Overcoming Challenges in the Emerging *Biosimilar* Landscape

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Natural **Growth** in Pharmaceutical Industry

- **Core Pharma:** Treating Symptoms 1950-1970
- **Advanced Pharma:** Managing Disease 1970-2000
- **Biotechnology:** Changing Disease’s Impact 1990-2020
- **Personalized Treatment:** Repairing and Eliminating Disease 2015-2030
An Overview of Biosimilars

- A biosimilar is **not considered to be identical** to the originator biologic, as manufacturers of biologics use their own unique **cell lines**, **post-translational modifications** and proprietary **manufacturing processes**

- In March 2010, the **Biologics Price Competition and Innovation Act** was enacted, authorizing the FDA to establish a regulatory pathway for biosimilars

- In 2012 the FDA issued draft guidance with proposed criteria for a pathway for biosimilar approval. **As of today this FDA guidance is not finalized.** Several critical issues remain unanswered, including:
  - To what extent the **biosimilars pathway** should be abbreviated
  - **How much clinical data** should be required for approval
  - When an agent could be designated as comparable or **interchangeable** with the originator biologic
  - Biosimilar **nomenclature** and suffixes
What is a Biologic

**USA - FDA**
- A biological product that is **highly similar** to a United States licensed reference biological product not with standing minor differences in clinically inactive components, and for which there are **no clinically meaningful differences** between the biological product and the reference product in terms of the **safety, purity and potency** of the product.

**EMA & WHO**
- A biosimilar is a biological medicinal product that contains **a version of the active substance** of an already authorized original biological medicinal product (reference medicinal product). A biosimilar demonstrates **similarity** to the reference product in terms of quality characteristics, **biological activity**, **safety and efficacy** based on a comprehensive comparability exercise.
- A biotherapeutic product which is **similar** in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

FDA Authority to establish a Biosimilar Pathway

- The Biologics Price Competition and Innovation Act allowed for a companion process to 351A "biologics"
- The act authorizes the FDA to establish a regulatory pathway for "biosimilars" titled 351K:
  - Abbreviated 351k pathway for the approval of biosimilars of originator biologics that have **previously been licensed through a BLA**
  - Authorizes the FDA to designate a biosimilar as being either "**comparable**" or "**interchangeable**" with the reference product
  - Establishes the **evidentiary requirements** and process for evaluating biosimilarity, and post-marketing **pharmacovigilance**
Biologic (traditional) vs Biosimilar (new)
BLA Pathways

- Recognition of intricate manufacturing, purification process and complexity of living cells from which they are made, biologics cannot be copied exactly.

- Biological products, “biosimilars” have come to market in the U.S., highly similar to biologic treatments, yet not exact copies of originator (reference biologics)— even when using sophisticated scientific techniques.

- A biosimilar product is approved by the U.S. Food & Drug Administration (FDA), if it has the same mechanism of action, route of administration, dosage form and strength as the reference product.

- Only be approved for the indication and condition of use that have been approved for the reference product. FDA may allow the manufacturer of a biosimilar studied in one indication or disease area, to receive approvals for additional indications, if consistent with the reference biologic product.
Impact of Government Payment Mechanisms

“limitations on the uptake of biosimilars?”

- **Interchangeable** designation for biosimilars is not expected soon, FDA has not yet offered guidance on receiving this designation.

- October 2015, CMS issued a Final Rule that groups all biosimilars for a given reference product in one **Medicare Part B** reimbursement code, thereby setting reimbursement at a blended average of the biosimilars’ prices.

- **Federal anti-kickback** statute precludes Medicare Part D insurance providers and Medicaid managed care organizations from offering physicians financial incentives to prescribe follow-on biologics.

- The **ACA** set reimbursement at the biosimilar’s ASP plus 6 percent of the reference product’s ASP, making the reference biologic’s ASP higher than a biosimilar’s ASP.

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**FDA Current and Future Guidance**

<table>
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<tr>
<th>Released in 2014</th>
<th>Released in 2015</th>
<th>Planned for 2016</th>
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<tbody>
<tr>
<td>Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (Draft)</td>
<td>Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (Final)</td>
<td>Considerations in Demonstrating Interchangeability to a Reference Product</td>
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<tr>
<td>Reference Product Exclusivity for biologic Products Filed Under Sec. 351(a) of the PHS Act (Draft)</td>
<td>Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Final)</td>
<td>Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity</td>
</tr>
<tr>
<td>Nonproprietary Naming of Biological Products (Draft)</td>
<td>Labeling for Biosimilar Biological Products</td>
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<td>Biosimilars: Questions and Answers Regarding the implementation of BPIA</td>
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<td></td>
<td>Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants</td>
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Biosimilar vs Generic Business Impact

Similar to Reference Product
- 20-30% discount
- $100-200 M development costs
- 8-10 year in development
- Interchangeability challenges

Identical to Reference Product
- 80-90% discounts
- $1-5 M development costs
- 3-5 year in development
- Guaranteed interchangeability

Comparative Pathways by Regulatory: Originator vs Biosimilar
“the Clinical (70%) vs Analytical (10-15%) Cost Burdon”
**Differences in Required Development Stages:**
$1+$ Billions vs $100-220$ Million

**Biosimilars Are Not as Valuable as Generics:**
Positioning a Brand in a Biosimilar World

- Traditional drug prices routinely decline by 60% or more through generic competition after patents expire
- As a result, brand name manufacturers lose roughly about 80% of their market share

**Will this happen in biosimilars:**
Biosimilar competition with branded biologics more closely resembles brand-to-brand competition within a category:
- Much harder for biosimilars to compete because of the quality difference in the product
- Production and delivery failures take place more frequently for large molecules
- Doctors cannot learn from branded product because biosimilar is not the same

The European example shows that - biosimilars have not taken over the market as aggressively as generics in small molecule markets
Price Discounts vs Marketshare Penetration

- In countries with biosimilar markets, median price reduction due to biosimilar competition was substantially lower than price reductions seen with generic competition in the small-molecules market: 28% (2006-2013).

- EU price discounts range primarily between 6-54%.

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<tr>
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<tr>
<td></td>
<td>HGH</td>
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<tr>
<td>AUSTRIA</td>
<td>12%</td>
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<tr>
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<td>FRANCE</td>
<td>12%</td>
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<tr>
<td>GERMANY</td>
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<td>53%</td>
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<tr>
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<td>NORWAY</td>
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<td>58%</td>
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<tr>
<td>POLAND</td>
<td>99%</td>
<td>21%</td>
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<tr>
<td>PORTUGAL</td>
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<td>13%</td>
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<tr>
<td>SLOVAKIA</td>
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<tr>
<td>SLOVENIA</td>
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<td>17%</td>
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<td>SPAIN by Region</td>
<td>19%</td>
<td>28%</td>
</tr>
<tr>
<td>SWEDEN</td>
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<td>53%</td>
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<tr>
<td>SWITZERLAND</td>
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<tr>
<td>UK by Region</td>
<td>5%</td>
<td>20%</td>
</tr>
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HGH = human growth hormone; EPO = erythropoietin; G-CSF = granulocyte colony-stimulating factor
Source: IMS 2014

Sources of Complexity and Uncertainty
Sample Pathways Based on Origin

- **Type**
  - True innovator
  - Bio-betters
  - Biosimilars
  - Non-original biosimilars

- **Example**
  - Eprex® (Amgen)
  - Aranesp® (Amgen)
  - Binocrit® (Sandoz)
  - Ceritin® (Ranbaxy – India)

- **Description**
  - Disruptive technologies, big advances in efficacy
  - Efficacy/safety improvements
  - Affordable, high quality
  - Less stringent comparability

- **Target**
  - New drug against new target
  - Same target, but differentiated (e.g., better efficacy, safety, administration)
  - Clinical equivalence and comparability to originators
  - Drug aiming at a copy of innovator

Potential Financial Impact: by 2020
Biosimilars will be over 30% of the market
Changing “losses” to Patent Protection Pathway

Implications on future spending:
savings to $250B over 10 years and 11 products
Biosimilars are often priced at an average discount of 10-30%

<table>
<thead>
<tr>
<th>Source: Citation</th>
<th>Effect of Country variation on pricing</th>
</tr>
</thead>
</table>
| Megerlin et al. (2013) Biosimilars And The European Experience: Implications For The United States | - Biosimilars are priced at roughly 25% less (the average discount in the EU) than their reference products.  
- Some originators have reduce their prices in the UK and Germany to remain competitive.  
  • Amgen reduced the German price of darbepoetin by 13% in early 2008 and subsequently by 16% (post AMNOG)  
  • Some manufacturers of originator biologics are lowering their prices prior to patent expiry, as in the case with erythropoetins. |
| Rovira et al. (2011) The Impact of Biosimilars' entry in the European Market | In the UK, the prices of two reference products show a substantial reduction: Eprex, 23% and Neupogen, 30%. These changes might have been caused by the launch of biosimilars at relatively lower prices. |
| Benassi. F. (2014) Norway's discount on infliximab: A litmus test for biosimilar expansion in Europe | In Norway, biosimilar Remsima (biosimilar of Remicade) is offered at a discount of 39%, a substantially high discount compared to the average discount of 15-30%. |
| Grabowski et al. (2007) Entry and competition in generic biologics | In some cases, the biosimilars will relatively close in price to their reference products, due to the high fixed costs of manufacturing and testing and thus fewer entrants into the market. (e.g. biosimilars prices 90% of the branded price) |

Estimates of when Biosimilars will pass 50% “marketshare” for on-label indications 3-5 years
Payer Drivers on Biosimilars: Cost & Access

- **64%** - Lowest net cost
- **52%** - Maintain brand access unless the biosimilar is significantly less expensive
- **20%** - Biosimilar preference over the brand
- **16%** - Maintain brand until biosimilars have more market experience
- **16%** - Provide parity access at launch of the biosimilar

Payer Discount Threshold on Biosimilars

- Only 16% would change preference and access with less than "20% discount"
- 44% of respondents would require a "40% or greater discount" to WAC to change preference and access
### Market protection for top 10 best-selling biologics: “The Patent Cliff”

<table>
<thead>
<tr>
<th>Company</th>
<th>Biologics</th>
<th>2011 Sales</th>
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<tbody>
<tr>
<td>Amgen</td>
<td>Enbrel*</td>
<td>$7.9</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>Novolog</td>
<td>$2.4</td>
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<td>Amgen</td>
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<td>Abbott</td>
<td>Humira</td>
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<td>Genentech</td>
<td>Remicade</td>
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<td>Janssen</td>
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<td>Genentech</td>
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<td>Genentech</td>
<td>Lucentis</td>
<td>$3.8</td>
</tr>
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### Relative Molecular Size: from Powder to Complex Proteins a “1000X greater mass”

[Diagram showing molecular sizes from Aspirin to mAbs, with scale indicating 1000X greater mass]
Biopharmaceutical Complexity: One Pathway to Product Variation

• FDA statement:
  "Even minor structural differences...can significantly affect a protein's safety, purity, and/or potency"

• Biosimilars are not structurally identical to the reference product

Distinct batches produced by the same manufacturer can have clinically meaningful variation in both efficacy and side effects

• Batch-to-batch variation in important quality characteristics observed in EU marketed biologics

Manufacturing processes are protected information, so biosimilars producers must develop processes de novo, which may increase the likelihood of important quality differences

For small-molecules, a ±20% difference is within the acceptable limits of bioequivalence
Similar metrics are not available for biologics, whose complexity require case-by-case analysis
Biologics and Immunogenicity

- Protein based pharmaceuticals can induce antibodies in humans, leading to immunogenicity problems. This in turn can lead to either increased dose requirements or even loss of potency.

- Although some agencies believe current methods are adequate, technology cannot perfectly predict immunogenicity and its incidence for protein based drugs.

- Example: a new formulation and form of administration for recombinant human erythropoietin (Epo) outside the US was associated with an unexpected increase in the severe hematological disorder pure red cell aplasia in patients.

Variations on the Biologic Originator

"not a true generic but close"
Biologic vs Biosimilar vs Biobetter

*a stepwise “investment” stratification*

**Biologic**
- Novel therapeutic
- 15 years to develop
- $1,200MM cost
- Patented
- Reference price

**Biosimilar**
- Competitive bioequivalence
- 8-10 years to develop
- $100-200MM cost
- Non-patented
- Reduced price

**Biobetter**
- Improved efficacy/safety
- 10 years to develop
- $500MM cost
- Patented
- Premium price

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**Rapid Biosimilar Expansion Across Indications**

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<tr>
<th>Pfizer</th>
<th>Roche</th>
<th>AMGEN</th>
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<th>Novartis</th>
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<td>Boehringer Ingelheim BI 695502</td>
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**NAMCP, 11.11.2016, V2.0**
Phase III or later Predicted US Filing Biosimilar Timelines By Company

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<td>2018</td>
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<td>Infliximab</td>
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Key

- NAMCP, 11.11.2016, V2.0

The “Golden Period” of Biosimilars 2012-2019 representing over $50B in annual sales off patent
Defining the Interchangeable Biosimilar

- An interchangeable biological product, in addition to meeting the bio-similarity standard, is expected to produce the same clinical result as the reference product in any given patient, and for a product that is given to a patient more than once, the risk in terms of safety and effectiveness of alternating or switching between the interchangeable and the reference product is not greater than the risk of using the reference product without alternating or switching.

- The FDA “Purple Book” for biological products
  - Enables a user to see whether a biological product licensed under section 351(k) of the PHS Act has been determined by FDA to be biosimilar and/or interchangeable with a reference biological product.
Payer-Perceived Barriers to Biosimilars

About one-third each are concerned with innovator “rebates” and limited “interchangeability”

- Provider acceptance (16%)
- and state laws (12%) were lesser concerns
- Member acceptance was the lowest concern (4%)

Pharmacovigilance: a limited mechanism for post-market detection of safety issues with biologics

- Safety problems may be difficult to identify in a timely manner because
  - They are rare and require high utilization rates to detect
  - They may mimic symptoms of the disease being treated or existing conditions in the population
- Recent analysis of the FDA Adverse Events Reporting System found only about 24% of suspected biologics reported could be identified at the batch level
- Interchangeability may exacerbate pharmacovigilance difficulties if documentation does not adequately identify which drug was utilized
- Poor pharmacovigilance systems may exacerbate the costs and scope of a safety problem.

Note: An AMCP Task Force recently recommended development of a distributed research network-based surveillance system to monitor biosimilars and innovator biologics for clinical and safety outcomes
States are passing legislation governing biosimilar pharmacy substitutions in anticipation of FDA approvals

Biosimilar Substitution Policies
The European Union: a common comparator for predicting the US biosimilars market

- First approved and available since 2006
- Europeans established directive 2001/83/EC as the legal basis for biosimilars introduction.
- EU recognized that biosimilars cannot be considered analogous to generics and 2001/83/EC makes clear the distinction.
- Common regulatory system for biosimilar approval (EMA), but different reimbursement practices, incentives, and medical practices - leading to different EU country-to-country outcomes.
- EU regulations focus on establishing biosimilarity of products, not on re-establishing drug benefits.

Budget Impact of Biologics on Europe

- Biosimilar:products have been available for nearly a decade in Europe, where biosimilar prices average 10-35 percent lower than the reference product prices.
- Biosimilars have been approved in Europe for 10 years, with Growth Hormone being first in 2006.
  Note: First US Biosimilar was introduced 2015 as a G-CSF, followed in 2016 by TNF inhibitor.
- Combined spending in the EU 5 major countries, on the eight originator biologic medicines identified above is expected to reach $53 billion over the period 2016-2020, if no new biosimilar competition vs $225 billion in the USA.
- Assuming a 30% reduction in price for the eight key originator biologics losing exclusivity in 2016-2020, could save the EU 5 over $20 billion over the next five years.
Introduction by Country and Agency

Price Changes after Biosimilars access the Market by Country
Why such wide variation by country?

Direction of Future Specialty Drug: Therapeutic Sales vs Market Share

Belgium, Ireland, France and Switzerland are the lowest users of biosimilar versions of erythropoiesis-stimulating agents (EPO) and granulocyte colony stimulating factors (G-CSF); Bulgaria, Germany, Hungary, Norway, Slovakia, and Sweden are among the highest.

Source: Assessing biosimilar uptake and competition in European markets (2014) IMS Institute of Healthcare Informatics
Exponential Growth in Cancer Costs over time

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval 1965-2015

Biotech meets Wall Street

Biotech BOOM
Biotech ETF has crushed the rest of the market
Biotech vs Wall Street: Performance

Declining Cost of Biotech’s Basic Tools
Advantage of a Confluence of Events

Biopharmaceuticals have high Start-up Costs

- High start-up costs in biopharmaceuticals may lead to lower price discounts than observed in the small-molecules market
- Biologics are more costly to bring to market
- As a result, a smaller number of competitors will likely enter the market.
- Fewer competitors in turn suggest price discounts will be less deep
“Competition” will drive future changes

• The global biologic medicines market is projected to exceed $390 billion by 2020, when biologics will account for up to 28% by value of the global market for pharmaceuticals. By competing with original biologic across a wide range of therapy areas, stakeholders – including payers, physicians, and patients – to benefit from greater choice in treatment options.

• By 2020, biosimilars could enter markets for a number of biologics that have current sales of more than $45 billion. The cumulative potential savings to health systems in the five major European Union (EU) markets and the U.S., the use of biosimilars, could exceed $ 55 to $ 110 billion in aggregate over the next five years, representing a 25-50% potential savings.

Dog-Eat-Dog World of Competition
Pushing Competition & Uptake for Biosimilars

1. Provider Incentives:
   • Increase Generic and Biosimilar Utilization
   • Improve Provider Compensation based on low cost alternatives

2. Patient and Employer Incentives:
   • Lower Co-Pays and OOP obligations
   • Lower Premiums and forecasting

3. Integration of Outcomes to Value:
   • Interchangeability
   • Competition among the largest groups (G-CSF, TNF, EPO, Insulin, etc.)

4. Mixed results may dampen overall savings:
   • Decreased unit cost: due to biosimilar competitors will decline
   • Increased volume: lower-cost competitors will cause patients and payers to choose greater biologic treatment over traditional therapy

“Positive” Drivers of Biosimilar Cost Savings

• A product competitive market place is needed to deliver sustainability for payers, physicians and manufacturers alike
• Physicians, patients, payers education on roles of biosimilars
• Payers need to ensure that physicians and manufacturers are fully incentivized to drive uptake of biosimilar products
• New focus by payers from cost to utilization and outcomes
• Physicians, financial incentive for biosimilars and while protecting prescribing flexibility
• Manufacturers, incentives to invest in new products, ensuring that qualified and capable sources of supply remain
Manufacturing Quality may Establish Discounts

- **Innovator Manufacturer**: <10% discount
- **Known Manufacturer**: 10-20% discounts
- **Emerging Manufacturer**: 30-50% discounts

+++ TRUST +/-

$$$ COSTS $$

What factors could “derail” Biosimilar savings

- **Innovation is King**: Innovation will continue constantly pushing up therapeutic costs
- **HC Services & Medical Tech**: Diagnostics, Biomarkers, Devices, and Personalized Medicine will continue to drive up costs
- **Trusted Partners**: Manufacturers with proven quality products, may demand a price premium for: patient and provider confidence, avoided immunogenicity, consistent delivery
- **Overall Utilization**: Will likely increase, may impact outcomes resulting in a net savings overall
- **Provider Incentives**: Will greater placement of Physicians into ACO, IDN, Narrow Networks actually change prescribing habits, limiting overall biologic use or rebalance to total cost of care
What factors could “derail” Biosimilar savings

• **Shadow Pricing**: The originator match discounts to limit competition from entering a market

• **Bundled Contracts**: Originator manufacturers will also produce biosimilars of competitors, offering a single contract for category saturation to grab market share

• **Coupled Payments**: Blending a single contract for the biologic and test, at a guaranteed package price (limiting excess NNT testing risk) = stable value

• **Loss of Small Biotech**: If prices get too low, will that serve to drive smaller Biotech and manufacturers out-of-business, favoring larger Pharma

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A financial call on the future of Biotech