Biosimilars: Evolution and trends

Dr. Gabriel Morelli, Country Manager Spain, IMS HEALTH
Biosimilars promised the Moon but did not deliver
Were we expecting too much and is it time to be optimistic again?

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$16BN</td>
<td>$0.6BN</td>
<td>$25BN</td>
</tr>
</tbody>
</table>

Biosimilars are approaching a turning point

Positive moves are apparent, but still much has to change

How have events and key stakeholders been shaping the biosimilars landscape?

- A mirage
- An opportunity, but still a long way to go
- Just around the corner

- Physicians reaction
- Japan legislation
- Payers pushing for larger adoption
- Potential biosimilars pipeline
- Ongoing BigPharma deals
- Financial returns for aspiring players
- New US guidance on biosimilars
- Latest EU trends
- First MAb submitted in EU
- Eastern Asia dynamics

Biosimilars: Evolution and trends • February 12th 2013
This trend is supported both from demand and supply drivers

Mature economies look at them in the attempt to stem costs; emerging ones to ensure access and sustainable growth

**Demand side**

- Cost-saving lever for mature economies experiencing increasing pressure on resources
- Growth engine for emerging economies while ensuring broader access to medicines and sustainability
- Regulatory framework still fragmented across regions
- Exposure to biosimilar real world evidence limited to a few areas (mostly Europe)

**Supply side**

- Increasing inflow of capital and “branded” capabilities through BigPharma and more “unusual” players (Samsung, Fujifilm, GE Healthcare)
- Increasing specialization along the value chain unlocking the potential of successful partnerships
- Biologics capacity oversupply, pushing manufacturers to find ways to leverage unexploited capacity
Biologics growth is nearly double that of total pharma

Such a trend is putting additional financial pressure on healthcare budget, whereas for PharmaCos represents a great opportunity.

**Global market trends**

MAT 09/2012, US$

**Biologics – Share of sales**

- Canada: 12,5%
- E7: 2,6%
- EU5: 5,4%
- Japan: 9,2%
- Others: 21,9%
- US: 48,5%

**Biologics – Share of growth**

- Canada: 13,3%
- E7: 4,3%
- EU5: 11,6%
- Japan: 12,2%
- Others: 49,5%
- US: 9,2%

*Source: IMS Health, MIDAS, MAT 09/2012*
Three geographical clusters arise

Emerging economies anticipated to be a potential growth driver due to local policies and “biosimilar” attitude

1. US
   Potential leading market for biosimilars

2. Advanced economies
   Established framework for biosimilars, but slow uptake

3. Emerging economies
   Biosimilars* already established (looser regulatory pathway) and fast-growing biologics market

Source: IMS MIDAS, 2006-11, *biosimilars in emerging economies have not gone through a thorough screening like in Europe

Biosimilars: Evolution and trends • February 12th 2013
The global regulatory framework is still quite heterogeneous

Some key emerging markets still lag behind in terms of regulatory guidance

Lack of a clear framework

- Behind in terms of regulation, particularly on clinical requirements and length of regulatory process
- Unclear regulatory framework, limited clinical requirements

REGULATORY FRAMEWORK MATURITY

- Guidance finalized in 2010. Dual pathway with abbreviated non-clinical and clinical data
- Guidance recently finalized (Apr 2012), although it does not set clear clinical criteria for biosimilar approval (case-by-case approach)
- Legal pathway established, draft FDA guidelines published. Pathway not tested yet
- Established biosimilar legislation and guidance aligned to EMA framework.

Fully established framework

- Fully established framework and solid draft guidance for biosimilar Mab. Substitution not allowed
- Established biosimilar legislation and guidance (PMDA)

Current hurdles to global biosimilar market

- Patient ethnicity, Opportunity to leverage evidence from other geographies, PK testing, Clinical testing requirements, Interchangeability
Biologic market is still at its early stage in emerging markets

Bioclusters are rapidly emerging in the major Asian emerging markets and will fuel growth of the biopharmaceutical sector in this area.

Source: IMS MIDAS, MAT Q4 2010, OECD 2010

Anticipated new patients flow in emerging markets will ease biosimilars uptake

Concentration of Global Biopharmaceutical Manufacturing

- **Bioclusters** are emerging in Eastern Asia, driven by local government-led initiatives (South Korea, China)
- Based on BioPlan's Top 1000 Global Biopharmaceutical Facilities Index™ (Index considers variables such as overall fixed capacity, manufacturing-related employment, number of commercial and clinical biological products)
In Europe, biosimilar uptake exhibits different paces
A few countries have reached or approached the maturity stage

Biosimilar uptake across Europe
MAT 06/2007 – 09/2012 (Volumes, SU)

Fast uptake at launch, now mature
Consistent uptake
Slow uptake, cultural resistance
Fast growing due to faster growing market trend
Biosimilar replaced originator supply

Total 10 countries
314M €
MAT 09/2012

Source: IMS MIDAS, MAT 09/2012

Biosimilars: Evolution and trends • February 12th 2013
Similar variations can be observed at therapy area level

Biosimilar filigrastim resembles generic performance in some countries (UK, France, Germany)

**Biosimilar uptake across TA/Countries**

*MAT 09/2012 (Volumes, SU)*

<table>
<thead>
<tr>
<th>Values, M€</th>
<th>73.1</th>
<th>61.9</th>
<th>58.7</th>
<th>31.2</th>
<th>30.7</th>
</tr>
</thead>
</table>

0% 10% 20% 30% 40% 50% 60% 70% 80%

% Uptake, SU

Source: IMS MIDAS, MAT 09/2012

Biosimilars: Evolution and trends • February 12th 2013
Commodity or differentiated?

Stakeholder landscape – payer-driven vs. multiple influencers – and treatment cycle are the key determinants

**Filgrastim uptake**
*SU 09/2012, quarterly*
*Commodity market*

- Payer-driven market access (e.g. Tender, step-wise algorithms)
- Price-driven competition
- Acute treatment and/or frequent cycling among therapies

**Somatropin uptake**
*SU 09/2012, quarterly*
*Differentiated market*

- Complex stakeholder landscape with higher physician influence
- Competition based on multiple marketing levers
- Chronic treatment and/or long therapeutic cycles

Source: IMS MIDAS, 09/2012
Biosimilars have in some cases generated expanded access

As shown by G-CSFs, biosimilars improve access to therapies based on efficacy and costs

**UK case study**

- Physicians moved G-CSF back in 1st line cancer treatment due to lower biosimilars cost
- G-CSF prevents hospital readmission due to infections
- The volume effect has both created new market and cannibalized the share of follow-on products (e.g. peg-filgrastim)

Source: *IMS MIDAS, MAT Q4 2010, NHS. *t-1 =100%, t0 = year of biosimilars introduction*
Although the opportunity for volume expansion is therapy area (and geography) dependent

- Largest volume expansion potential undoubtedly in **pharmerging**, but probably at a much lower price point
- **Europe** has lower and also variable biologic uptake relative to US
- **US** has highest penetration of biologics/head – least volume expansion potential?
- Volume expansion potential will also be affected by introduction of new, better innovative therapies (eg pertuzumab, Roche)

**Human Growth Hormone** and other **orphan drug biologics** show typically show high percentage of available patients treated
Erythropoetins for oncology

**Erythropoietin** for renal dialysis

**Oncological biologics** always have the competitive threat of innovation to reduce volume for biosimilars

**Oncological biologics** in some European countries (eg UK) show significantly lower levels of use than elsewhere on cost grounds

Filgrastim has already shown price elasticity

**Biologics for autoimmune** show highly variable levels of use across patient populations, driven by access in Europe (>5% of patients to >30% across Europe*)
In Spain, biologics represent one of the major cost drivers. However, biosimilars still represent a minimal portion of the total market.

Spain Pharmaceutical expenditure (2006 – 2012, Millions €)

CAGR 2006 – 2012

8% 63% 17% 53% 24%

Source: IMS MIDAS, MAT 09/2012
Payers and policy-makers are rising as biosimilar advocates

Biosimilar strategies and business models will be another critical factor to shape the future scenario.

**Stakeholder drivers**

<table>
<thead>
<tr>
<th>Payer / Government</th>
<th>Patient</th>
<th>Aspiring player</th>
<th>Originator</th>
</tr>
</thead>
</table>
| • Increasing pressure on public/private budgets  
  • Ensure safety and clinical efficacy of biosimilars  
  • Leverage macroeconomic growth through biosimilars (EM)  
  • Broaden access to life-saving drugs | • Broad access to life-saving / disease-modifying drugs  
  • Safety profile of biosimilar drugs  
  • Access to affordable therapies (EM, partly US) | • Massive capital invested on biosimilars  
  • BigPharma bringing in R&D and manufacturing capabilities as well as brand equity  
  • Growing specialization along the value chain (CRAMS providers) and availability of new leading technologies | • IP challenges to delay/block biosimilar entry (e.g. Enbrel in US)  
  • Timely implementation of lifecycle management strategy (e.g. Roche with HER2 franchise)  
  • Leverage dual brand strategies / licensing in developing markets |

**Impact on biosimilars market**

<table>
<thead>
<tr>
<th></th>
<th>Strong barrier</th>
<th>Neutral</th>
<th>Strong driver</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU, 2020</td>
<td>EM, 2020</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EM = emerging markets

Biosimilars: Evolution and trends • February 12th 2013
Overall these events lean closer to the $25 billion 2020 scenario

The verdict on the new wave of biosimilars will act as a cornerstone for this market

Core scenario drivers 2020

- **US uptake**
  - Latest US biosimilar guidance setting a clearer framework for biosimilars and leveraging *totality of evidence* approach
  - Limited uptake in the US due to unclear regulation favouring innovators

- **Emerging markets**
  - Latest law provisions striving to promote harmonization of regulatory standards and pivotal role of emerging countries
  - Moderate spread of biosimilars along with EM not emerging as a leading exporter due to quality standards

- **Europe**
  - Accelerating uptake in EU, including typical laggard countries as they are under increasing financial pressure
  - Growth hormones still exhibits limited uptake rates

- **Technology, second wave**
  - Successful development of some of the key biological blockbusters (*infliximab, rituximab, trastuzumab*)
  - Extension of Enbrel’s patent coverage to 2028 (US only). Disputes on Humira

- **Volume effect**
  - Significant volume effect on biologics consumption (as exhibited by gCSF) replicated in other therapy areas
  - Limited volume effect as biosimilars are exclusively used as a cost-containment tool

- **Competitive dynamics**
  - Increasing manufacturing efficiencies and large competitive arena trigger price competition and promote uptake
  - Pfizer calling off deal with Biocon may signal potential difficulties and delays in the development of biosimilars
Among the new TAs, anti-TNF and MAbs are the key ones. Along with insulins, another key investment area for biosimilar players, they account for more than 40% of the overall biologic market.
Twelve compounds will present a US$ 67 billion opportunity

All these products will lose patent protection by 2020, but Enbrel whose US patent has been extended until 2028

### Global Sales (MAT 09/2012), US$ billion

<table>
<thead>
<tr>
<th>Compound</th>
<th>Global Sales (US$ billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>8.1</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>7.3</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>7.1</td>
</tr>
<tr>
<td>Insulin Glargine (Lantus)</td>
<td>6.2</td>
</tr>
<tr>
<td>Rituximab (Mabthera)</td>
<td>5.9</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>5.3</td>
</tr>
<tr>
<td>Interferon Beta-1A (Avonex, Rebif)</td>
<td>5.0</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>5.0</td>
</tr>
<tr>
<td>Insulin Aspart (Novomix, Novorapid)</td>
<td>4.9</td>
</tr>
<tr>
<td>Glatiramer Acetate (Copaxone)</td>
<td>4.3</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta)</td>
<td>4.3</td>
</tr>
<tr>
<td>Ranibizumab (Lucentis)</td>
<td>4.0</td>
</tr>
</tbody>
</table>

**Total ~ US$ 67 billion**

### EU expiry date | US expiry date

<table>
<thead>
<tr>
<th>Compound</th>
<th>EU expiry date</th>
<th>US expiry date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>2018</td>
<td>2016</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>2015</td>
<td>2016</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>2014</td>
<td>2018</td>
</tr>
<tr>
<td>Insulin Glargine (Lantus)</td>
<td>2014</td>
<td>2014</td>
</tr>
<tr>
<td>Rituximab (Mabthera)</td>
<td>2013</td>
<td>2016</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>2019</td>
<td>2017</td>
</tr>
<tr>
<td>Interferon Beta-1A (Avonex, Rebif)</td>
<td>2012</td>
<td>Expired</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>2015</td>
<td>2015</td>
</tr>
<tr>
<td>Insulin Aspart (Novomix, Novorapid)</td>
<td>2014</td>
<td>2019</td>
</tr>
<tr>
<td>Glatiramer Acetate (Copaxone)</td>
<td>2017</td>
<td>2015</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta)</td>
<td>2015</td>
<td>2014</td>
</tr>
<tr>
<td>Ranibizumab (Lucentis)</td>
<td>2016</td>
<td>2016</td>
</tr>
</tbody>
</table>

*Not considered existing biosimilars such as Epoetin Alfa expired in EU, but still patent protected in US*

Source: IMS MIDAS, 09/2012, IMS Patent focus

Biosimilars: Evolution and trends • February 12th 2013
Monoclonal antibodies dominate the biosimilars pipeline

Biosimilars pipeline by class

<table>
<thead>
<tr>
<th>Class</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Prefiling/Pending</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAb immunomodulators</td>
<td>55</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cytotoxic Mabs</td>
<td>28</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Other hormones (excl. insulins)</td>
<td>19</td>
<td>3</td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>G-CSF</td>
<td>16</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Insulin</td>
<td>14</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Others (enzymes, BCF)</td>
<td>15</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Interferons</td>
<td>14</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>14</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>183</strong></td>
<td><strong>25</strong></td>
<td><strong>19</strong></td>
<td><strong>28</strong></td>
<td><strong>8</strong></td>
</tr>
</tbody>
</table>

Source: FirstWord September 19th 2012
Among the core areas, anti-TNF are at higher risk of erosion.

Uptake patterns will vary across geographic clusters, e.g. biosimilar insulins may perform better in emerging countries.

**Positioning of upcoming biosimilars**

**Commodity**
- Payer-driven
- Price-driven
- Acute treatment / progressive therapy
- High competition
- Fully understood MoA
- Lower risk of immunogenic reaction

**Differentiated**
- Multiple influencers
- Multiple marketing levers (incl. device)
- Chronic treatment / multiple therapies
- Limited competition
- MoA unclear / limited benefits
- Higher risk of immunogenic reaction

Biosimilars: Evolution and trends • February 12th 2013

20
The next wave will be pivotal to determine future scenarios

The way the industry as a whole will pave the way to it and continue building the learning curve will shape the uptake through 2020

**Biosimilar learning curve – 4 key drivers**

1. Business model design and alliance management
2. Economies of learning on manufacturing and R&D
3. Pre- and post-launch stakeholder management
4. Branding and go-to-market strategy

**2012 - 13**
Building learning curve on existing biosimilars

**2014 - 16**
New wave of biosimilars: accelerating impact

**2016 +**
Converging towards a generic-like model

- **Commodity-like uptake**
- **Differentiated-like uptake**
- **Development setbacks / post-launch drawbacks**
- **Biosimilar boom delayed**
- **Generic-like scenario** (automatic substitution limited to a few TAs)
- **Favorable framework but moderate uptake**
Biosimilars have been a hot topic in the last 12-18 months. The landscape is becoming over-populated. Is there a market for everybody?

<table>
<thead>
<tr>
<th>Innovator companies</th>
<th>Generics companies</th>
<th>Other players</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>MERCK SERONO</td>
<td>MERCK</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>Daiichi-Sankyo</td>
<td>AMGEN</td>
</tr>
<tr>
<td>Lilly</td>
<td>Baxter</td>
<td>Potential entrants**</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Sanofi</td>
<td></td>
</tr>
<tr>
<td>TEVA Pharmaceutical Works</td>
<td>Sandoz</td>
<td>Hospira</td>
</tr>
<tr>
<td>Actavis</td>
<td>Mylan*</td>
<td></td>
</tr>
<tr>
<td>Cipla</td>
<td>Watson</td>
<td>Gedeon Richter</td>
</tr>
<tr>
<td>STADA Arzneimittel</td>
<td>Dr. Reddy’s</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRAMS* providers / Emerging market domestic players

<table>
<thead>
<tr>
<th>Biocon</th>
<th>Lonza</th>
<th>INTAS</th>
<th>Zydus</th>
<th>QUINTILES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvest Moon PHARMACEUTICALS USA, INC</td>
<td>CELLTRION</td>
<td>IBA BIOTON</td>
<td>PAREXEL</td>
<td>WOCKHARDT</td>
</tr>
</tbody>
</table>

*CRAMS, Contract Research and Manufacturing Services ** Based on press release news
Original manufacturers will employ a range of defence approaches to contain the impact of biosimilars.

**Moderate risk to original brand**
- Focus on brand value/patient segments:
  - Consider splitting business high value brand and a low price alternative

**High risk to original brand**
- File legal challenges
- Consider new IP protected offerings
- Fight on price, if you are prepared to go to commodity levels

**Low risk to original brand**
- Focus on building brand value and patient/prescriber loyalty
- Monitor market closely to detect signs of movement to one of the other scenarios

**Moderate risk to original brand**
- Fight on price even where discounts are low: ensure that small price discounts do not let biosimilars gain significant traction

- New IP (for example Roche’s pertuzumab, Amgen’s Neulasta) is the most effective measure to protect brands
- HgH has shown that brand loyalty can protect under certain circumstances – for a period of years
- Current experience has not been of interchangeable biosimilars (USA), or substitution (Europe). Either is likely to be a game changer

Willingness to use (physician/patient acceptance)
New biologics represent a threat for upcoming biosimilars

When engaging stakeholders, the biosimilar value proposition should include both the originator and follow-on biologics in the same TA

**Originators**
- MabThera
- Remicade
- Erbitux
- Lantus
- Herceptin
- Enbrel
- Humira
- Avastin

**Biosimilars**
- adalimumab
- cetuximab
- infliximab
- interferon beta
- etanercept
- trastuzumab
- insulins

**New biologics (future generation)**
- Simponi
- Cimzia
- tofacitinib
- Other JAK-1 inhibitors
- Perjeta (pertuzumab)
- T-DM 1
- Dimethyl fumarate
- Omontys (peginesatide)
- Novel OADs
As biosimilars are mainly copies, speed to market remains key.

Going forward, while the scientific aspects will remain a basic pre-requisite, commercial models could drive differentiation at local level.

**Biosimilars value chain**

- **Clinical development**
  - Leverage of internal assets or outsource of capabilities from third parties.

- **Manufacturing**
  - Scale up production to achieve economies of scale, although in the short-term is quite unlikely to happen.

- **Regulatory & Market access**
  - Optimize time to market and ensure key stakeholders (KOLs, payers) are onboard and supportive to drive advocacy and acceptance.

- **Sales & marketing**
  - Tailor go-to-market approach to local dynamics, both in terms of sales force model and marketing offering (e.g. device, patient management services).

**SPEED TO MARKET, ALLIANCE MANAGEMENT, INFRASTRUCTURE DEVELOPMENT TO OPTIMIZE COST STRUCTURE**

**Key short-term drivers PRE-REQUISITE**

**Critical at local level DIFFERENTIATOR**
Go-to-market models are soon expected to transform

The evolving competitive arena and more complex biosimilars portfolios to manage will drive the transition

**Biosimilar go-to-market evolution**

### First wave

- **Payer-driven model**
  - Focus on creating awareness and building trust among stakeholders (payer focus)
  - Price-driven value proposition
  - Tender-based competition
  - Simple portfolio (maximum 3 products)

### Second wave

- **Branded specialty model**
  - More complex portfolio to manage
  - Higher incidence of differentiated products
  - Increasing and more diverse competition (GenericCos and PharmaCos)
  - Go-to-market shifting towards branded infrastructure
  - Need to consider the broader marketing mix

### Established market

- **Innovative go-to-market model?**
  - Need to offset the value losses from price competition by growing demand pools (e.g., Expanded access, new developing geographies)
  - Promote one-stop-shop for affordable medicines (generics + biosimilars)
  - Shift focus away from drugs to solution (to differentiate the value proposition in a commodity-like environment)
Biosimilars: Evolution and trends

Dr. Gabriel Morelli, Country Manager Spain, IMS HEALTH