Biological/biotechnological and biosimilars market: the global outlook with special focus on Europe

Biosimilar Medicines: 12th EGA International Symposium
London, April 3rd 2014

Agenda

• The Global Biologic Market
  – The increasing importance of biosimilars in the pharma portfolios
  – Recombinants shaping the industry

• The Macro Biosimilars Environment
  – NOB Players in emerging markets
  – The biosimilar pipeline a focus on RA

• Policy Implications
  • The trade-off between access and innovation
Biologics growth continues to outstrip growth rate of total pharma

Such a trend is putting additional financial pressure on healthcare budgets

Global market trends
Sales and Growth

Biologics – Share of sales

Biologics – Share of growth

Source: IMS Health, MIDAS, MAT June 2013

Key therapies in today’s world
LoEs have reset the stage from small molecules to biologics

Europe Top 10 products 2008-13

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
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<tr>
<td>1</td>
<td>LIPIOR</td>
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<td>HUMIRA</td>
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<td>MABTHERA</td>
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<td>HUMIRA</td>
<td>LOVENOX</td>
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<td>MABTHERA</td>
<td>REMICADE</td>
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<td>LOVENOX</td>
<td>AVASTIN</td>
<td>MABTHERA</td>
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<td>MABTHERA</td>
<td>AVASTIN</td>
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<td>REMICADE</td>
<td>AVASTIN</td>
<td>LUCENTIS</td>
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<td>MABTHERA</td>
<td>ZYPREXA</td>
<td>GLIVEC</td>
<td>SPIRIVA</td>
<td>LYRICA</td>
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</table>

Source: IMS Health, MIDAS, MAT June 2013
It’s the loss of exclusivity that drives interest.
12 compounds represent US$ 73 billion in sales

All these products will lose patent protection by 2020, except Enbrel (US patent extended until 2028)

**Global Sales (MAT 09/2013), US$ billion**

<table>
<thead>
<tr>
<th>Product</th>
<th>Global Sales (US$ billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>9.4</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>7.8</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>7.5</td>
</tr>
<tr>
<td>Insulin Glargine (Lantus)</td>
<td>7.3</td>
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<tr>
<td>Rituximab (Mabthera)</td>
<td>6.2</td>
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<tr>
<td>Bevacizumab (Avastin)</td>
<td>5.6</td>
</tr>
<tr>
<td>Insulin Aspart (Novomix, Novorapid)</td>
<td>5.6</td>
</tr>
<tr>
<td>Interferon Beta-1A (Avonex, Rebif)</td>
<td>5.4</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>5.1</td>
</tr>
<tr>
<td>Glatiramer Acetate (Copaxone)</td>
<td>4.8</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta)</td>
<td>4.3</td>
</tr>
<tr>
<td>Ranibizumab (Lucentis)</td>
<td>4.3</td>
</tr>
</tbody>
</table>

**Total ~ US$ 73 billion**

Source: IMS MIDAS, 09/2013, IMS Patent focus

**EU expiry date | US expiry date**

- 2018             | 2016
- 2015             | 2028 (extended)
- 2015             | 2018
- 2014             | 2015
- Expired           | 2018
- 2019             | 2019
- Expired           | Expired
- 2015             | 2016
- 2014             | 2019
- 2017             | 2014
- 2015             | 2015
- 2016             | 2016

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

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  - Recombinants shaping the industry

- **The Macro Biosimilars Environment**
  - NOB Players in emerging markets
  - The biosimilar pipeline a focus on RA

- **Policy Implications**
  - The trade-off between access and innovation
In Europe, biosimilar usage exhibits different rates with Italy and Spain now catching up.

Biosimilar sales across EU5
QTR 03/2007 – 12/2013 ($US)

- Fast uptake at launch
- Consistent uptake
- Cultural resistance at first but change undergoing

EU 5 countries
490M $ MAT 12/2013

Filgrastim excels in each major EU market
Almost resembles small molecule generic efficiency in some countries

Biosimilar uptake across TA/Countries
MAT 12/2013 (Volumes, SU)

Values, M$
ITALY
GERMANY
FRANCE
SPAIN
UK

Source: IMS MIDAS, MAT Dec 2013

Source: IMS MIDAS, MAT 12/2013
Dynamics differ not only by molecule and country but also by channel
Biosimilars and originals breakdown (molecule vs. molecule only; and only reference products)

Source: IMS MIDAS. Q2 2013. Analysis in DDD (Defined Daily Doses).

The temperature is rising again, biosimilar events are warming the global agenda

ROW

Market trends

Regulatory

FDA approved Tbo-filgrastim but filed in the U.S. as BLA
2nd GSF approved in Japan

2012 2013 Mar Jun Jul Nov 2014

Europe

Market trends

Regulatory

N° of Biosimilar applications (EMA) all-time high (8)
Biosimilar G-CSF (Zarzio) prescribed more than originator

Source: Secondary research. List not exhaustive. (*) at ex-manufacturer price levels, not including rebates and discounts.
(8) Recommended for RA (Rheumatoid arthritis), CD (Crohn’s disease), UC (Ulcerative colitis), AS (Ankylosing spondylitis), PsA (Psoriatic arthritis)
Relaxed regulatory requirements drives proliferation of Non Original Biologics in emerging markets

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Target</th>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>True Innovator</td>
<td>• Disruptive technologies, big advances in efficacy</td>
<td>• New drug against new target</td>
<td>EYLEA</td>
</tr>
<tr>
<td>Bio-betters</td>
<td>• Efficacy/safety improvements</td>
<td>• Same target but differentiated (e.g. Better efficacy, safety, administration)</td>
<td>pegasis</td>
</tr>
<tr>
<td>Biosimilars</td>
<td>• Affordable, high quality</td>
<td>• Clinical equivalence and comparability to originators</td>
<td>inflectra</td>
</tr>
<tr>
<td>Non Original Biologics</td>
<td>• Less stringent comparability</td>
<td>• Drug aiming at copy innovator</td>
<td>RediFlux RituNam</td>
</tr>
</tbody>
</table>

Major opportunity exists in BRICs where NOBs account for 91% of the 16 markets

BRICs countries account for 91% in value of the NOBs Pharmerging market. Three of them also come on top with regards to NOBs penetration

Bubble size: NOBs 2012 $US Mn

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NOBs have made significant impact in major biologic therapy areas

**Oncology**
- Reditux was the world’s first non-originator mAbs
- In 2007, it was priced at $243 for a 100 mg dose in a 10 ml vial, about 50% lower than the price of originator Mabthera (Roche)*
- Between 2007 and 2012, Reditux achieved in India 81% CAGR, it is now the 2nd largest oncology product in India (not considering Roche)

**Anti-TNF**
- Launched in 2006, one year before Enbrel, Yi Sai Pu had the highest anti-TNF sales in China, with ~$41m in 2012
- China has one the lowest RA prevalence in the world (undiagnosed contribute). As its population continues to grow, monitoring RA cases and biologic’s use important
- Yisaipu is also the least expensive among Anti-TNF

**Interferons**
- Launched end 2010 by Laboratorio Tutuer (AR)
- Genfaxon won back market share from direct competitors (Rebif and Avonex) in tenders for Multiple sclerosis products within 7 Nosologies program (high cost part of DLO)
- Genfaxon is now the 5th biologic product in Russia (PPG 90%)

Source: IMS Health, MIDAS, MAT Dec 2012. AR: Argentina (*) Bloomberg

The global playing field continues to expand with players finding niches

Players differ not only in geographical spread but also a wider biologic portfolio

International Reach

Emerging markets players

Serving 2+ countries

Domestic players

Serving domestic market only*

Source: IMS Health, MIDAS, MAT Dec 2012. (*) restricted to MIDAS sales data and recombinant and synthesised prods only.
RA biosimilar development is a hive of activity

Preclinical
- rituximab for unknown indication
- Atevux (Avesthagen)
- Amgen/Watson
- AP052 (Aprogen)
- Coherus/Daiichi Sankyo

Early phase
- infliximab
- Biopress
- GS01 (Aprogen)
- Harvest Moon
- BOW 015 (Epitrix)

Phase 3
- Tocilizumab
- BioXpress
- PRX-106 (Protalix)
- Harvest Moon
- Abatacept

Filled in EU/approved
- rituximab for RA
- MabionCD20 (Mabion)
- CT-P10 (Celltrion)
- GP2013 (Sandoz)
- CT-P10 (Celltrion)
- NTL11 (Teva)
- APL-1566 (Protagenic)
- BioXpress
- LBECD011 (LG Life Sciences)
- TunEM
- BioXpress
- Biocon/Mylan
- BI-695501 (BI)
- Adalimumab
- Harvest Moon
- Harvest Moon
- Harvest Moon
- Harvest Moon
- Harvest Moon

etanercept
- Coherus/Daiichi Sankyo
- Biocon/Mylan
- Biocon/Mylan
- Biocon/Mylan
- Harvest Moon
- Harvest Moon
- Harvest Moon
- Harvest Moon
- Harvest Moon

Source: IMS consolidation from public data
The list is not exhaustive
Trials may have moved forward or been discontinued

Could we soon see the introduction of biosimilars shortly after patent expiry in this area?

Each LOE could be closely followed by a biosimilar entry
- Inflectra (Remicade - Celltrion*)
- GP 2013 (Rituximab - Sandoz)
- GP2017 (Adalimumab - Sandoz)

Rheumatoid Arthritis market

New European market Entrants (estimate)
2013 2014 2015 2016 2017 2018+

Patent Expiries in EUS
(France, Germany, Italy, Spain & UK)
- Rituxan
- Remicade
- Enbrel
- Humira
- Cimzia
- Orencia
- Simponi
- RoActemra

* Approved Sep 2013

Source: IMS Knowledge Link, PADDS

Products in Phase 2 or 3 may not receive approval; pipeline view does not necessarily align with the projected competitive landscape in a given year
Anti-TNF and MAbs are the key RA biologics

Surveyed physicians estimate only around half of RA patients are currently still receiving their first line therapy

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>35.1%</td>
<td>35.0%</td>
</tr>
<tr>
<td>Cox-2 inhibitors</td>
<td>17.2%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Traditional DMARDs</td>
<td>66.4%</td>
<td>67.7%</td>
</tr>
<tr>
<td>Biologic TNF inhibitors</td>
<td>8.6%</td>
<td>28.5%</td>
</tr>
<tr>
<td>Biologic non-TNFs</td>
<td>3.9%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Novel small molecules</td>
<td>2.1%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Traditional Chinese medicine</td>
<td>19.3%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Traditional Herbal Medicine</td>
<td>3.8%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>15.8%</td>
<td>22.3%</td>
</tr>
</tbody>
</table>

Source: IMS Health Disease Insight

Thus a high rate of treatment switching exists in RA

After 2 years, physicians estimate ~50% of RA patients switch to another therapy...an opportunity for biosimilars?
One key understanding should be the role of medicines within overall cost of treatment

The per-patient cost of RA biologic treatment is high, with biologics representing ~22% of direct medical costs

RA treatment cost distribution, 2008

New biologic launches continue and represent an ongoing challenge for upcoming biosimilars

Superior clinical results will gain clinician and patient attention whilst associated costs will prove problematic for payers

**New biologics**

- New modern insulins
- Gazlyva
- Perjeta (pertuzumab)
- Lonquaex (lipogliflurastim)
- Kadcyla (trastuzumab-drug conjugate)
- SC Herceptin and Rituxan

**Originators**

- adalimumab
- cetuximab
- infliximab
- interferon beta
- etanercept
- bevacizumab
- trastuzumab
- insulins

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Policy Implications
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Payers and policy-makers rise as biosimilar advocates

Biosimilar strategies & business model will shape future scenarios

Stakeholder drivers

- **Payer / Government**
  - Healthcare rationalization
  - Ensure safety and clinical efficacy
  - Leverage macroeconomic growth through biosimilars

- **Physician**
  - Safety and clinical efficacy concerns
  - Need to build learning curve on biosimilars
  - Reaction to differ by therapy area

- **Patient**
  - Looking for broader and affordable access
  - Likely to be influenced by physician advice

- **Aspiring player**
  - Massive capital invested on biosimilars
  - Branded players bringing in R&D capabilities
  - Growing specialization along the value chain (CRAMS providers)

- **Originator**
  - Lifecycle management
  - Patient disputes
  - Active players in the biosimilar arena

Impact on biosimilars market

- **Strong barrier**
- **Neutral**
- **Strong driver**

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The Biosimilar market of mature countries faces a paradox

The largest biologic market potential and cost burden
- The US and European biologic markets comprise the majority of value size and growth, we expect this to continue
- As such, the majority of biologic cost burden falls on these markets—and potentially the most attractive non originals opportunity

Low overall current impact of biosimilars
- Despite 7 years of biosimilars in the EU, and recent FDA guidelines, biosimilars comprise a very small % of the mature markets
- Significant impact in certain TAs and countries, low overall

Next wave of biosimilars will be challenging
- MAbs for oncology and autoimmune pose incremental acceptance and uptake challenges
- Originators seek to move standard of care on bio-betters

There are several indications that the status quo is about to change
- We are entering an era with great potential for change in the biosimilars market...
- Marked by the LoE of complex compounds used in large populations and foreshadowed by a number of “firsts” in what is being brought to market, by whom, and where.

Will payers push for greater BS adoption as costs escalate?

What adoption do we expect for the next wave of BS?

To what extent is BS experience an indicator of future dynamics?

To what extent is competition intensifying?

The potential exists for a reverse innovation business model producing a threat to R&D in the West

Biopharmaceutical industry

Globalization
- Step 1
  - Biologics R&D in mature markets and made in mature markets for EMs
  - Classic biologics R&D in mature markets

- Step 2
  - Biologics R&D in mature markets but made in EMs for EMs
  - Emcure/Roche deal to manufacture anti-cancer drugs in India

Reverse Innovation
- Step 3
  - Biologics R&D in EMs and made in EMs for EMs
  - Molecules marketed in EM but not in Western markets (e.g. Ninotuzumab)
  - MedImmune JV with WuXi to develop novel biologics for China

- Step 4
  - Biologics R&D in EMs and made in EMs for the world
  - Celltrion’s bio-innovative pipeline CT-P19 (rabies virus)
  - Celltrion developing an armed antibody

IMS Health

Thank You

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