AMCP’s 25th Annual Meeting & Expo

April 3-5, 2013 ◆ San Diego Convention Center ◆ San Diego, CA

RT3: Biosimilars: Becoming a Reality in the United States

Friday, April 5, 2013

8:30 am - 10:30 am

Room: 2

Diana Dobrovolny
BIOSIMILARS: BECOMING A REALITY IN THE UNITED STATES
Diana Dobrovolny, Joanna Lui, Niranjan Kameswaran, Amar Patel
AMCP Annual Meeting: April 2013, San Diego, CA

Conflict of Interest Disclosure Statement

I, DIANA DOBROVOLNY, declare no conflicts of interest or financial interests with any pharmaceutical manufacturers, medical device company, or in any product or service mentioned in this program, including grants, employment, gifts, stock holding, and honoraria.
## Agenda

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Roundtable Learning Objectives

After attending this roundtable, attendees should be better able to:

01 Understand the relevant key trends in the evolving biosimilar landscape

02 Discuss key components of the US biosimilar FDA approval process as it currently stands

03 Evaluate current US payer approaches to managing biologics and available biosimilars, including use of specialty pharmacy

04 Identify future implications to health plan management and decision-making
Overall biosimilar market growth is expected – especially in HGH, G-CSF and EPO classes

**Current biosimilar market size and projected growth**

- **2010: $172M**
- **2015: $2B**
- **2018: $20B**

**Biosimilar products – current and pipeline**

- In 2006, the EMA approved the first formal “biosimilar”, Omnitrope (somatropin). Omnitrope was launched in January 2007 in the US.
- In 2012, the first biosimilar of infliximab was approved in Korea.
- To date, most of the biosimilars that have been approved fall within the HGH, G-CSF and EPO product classes.
- Biosimilar manufacturers are ramping up efforts to expand the product classes.

**Major biosimilar manufacturers:**

- SANDOZ
- Ranbaxy
- Intas
- Boehringer Ingelheim
- AMGEN
- Teva
- Samsung
- LG Life Sciences

**Key Product US Expiries**

- **Erbitux (cetuximab) – Q1 2016**
- **Humira (adalimumab) – Q4 2016**
- **MabThera (rituximab) – Q3 2018**
- **Remicade (infliximab) – Q3 2018**
- **Avastin (bevacizumab) – Q3 2019**
- **Herceptin (trastuzumab) – Q2 2019**
- **Entrel (etanercept) – Q4 2028**

**Other notable biosimilar targets**

- Filgastrim
- Pegfilgastrim
- Somatropin
- Epoetin Alfa
- Epoetin Zeta

Recent biosimilar market dynamics are resulting in delays and fewer competitors

**Key challenges faced by biosimilar manufacturers**

- Cost estimates for biosimilar development range from $100-250 million.
- Development of biosimilars could take 6 to 9 years.
- Uncertainty around the regulatory and reimbursement framework.
- Different standards around “comparability” across established and emerging markets.

**Recent US trends**

- Challenges associated with biosimilar development resulting in manufacturers suspending trials in recent months.
- Anticipated entry of mAb biosimilars is expected to be delayed to at least 2016 per recent Roche information.

**Implications**

- Anticipated delays in biosimilar market entry could result in delayed realization of any potential cost savings or pricing pressures on manufacturers (although reimbursement restrictions and contracting will continue to play a strong role).
- Fewer biosimilar entrants and regulatory burden could result in reduced competition than initially anticipated, and may result in reduced downward pressure on biologic/biosimilar costs to payers.
The EU has high standards – with biosimilars marketed since 2006

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Active Substance</th>
<th>Authorization Date</th>
<th>Manufacturer / Company Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abseamed</td>
<td>epoetin alfa</td>
<td>28 Aug 2007</td>
<td>Medice Arzneimittel Pütter GmbH &amp; Co KG</td>
</tr>
<tr>
<td>Binocrit</td>
<td>epoetin alfa</td>
<td>28 Aug 2007</td>
<td>Sandoz GmbH</td>
</tr>
<tr>
<td>Biograstim</td>
<td>filgrastim</td>
<td>15 Sep 2008</td>
<td>CT Arzneimittel GmbH</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>epoetin alfa</td>
<td>28 Aug 2007</td>
<td>Hexal AG</td>
</tr>
<tr>
<td>Filgrastim Hexal</td>
<td>filgrastim</td>
<td>6 Feb 2009</td>
<td>Hexal AG</td>
</tr>
<tr>
<td>Filgrastim ratiopharm</td>
<td>filgrastim</td>
<td>15 Sep 2008 Withdrawn on 20 Apr 2011</td>
<td>Ratiopharm GmbH</td>
</tr>
<tr>
<td>Nivestim</td>
<td>filgrastim</td>
<td>8 Jun 2010</td>
<td>Hospira UK Ltd</td>
</tr>
<tr>
<td>Omnitrope</td>
<td>somatropin</td>
<td>12 Apr 2006</td>
<td>Sandoz GmbH</td>
</tr>
<tr>
<td>Ratiograstim</td>
<td>filgrastim</td>
<td>15 Sep 2008</td>
<td>Ratiopharm GmbH</td>
</tr>
<tr>
<td>Retacrit</td>
<td>epoetin zeta</td>
<td>18 Dec 2007</td>
<td>Hospira UK Ltd</td>
</tr>
<tr>
<td>Silapo</td>
<td>epoetin zeta</td>
<td>18 Dec 2007</td>
<td>Stada R &amp; D AG</td>
</tr>
<tr>
<td>Tevagrasitim</td>
<td>filgrastim</td>
<td>15 Sep 2008</td>
<td>Teva Generics GmbH</td>
</tr>
<tr>
<td>Valtropin</td>
<td>somatropin</td>
<td>24 Apr 2006</td>
<td>BioPartners GmbH</td>
</tr>
<tr>
<td>Zarzio</td>
<td>filgrastim</td>
<td>6 Feb 2009</td>
<td>Sandoz GmbH</td>
</tr>
</tbody>
</table>

- The EMA does not make any decision on interchangeability of biosimilars for the reference product.
- The Medicines and Healthcare Regulatory Agency (MHRA) in Europe advises that biosimilars should be prescribed on a brand name basis to avoid possibility of substitution at the pharmacy.
- However, the EMA has high standards for safety and efficacy which may play a role in reassuring physicians to prescribe biosimilars instead of the reference biologic.

In the US, FDA guidance on biosimilars is in final stages of review

**FDA (US) Guidance – Current Status**

**Biosimilar Definition**

A biological product highly similar to the reference product notwithstanding minor differences in clinically inactive components with no clinically meaningful differences ... in terms of the safety, purity, and potency of the product.

**Therapeutic Equivalence**

- Defined as ‘biosimilarity’ with the additional conditions of having the same clinical result as the reference product, with the risks of use being the same as the reference product.
- Products deemed ‘interchangeable’ may be substituted without intervention from a healthcare provider, but will require additional burden of evidence and a formal designation by the FDA.

**Regulatory Approval Requirements**

- The FDA intends to use a risk-based “totality-of-the-evidence” approach to evaluating a submission.
- The 351(k) biosimilar submission must contain the following:
  - Analytical studies demonstrating similarity (structural and physiochemical properties) to the reference product.
  - Animal studies, including a toxicity assessment.
  - Clinical studies evaluating safety, immunogenicity, purity and potency in one or more appropriate conditions for use.

**Extrapolation to Additional Indications**

- The FDA is capable of determining if one of these elements is unnecessary for a submission.

**Guidance on Market Entry**

Depend on the strength of the information, a biosimilar may not require individual studies for each of the indications approved for the innovator product.

- A biosimilar product can only be approved by the FDA 12 years after the approval date of the reference product. An additional 6 months of pediatric exclusivity is also available. In the case of orphan drugs, the law provides 7 years of exclusivity (7.5 years with pediatric exclusivity).
- Applications for marketing approval of a biosimilar product can be filed with the FDA 4 years after approval of the reference product although the FDA cannot act on this.
- The first market entrant that demonstrates interchangeability will have a 1-year period of exclusivity before another interchangeable product can launch, which may be extended to 42 months if under litigation.


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Biosimilar legal challenges are expected at the state level with a focus on the pharmacists role of substitution

**Regulatory Guidance**

- In February 2012, the FDA issued 3 draft guidance documents on biosimilars
- This was followed by a one-day public hearing in May 2012 - stakeholders urged the FDA to reconcile its guidance with the EMA’s.¹
- FDA is scheduled to release guidance on “Submission of Clinical Pharmacology Data as Evidence of Biosimilarity for Biologics and Protein Products” in 2013²

**Defining similarity**

- There is no standard data set that can be applied to all classes of innovator biologics³ – it is likely that FDA will have to issue product class-specific guidelines providing details on the comparative studies that a biosimilar manufacturer is expected to conduct
- However, the EMA has also eschewed establishing fixed standards around equivalence margins – it is likely the FDA will follow suit

**Potential Legal Challenges for Biosimilars in the US**

- Legislation has been introduced in many states to amend existing substitution laws to address or regulate biosimilar substitution⁴
- Manufacturers and other interest groups have proposed state legislation that would restrict the ability of pharmacists to substitute brand name biological drugs with biosimilars⁵
- According to the proposed legislation, pharmacists in some cases would be required to notify a physician ahead of a substitution, or obtain the consent of the patient about the switch⁴
- Additionally, there is intense lobbying under way to prevent a biosimilar from having the same generic name as the originator treatment⁴

Source:
1. Generics and Biosimilars Initiative (GaBI), 2013.

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**Biosimilars launched or in development in the US**

**Biosimilars Currently in Review by FDA**

- FDA has received 50 requests for initial meetings to discuss biosimilars development covering 12 different reference products¹
- FDA has already carried out 37 initial sponsor meetings and has received 14 Investigational NDAs for biosimilars¹

03: Approach and methodology: Payer research on future management of biosimilars

GfK Bridgehead surveyed active US payers to understand their expected management of biosimilars

- N=17
  - 10 pharmacy directors and 7 medical directors
  - Survey conducted March 2013

Distribution by plan type:

- National Plan: 6
- Regional affiliate of a national organization and subject to national formulary: 1
- Regional affiliate of a national organization with formulary autonomy: 1
- Independent regional plan: 3
- Integrated Health System/Integrated Delivery System: 1
- Pharmacy Benefit Manager: 5

US Payer Sample By Benefit (N=17) TOTAL: 134.4M MCO Lives

- Commercial Lives: 10,000,000
- Medicare Part D Lives: 30,000,000
- Managed Medicaid Lives: 94,400,000
A significant majority of surveyed payers (94%) note that they are tracking the biosimilar pipeline closely, with anti-TNFs and HGH garnering the most attention.

**Degree to Which Payers are Aware of and Tracking the Biosimilar Pipeline (n=17 payers)**

- 35% Low
- 24% Medium
- 35% High

**Biosimilar Pipeline Products that Payers are Tracking Closely (n=17 payers)**

- Anti-TNFs
- Human Growth Hormones
- mAbs for Oncology
- Epoetins
- Insulin

Other biosimilar targets being tracked include MS and G-CSF agents.
The majority of surveyed payers see only minor non-clinical differences between an approved biosimilar and the reference product, regardless of a formal "interchangeable" designation. There still exists some debate around the significance of the differences that result from the complexity of the biologic and the manufacturing process, and the extent that biosimilars are similar but not identical to the reference biologic.

Payers expressed some optimism that biosimilar entry will drive down costs and overall patient spend but may adopt a cautious approach in the near term until they develop more experience with biosimilars.
Surveyed payers suggest that the evidence submitted to the FDA will be sufficient to make reimbursement decisions.

As an abbreviated regulatory pathway, it is expected that the body of evidence required will be less than what was required of the innovator.

Would evidence requirements for FDA regulatory submission be sufficient for equivalent or better access than the innovator? (n=17 payers)

- Yes for equivalent access: 74%
- Yes for better access: 16%
- No, I would need additional evidence: 10%

What additional evidence might be considered for equivalent or better access than the innovator? (n=17 payers)

- Superior data (h2h): 6%
- Post-marketing studies / Review of claims data: 35%
- Price discounts: 18%
- Interchangeability (FDA or national guidelines): 23%
- KOL endorsement: 18%

Source: GfK Bridgehead. Online Survey of US Managed Care Payers. Conducted March 2013. n=17

Cost will be the major determinant that will drive any changes to payer management; however, payers may take a particularly cautious approach with certain therapeutic areas over others.

Payers indicate that biosimilar entry may change their management of a class but how payers do so may vary by therapeutic area.

Under what circumstances would the launch of a biosimilar cause changes to payer management? (n=17 payers)

- Discount vs. originator: 65%
- Availability of biosimilar: 12%
- No change: 17%
- Interchangeability: 6%

Would this apply across all biosimilar classes? (n=17 payers)

- Yes: 71%
- No: 29%

Of the payers who indicate there may be differences in approach by class, many cited specific concerns relating to equivalency and difficulty implementing substitution or fail first approaches in life threatening conditions.

“…We will assess agents for life sustaining (enzyme replacements or oncology) conditions more carefully than those which may allow trial and failure.”

– US National Medical Director

Source: GfK Bridgehead. Online Survey of US Managed Care Payers. Conducted March 2013. n=17
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While most payers indicated that their willingness to consider changes to management applied across all classes, how they would change their management of the space did show variation by class.

For each of the drug classes listed below, please select ALL management approaches that apply below in the case of the product is designated a BIOSIMILAR ONLY (n=17 payers).

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>EPO</th>
<th>HGH</th>
<th>Insulin</th>
<th>Anti-TNF</th>
<th>mAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change in management</td>
<td>8</td>
<td>8</td>
<td>9</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Limit biosimilar to approved indications</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Limit biosimilar to populations</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Prior Auth on the Biosimilar</td>
<td>6</td>
<td>7</td>
<td>2</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Prefer biosimilar through differential tiers</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Prefer biosimilar by requiring step-through</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Promote substitution at pharmacy</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Require new starts on biosimilar</td>
<td>9</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Promote switching existing patients to</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Displace innovator with biosimilar</td>
<td>4</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Defer to physicians for prescribing</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

When asked the same question for a product designated as Interchangeable, payers were more likely to consider all management approaches, but a significant number still indicate they may not change management.

There is divergence in payer opinion around coverage of biosimilars for off-label indications if the FDA does not extrapolate and approve use in other indications that the originator is approved for:

- **Likelihood to actively restrict off-label use (n=17 payers)**
- **Likelihood to allow off-label use in other originator indications (n=17 payers)**
- **Likelihood to explicitly include in coverage policies (n=17 payers)**

There are different perspectives on how biosimilars should be managed. Some payers believe in active restrictions, while others support allowing off-label use based on evidence. There is also significant variation in how explicitly coverage policies are defined for biosimilars.
Economic factors are expected to be the primary driver of decisions to encourage utilization of biosimilars, assuming clinical equivalency & safety.

**What factors may DRIVE utilization of biosimilars? (n=17 payers)**

- Equivalent efficacy/safety of biosimilars to innovators: 100.0%
- Lower costs to payers: 94.1%
- Biosimilar contracting/Interchangeable designation: 88.2%
- Laws allowing automatic substitution at pharmacy: 76.5%
- Lower costs to patients: 70.6%
- Endorsement by KOLs: 58.8%
- Physician familiarity/comfort with biosimilars: 41.2%
- Promotional efforts of biosimilars' manufacturers and/or payers: 11.8%
- Size/complexity of the molecule: 5.9%

Source: GfK Bridgehead. Online Survey of US Managed Care Payers. Conducted March 2013. n=17

Since economics is expected to drive management, payers note that insufficient cost savings will be a key factor in a decision to limit biosimilar utilization.

**What factors may LIMIT utilization of biosimilars? (n=17 payers)**

- Innovator contracting: 88.2%
- Insufficient cost savings: 88.2%
- Concerns about safety: 76.5%
- Concerns about efficacy: 64.7%
- Concerns about immunogenicity: 58.8%
- Delivery/device platform differences: 35.3%
- Lack of confidence/experience with biosimilar manufacturer: 23.5%
- Biosimilar is used in a combination regimen: 11.8%
- Patient/physician preferences for branded biologic: 5.9%
- Promotional efforts of innovators: 5.9%
- Existing relationship with innovator manufacturer: 5.9%

Source: GfK Bridgehead. Online Survey of US Managed Care Payers. Conducted March 2013. n=17
06: Contact Information

Key contacts and office locations

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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF</td>
<td>Anti-Tumor Necrosis Factor</td>
</tr>
<tr>
<td>BLA</td>
<td>Biologics License Application</td>
</tr>
<tr>
<td>CAGR</td>
<td>Compound Annual Growth Rate</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EPO</td>
<td>Erythropoietin</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Granulocyte-Colony Stimulating Factor</td>
</tr>
<tr>
<td>H2H</td>
<td>Head-to-head</td>
</tr>
<tr>
<td>HGH</td>
<td>Human Growth Hormone</td>
</tr>
<tr>
<td>KOL</td>
<td>Key Opinion Leader</td>
</tr>
<tr>
<td>mAb</td>
<td>Monoclonal antibodies</td>
</tr>
<tr>
<td>NDA</td>
<td>New Drug Application</td>
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<tr>
<td>P&amp;T</td>
<td>Pharmacy and Therapeutics Committee</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
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</table>
As outlined in the Accreditation Council for Pharmacy Education (ACPE) *Criteria for Quality and Interpretive Guidelines*, every ACPE-accredited provider is ultimately responsible for program planning, and assurance that the program is fair, balanced and free from bias and/or promotion. In addition, the provider is responsible for explaining and guiding the faculty in its expectations regarding development of learning objectives and instructional materials and incorporation of active learning and learning assessment mechanisms within the offering.

To this end, please draft between three and five self-assessment questions that participants will use to test their application and understanding of the material presented. The questions will be contained in the handout packet and provided to each session attendee onsite.

1. What is the current regulatory status of biosimilars in the U.S.?

2. What classes of drugs are most likely to have biosimilar entry in the U.S.?

3. How are U.S. Health plans planning to manage biosimilars?

4. What type of evidence will health plans expect from biosimilars?