to support a demonstration of biosimilarity if there are residual uncertainties about the biosimilarity of the two products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment. A sponsor may provide a scientific justification if it believes that some or all of these comparisons on clinical safety and effectiveness are not necessary.

The following are examples of factors that may influence the type and extent of the comparative clinical safety and effectiveness data needed.

1. The nature and complexity of the reference product, the extensiveness of structural and functional characterization, and the findings and limitations of comparative structural, functional, and nonclinical testing, including the extent of observed differences

2. The extent to which differences in structure, function and nonclinical pharmacology and toxicology predict differences in clinical outcomes, as well as the degree of understanding of the MOA of the reference product and disease pathology

3. The extent to which human PK or PD predicts clinical outcomes (e.g., PD measures known to be clinically relevant to effectiveness)

4. The extent of clinical experience with the reference product and its therapeutic class, including the safety and risk/benefit profile (e.g., whether there is a low potential for off-target adverse events), and appropriate endpoints and biomarkers for safety and effectiveness (e.g., availability of established, sensitive clinical endpoints)

5. The extent of any clinical experience with the proposed product

Biosimilar Approval Requirements

- Post-marketing studies required on a case-by-case basis by regulatory agencies
  - Observational studies
  - Patient registries
  - Additional clinical trials
VIII. POSTMARKETING SAFETY MONITORING CONSIDERATIONS

Robust postmarketing safety monitoring is an important component in ensuring the safety and effectiveness of biological products, including biosimilar therapeutic protein products. Because some aspects of postmarketing safety monitoring are product-specific, FDA encourages sponsors to consult with appropriate FDA divisions to discuss the sponsors’ proposed approach to postmarketing safety monitoring.

Postmarketing safety monitoring should first take into consideration any particular safety or effectiveness concerns associated with the use of the reference product and its class, as well as the proposed product in its development and clinical use (if marketed outside the United States). Postmarketing safety monitoring for a proposed product should also have adequate mechanisms in place to differentiate between the adverse events associated with the proposed product and those associated with the reference product, including the identification of adverse events associated with the proposed product that have not been previously associated with the reference product. Rare, but potentially serious, safety risks (e.g., immunogenicity) may not be detected during preapproval clinical testing because the size of the population exposed likely will not be large enough to assess rare events. In particular cases, such risks may need to be evaluated through postmarketing surveillance or studies. In addition, like any other biological products, FDA may take any appropriate action to ensure the safety and effectiveness of a proposed product, including, for example, requiring a postmarketing study to evaluate certain safety risks.30

### EMA Approvals – Sample Sizes11

Most studies have 2-3 arms (Biosimilar, reference, ± placebo)

<table>
<thead>
<tr>
<th>Active Substance</th>
<th>Primary Indication</th>
<th>Secondary Indication</th>
<th>Additional Study</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
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<td>Filgrastim</td>
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<td>Follitropin alfa</td>
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11 EMA Approvals – Sample Sizes

Most studies have 2-3 arms (Biosimilar, reference, ± placebo)
Uptake of Biosimilars\textsuperscript{1,9,11}

- Since 2007, EMA has approved 19 biosimilars\textsuperscript{11}
  - 5 epoetin
  - 8 filgrastim
  - 2 somatotropin
- EMA refusal – Interferon $\alpha$-2a (2006)
- Two withdrawals – 1 filgrastim, 1 somatotropin
- Uptake varies by country
  - Germany > Italy > Spain > France > UK\textsuperscript{1}
  - Developing countries have more rapid uptake
- FDA approvals = 1
  - Zarxio® - biosimilar for filgrastim approved in March 6, 2015
  - Several in development

Relative Uptake of Biosimilars in EU\textsuperscript{1}
Potential Concerns with Biosimilars

- Less experience when marketed – Sample sizes smaller than biologic license approval
  - Limitations of equivalence efficacy studies
- Manufacturing differences may result in new of more frequent safety and immunogenic adverse effects
  - Peginestide and epoetin examples \(^2,7,8\)
  - Adverse event detection often takes 5+ years for newly marketed products with standard approval \(^{12}\)
- Naming and substitution rules are pending

Potential Concerns with Biosimilars – Immunogenicity\(^{13}\)

- Loss of efficacy
- Infusion reactions – e.g. anaphylaxis
- Antibody formation – e.g. pure red cell aplasia
- Contributing factors:
  - Patient-specific (age, genetics, co-morbidities)
  - Disease-specific (immune response, treatment intensity and route)
  - Product-specific (source of protein, manufacturing process, formulation)
Power to Detect Safety/Immunogenicity Problems

<table>
<thead>
<tr>
<th>Rate of adverse event</th>
<th>Sample size required to detect event</th>
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</thead>
<tbody>
<tr>
<td>Frequent (1/10)</td>
<td>30 (sufficient at approval)</td>
</tr>
<tr>
<td>Common (&lt;1/10 to 1/100)</td>
<td>30 to 300 (may be sufficient at approval)</td>
</tr>
<tr>
<td>Uncommon (&lt;1/100 to 1/1000)</td>
<td>300 to 3000</td>
</tr>
<tr>
<td>Rare (&lt;1/1000 to 1/10,000)</td>
<td>3000 to 30,000</td>
</tr>
<tr>
<td>Very rare (&lt;1/10,000 to 1/30,000)</td>
<td>&gt;30,000</td>
</tr>
</tbody>
</table>

Notes:
1. Approval studies with 2 or 3 arms, may have as few as 80 to 120 patients exposed to biosimilar.
2. Two filgrastim biosimilar approvals were limited to studies with only normal volunteers (Filgrastim Hexal, Zarxio).

Literature Review of Post-Marketing Studies of Biosimilars

- Purpose: To review published literature regarding post-marketing studies of biosimilars versus reference biologicals regarding:
  - Effectiveness (E)
  - Safety (S)
  - Immunogenicity (I)
  - Costs
Methods

• Databases: PubMed and International Pharmaceutical Abstracts, through March 2015
• Search terms:
  – MeSH terms "Biosimilar Pharmaceuticals"[Majr] AND “Humans” AND English [language]
• Inclusion criteria:
  – Study design = comparison of biosimilars to reference biological
  – Results included specific data
• Exclusion criteria:
  – Editorials, in vitro studies, descriptive summaries, full text unavailable, normal volunteers only, phase I or II studies

Data Summarization

• Biosimilar and reference biological
• Sample size and types of participants
• Outcomes: effectiveness, safety, immunogenicity
• Key findings
• Concerns or comments
• Additional summaries by therapeutic class
Results

Search results combined (n=193)

Exclusions (n=171):
- Editorials
- In vitro studies
- Descriptive summaries
- Normal volunteers only
- Article unavailable (n=3)

Remaining (n=23)

Effectiveness (n=19)
Safety (n=14)
Immunogenicity (n=5)
Cost (n=3)

Number of Articles by Therapeutic Class

- Epoetins = 4, plus 1 cost study
- Granulocyte colony stimulating factors = 13, plus 1 cost study
- Monoclonal antibodies/tumor necrosis factor blockers = 3, plus 1 cost study
Sample Size for Studies

- Minimum = 20
- Maximum = 6177
- Mean ± SD = 543 ± 1354
- Median = 104
- 4 Large studies
  - Epoetin: n = 6144, 1392
  - Filgrastim: n = 1302, 904
- Total patients included = 11,406

Summary for Each Article

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Drug</th>
<th>Study Design</th>
<th># Subjects</th>
<th>Treatment</th>
<th>Effectiveness, Safety, Immunogenicity</th>
<th>Summary of Results/Key findings</th>
<th>Negative findings</th>
<th>Positive findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castelli, R., et al. 2014</td>
<td>EPO</td>
<td>Observational</td>
<td>24 Patients (MDS patients)</td>
<td>Effectiveness</td>
<td>16 of the 24 patients got an erythroid response (&gt;66,67%) of the 24 patients got independent of transfusion (&gt;62,5%) 7 of the 24 patients didn’t respond to the biosimilar (&gt;29,1%)</td>
<td>Only tested in patients with the age of &gt;65 years No control group was used</td>
<td>Significant, positive relation between Hb-improvement and the variety in FACT-An scores Positive correlation between ER and improved cognitive functions + QoL in patients with MDS</td>
<td></td>
</tr>
</tbody>
</table>
Epoetin Comparison Studies

  – 6144 chronic kidney disease patients, observational study of an administrative database in Germany
  – 64% originator, 24% biosimilar, 15% received both
  – Effectiveness: All groups had similar defined daily dosage (DDD) requirements
  – Safety: Not mentioned in the study results or discussion

Epoetin Comparison Studies

  – 1393 chronic kidney disease patients, open label 6 month observational study in Germany
  – Single arm: All patients received biosimilar
  – Effectiveness: All maintained hemoglobin levels, 9% more achieved target range at end of study
  – Safety: “The observed AE profile was in line with expectations for this patient population.” 11 Adverse events suspected to be drug-related, 3 serious
  – Immunogenicity: No anti-epoetin antibodies were noted.
Filgrastim Comparison Studies

  – Pooled analysis of 5 post marketing studies: 1392 oncology patients with neutropenia after receiving cytotoxic therapy (49% breast, 17% lung, 15% blood)
  – Effectiveness: 2.2% febrile neutropenia and 8.5% grade 4 neutropenia. Within range of previous studies
  – Safety: Similar safety profile, 8% bone pain vs 22% in reference biological
  – Immunogenicity: No neutralizing antibodies detected during ongoing pharmacovigilance

  – 904 patients (donors or receiving stem cell transplant) identified through literature review (520 reference biological/384 biosimilar)
  – Effectiveness: No significant differences demonstrated
  – Safety: No reported increase in toxicity
  – Immunogenicity: Not addressed
  – Limitation: No data summarization or analysis was included.
  – Apparent conflicts of interest in authoship
Monoclonal Antibodies/Tumor Necrosis Factor Blockers Comparison Studies

• 3 studies met inclusion criteria
  – Biosimilar for Infliximab in rheumatoid arthritis
  – Biosimilar for Infliximab in ankylosing spondylitis
  – Biosimilar for rituximab, conducted in India

Biosimilar for Infliximab in RA

  – RCT Multi-center: infliximab (INX) (n=302), biosimilar (IBX BS) (n=304) with methotrexate
  – Effectiveness: 58.6% for INX vs 60.9% for INX BS (95% CI −6% to 10%)
  – Safety: drug-related adverse events (35.9% vs 35.2%)
  – Immunogenicity: detection of antidrug antibodies (48.2% vs 48.4%) for INX and INX-BS.
Biosimilar for Infliximab in Ankylosing Spondylitis

  – RCT Multi-center: infliximab (INX) (n=116), biosimilar (IBX BS) (n=113)
  – Effectiveness: 70.5% for INX vs 62.6% for INX BS (OR=0.91, 95% CI 0.53 to 1.54)
  – Safety: drug-related adverse events 63.9% for INX and 64.8% for INX-BS
  – Immunogenicity: detection of antidrug antibodies: INX 22.5% (n=25) and INX-BS 27.4% (n=32) at week 30.

Biosimilar for Rituximab

  – Retrospective, observational chart review of adult diffuse large B-cell lymphoma patients receiving CHOP-R (101 rituximab/ 72 biosimilar)
  – Effectiveness: No significant differences in any response(Complete or partial remission, survival, progression free survival
  – Safety: From 40 rituximab and 30 biosimilar patients- no differences in infusion reactions or other adverse reactions
Cost Studies


Epoetin Biosimilar Cost Study

  - Cost model of ESA alternatives for chemotherapy-induced anemia at different dosing levels in France, Germany, Italy, Spain, UK
    - Adjusted for dosing scenarios and pricing by country
  - Results: Depending upon comparator reference product (epoetin α, β, darbopoetin) and dosing.
    - Mean savings = 13.8% to 44.2%
    - Mean incremental cost savings for 15 week course
      - Epoetin α = 757€, Darbepoetin = 3738€
  - Conclusions: Savings impacted by reference product and dosing alternatives
Filgrastim Biosimilar Cost Study

  - Market penetration (2007-11) and costs across 5 countries: France, Germany, Italy, Spain, UK
  - Results: Distribution model (retail vs. hospital) impacted use and uptake (2011)
  - Greater use and lower uptake of biosimilars if retail>hospital: France-5.4%, Germany 8.5%
  - Less use and greater uptake if hospital>retail: Spain 12.4%, UK 20.4%
  - Italy had primarily hospital market (87.3%) but uptake was 7.5%
  - Costs (savings) had marginal impact
  - Formulary decision making influenced uptake and use

Infliximab Biosimilar (INX-BS) Cost Study

  - Budget impact model for in six countries
    • Bulgaria, the Czech Republic, Hungary, Poland, Romania and Slovakia
  - Among patients with rheumatoid arthritis, including patients on other biologicals
  - Scenario 1 – only new patients receive biosimilar
    • 15 million euros by year 3
  - Scenario 2 – switching from originator INX after 6 months among 80% of patients
    • 21 million euros by year 3
Limitations

- Studies available through search strategy and published in English
- Study selection - Focused upon comparisons of effectiveness, safety, immunogenicity, and costs which included reference biological

Summary of Findings

- Studies focus on effectiveness
- Reported safety data is often limited to major side effects, most studies do not assess immunogenicity
  - Need for much larger sample sizes (3,000+)
- Cost and uptake comparison studies needed
  - Limitations of administrative databases
  - Relationship between pharmaceutical policies and use
  - Biosimilar = competitive marketing and prices from reference pharmaceutical
Summary of Findings

- Sample sizes of most studies unable to detect ADEs at greater than a 5 to 10% rate
  - Few studies address immunogenicity
  - Cost savings studies, limited to models, suggest increased savings when:
    - Centralized formulary decision making
    - Uptake and savings when treatments are provided in hospital settings > retail (outpatient)
  - Biosimilars will likely increase competitive marketing and lower prices from reference pharmaceuticals

Need for Post-Marketing Observational Studies\(^\text{14}\)

  - Identified need for post-marketing surveillance of biosimilars
  - Proposed a multi-site data resource network (DRN) to monitor the rollout of biosimilars (Similar to the FDA’s MiniSentinel Program)
- Purpose: Monitor the long-term safety and effectiveness of biosimilar versus reference biological
- Active surveillance methods to identify/monitor ADEs in DRN:
  - Epidemiologic studies of a known safety concern
  - Sequential analysis of data, based on a potential safety signal
  - Data mining to identify new safety signals

Conclusions for Presentation

- Described basic principles regarding the approval of biosimilars
- Contrast the key concerns regarding effectiveness, safety, and immunogenicity of biosimilars
- Explained how biosimilars can lower costs of treatments
- Describe the relative importance of post-marketing studies of efficacy, safety and immunogenicity of biosimilars
- Literature review demonstrated a need for more post-marketing research of biosimilars

References

Multicriteria Decision Analysis of Biosimilars

- Identify the factors critical to uptake of biosimilars
  - Should regulators consider more data prior to approval?
  - Should post-marketing studies be required?
  - If so which objectives are most important?
    - Effectiveness
    - Safety
    - Immunogenicity
  - Are cost savings key to adoption?
  - Stakeholder differences in adoption of biosimilars.

Application of Results of MCDA of Biosimilars

- May save health care $ 
- May have lower effectiveness and/or concerns about safety and immunogenicity
  - Less data than for reference biological
- MCDA to inform manufacturers, regulators, payers, and providers regarding need for post-marketing research
- MCDA to inform manufacturers about pricing and market potential
  - Avoid catastrophic failure of a newly-marketed biosimilar
Application of Results of MCDA of Biosimilars

• Stakeholder perspectives may differ
  – Health payers
  – Physicians
  – Pharmacists
  – Pharmaceutical industry