The Business of Biosimilars

Doug Long, Vice President, Industry Relations, IMS Health Inc.
Perspectives on the evolving biosimilars landscape

Doug Long
Vice President Industry Relations
March 2015
Agenda

The Global Biologic Market
– The increasing importance of biologics
– LoE driving interest and investment
– Biosimilars gradually emerging

• Learning from the biosimilar experience
  – Countless variations: therapy area, country and molecule level
  – What really drives Biosimilars uptake
  – Understanding the role of 2\textsuperscript{nd} generation products
  – Next wave of Biosimilars

• Looking ahead
  – Key biologic areas and biosimilar’s targets
  – Originator strategies
  – The trade-off between access and innovation
A word on the data used in this presentation

- IMS Health historic and forecast data is presented at list price value
- This excludes rebates and discounts, which can vary across countries, products and over time
- We are very aware of this challenge, but at the moment, when a market-level view is taken of pharmaceutical sales, there is no good quality, consistent substitute for list price level data
Biologics growth continues to outstrip total pharma, showing a steep increase on 2013

Such a trend is putting additional financial pressure on healthcare budgets

Source: MIDAS IMS Health, MAT Q3 2014, Rx; Brazil and Mexico Non Retail Sales are included; Share of growth in LC$
Biologics increasingly feature as key therapies

Payers see their costs

Global top 10 products 2009-14

<table>
<thead>
<tr>
<th>Rank</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
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<tr>
<td>1</td>
<td>LIPITOR</td>
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<td>8</td>
<td>ZYPREXA</td>
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<td>ENBREL</td>
<td>PLAVIX</td>
<td>LANTUS</td>
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<td>9</td>
<td>CRESTOR</td>
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<td>Cymbalta</td>
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<td>10</td>
<td>SINGULAIR</td>
<td>ZYPREXA</td>
<td>ZYPREXA</td>
<td>LANTUS</td>
<td>MABTHERA</td>
<td>MABTHERA</td>
</tr>
</tbody>
</table>

Source: IMS Health, MIDAS, MAT Sep 2014
In Germany we really see the importance of biologic therapies

**Top 10 products 2009-14**

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
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<td>3</td>
<td>SERETIDE</td>
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<td>4</td>
<td>GLIVEC</td>
<td>AVASTIN</td>
<td>MABThERA</td>
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<td>HERCEPTIN</td>
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<td>5</td>
<td>REBIF</td>
<td>MABThERA</td>
<td>AVASTIN</td>
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<td>6</td>
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<td>SEROQUEL</td>
<td>LOVENOX</td>
<td>LYRICA</td>
<td>XARELTO</td>
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<td>SPIRIVA</td>
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<td>REBIF</td>
<td>LUCENTIS</td>
<td>REBIF</td>
<td>REBIF</td>
</tr>
</tbody>
</table>

Small molecule products

Biologic products

Source: IMS Health, MIDAS, MAT Sep 2014
It’s the loss of exclusivity that drives biosimilar interest

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

**Global Sales (MAT 06/2014), US$ billion**

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<thead>
<tr>
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<tr>
<td>Adalimumab (Humira)</td>
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<td>10.8</td>
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<tr>
<td>Insulin Glargine (Lantus)</td>
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<td>Etanercept (Enbrel)</td>
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<td>Infliximab (Remicade)</td>
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<td>Rituximab (Mabthera)</td>
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<tr>
<td>Insulin Aspart (Novomix, Novorapid)</td>
<td>6.3</td>
<td>6.3</td>
<td>5.9</td>
<td>5.5</td>
<td>5.3</td>
<td>4.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
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<td>Interferon Beta-1A (Avonex, Rebif)</td>
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<tr>
<td>Trastuzumab (Herceptin)</td>
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<tr>
<td>Glatiramer Acetate (Copaxone)</td>
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<tr>
<td>Pegfilgrastim (Neulasta)</td>
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<td>Ranibizumab (Lucentis)</td>
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</tbody>
</table>

**EU expiry date**

- 2015: Insulin Aspart (Novomix, Novorapid), Interferon Beta-1A (Avonex, Rebif)
- 2016: Adalimumab (Humira), Insulin Glargine (Lantus), Etanercept (Enbrel)
- 2017: Trastuzumab (Herceptin)
- 2018: Bevacizumab (Avastin)
- 2019: Glatiramer Acetate (Copaxone)
- 2020: Pegfilgrastim (Neulasta), Ranibizumab (Lucentis)

**US expiry date**

- 2015: Insulin Aspart (Novomix, Novorapid), Interferon Beta-1A (Avonex, Rebif)
- 2016: Adalimumab (Humira), Insulin Glargine (Lantus), Etanercept (Enbrel), Trastuzumab (Herceptin)
- 2017: Bevacizumab (Avastin), Glatiramer Acetate (Copaxone)
- 2018: Pegfilgrastim (Neulasta), Ranibizumab (Lucentis)
- 2020: Not considered existing biosimilars such as Epoetin Alfa expired in EU, but still patent protected in the US

**Source:** IMS MIDAS, 06/2014, Rx bound, IMS Patent focus
In contrast to small molecule GX, biosimilar development and marketing pose serious challenges for aspiring players.

**CLINICAL DEVELOPMENT**
Average cost is around 200M$, with a significant range of variation (from 40 to 375 M$) vs. 1 to 4M$ for a generic drug.

**MANUFACTURING COSTS**
Difficulties in rationalizing manufacturing costs due to limited scale, at least in the short term.

**REGULATORY AND MARKET ACCESS**
Uncertain regulatory framework (aside from Europe), price competition less relevant compared to generics.

**SALES AND MARKETING CAPABILITIES**
Need to adopt a branded mentality to win stakeholder trust.

**Biosimilars vs. Generics – a different game?**
Biosimilars are making steady progress...

**ROW**

**Market trends**

- **Remsima (Infliximab Biosimilar)** launched in Korea
- **Teva announce launch of GRANIX in USA**
- **Sandoz Omnitrope sole subsidised somatropin from Jan 2015 in NZ**

**Regulatory**

- **2nd GSF approved in Japan**
- **Infliximab BS approved in Japan**
- **FDA ODAC recommends filgrastim BS for approval (14-0)**

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**Europe**

**Market trends**

- **Italy, largest Biosimilars market in EU***
- **Biosimilar G-CSF (Zarzio) prescribed more than originator**
- **Norway infliximab BS 7% penetration first 3 months**

**Regulatory**

- **Inflectra# (Infliximab Biosimilar) approved EU**
- **Follitropin alfa biosimilar approved**
- **EMA approves Biosimilar insulin (Lilly/BI)**
- **Samsung submits Enbrel BS application to EMA**

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Source: Secondary research. List not exhaustive. (*) at ex-manufacturer price levels, not including rebates and discounts.

(#) Recommended for RA (Rheumatoid arthritis), CD (Crohn’s disease), UC (Ulcerative colitis), AS (Ankylosing spondylitis), PA (Psoriasis), PsA (Psoriatic arthritis)
Agenda

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  – The increasing importance of biologics
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Learning from the biosimilar experience
  – Countless variations: therapy area, country and molecule level
  – What really drives Biosimilars uptake
  – Understanding the role of 2\textsuperscript{nd} generation products
  – Next wave of Biosimilars

• **Looking ahead**
  – Key biologic areas and biosimilar’s targets
  – Originator strategies
  – The trade-off between access and innovation
What has been the uptake of biosimilars in Europe?

Experience with biosimilars illustrate variations at the therapy area, country and molecule level

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

<table>
<thead>
<tr>
<th>Values, M$</th>
<th>ITA</th>
<th>GER</th>
<th>FRA</th>
<th>SPA</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>130</td>
<td>104</td>
<td>102</td>
<td>86</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

% Uptake, DDD

- ITA
- GER
- FRA
- SPA
- UK

**Source:** IMS MIDAS, MAT 12/2013. Uptake is defined as penetration of accessible market. This includes reference and non reference prods
Penetration of biosimilars across different therapy areas has been variable for a number of reasons

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

- Payer-driven market access (e.g. Tender, step-wise algorithms)
- Price-driven competition
- Acute treatment and/or frequent cycling among therapies
- Complex stakeholder landscape with higher physician influence
- Competition based on multiple marketing levers
- Chronic treatment and/or long therapeutic cycles

Source: IMS MIDAS year 2013. (*) Uptake is defined as penetration of accessible market. This includes reference and non reference prods
What really drives Biosimilars uptake?

**Best evidence learnings**

- **Payer Environment**
  - Sets the market environment for other stakeholders
  - Maximum biosimilar uptake could be achieved if a national single sourced tender for coverage of the entire therapy area is implemented

- **Price Differential**
  - Doesn't always correlate to biosimilar uptake
  - Actions taken by manufacturers in specific markets are observed as having an impact on biosimilar uptake and affecting the competitive environment

- **Clinical/Device Innovation**
  - Moving patients to the next standard of care
  - Second generation products have in some cases had significant impact:
    - Sometimes by strategic pricing
    - Sometimes by recognized value or improved outcomes

**Source**: IMS Health insight
Under tender/blind-bidding procurement systems, market evolution may play differently.
Does accessible market price reduction correlate to biosimilar uptake?

EPO: 2013 uptake of Biosimilars vs. 2006-2013 price evolution of the accessible market

EPO: 2013 uptake of Biosimilars vs. 2006-2013 price evolution of the accessible market

Source: IMS Health MIDAS 2013
To what extent has usage shifted to 2nd generation products?

EPO: uptake of 2nd generation in the total market (% of treatment days 2013)

**Comments**

For EPO’s, patent protected 2nd generation products are available.

- Denmark has low uptake of EPO biosimilars as the market shifted to 2nd generation → successful originator strategy

- Differently in Italy and Poland, market remained on first generation EPO → Originators are successfully competing with pricing strategy despite significant biosimilar price differential (Poland)
Infliximab biosimilar has shown strong uptake in tender markets but much more moderated in others.

Will patterns of use and different mode of action influence the market?

**Infliximab Monthly uptake**

*Normalised uptake*

**Infliximab Monthly uptake**

*Cumulative uptake*

Will Infliximab BS be used instead of the originator? Will it impact the usage of other anti-TNFs such as Humira and Enbrel? Will MABs be used more widely?

Learnings so far...

- Biosimilar uptake is highly diverse across markets and between therapy areas.
- There is a weak correlation between biosimilar uptake and the price differential between biosimilar and originator.
- The payer framework establishes the decision drivers allowing for biosimilar uptake, although innovation strategies sometimes work.
- The next wave of Biosimilars is going to be different and the past is not necessary a good indicator of what will happen.
- Understanding and balancing payers’ needs will be necessary to drive biosimilars uptake or attempting to protect brands.
**Agenda**

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**Looking ahead**
- Key biologic areas and biosimilar’s targets
- Originator strategies
- The trade-off between access and innovation
Anti-TNF, insulins and onco MABs are the key biologics

Top Biologic Therapy Area, Global Sales (MAT 6/2014)

- Anti-TNF: 16.0%
- Insulins: 14.7%
- Antineoplastic (Mabs): 11.3%
- Vaccines: 7.6%
- Immunostimulants: 6.6%
- Anticoagulants: 4.8%
- Interferons: 4.4%
- EPO: 4.4%
- Osteoporosis: 2.0%
- Immunosuppr: 2.5%
- Immunoglobulins: 2.5%
- Ocular Antineovascularisation Products: 2.9%
- Blood Coagulation: 3.0%
- Osteoporosis: 1.9%

Other: 15.4%

(It includes old generation insulins which are unlikely to be targeted by biosimilar players)

Source: IMS MIDAS, Q2 2014; Rx
The most popular biosimilar targets under development

<table>
<thead>
<tr>
<th>Originator brand-name</th>
<th>Active substance</th>
<th>Originator company</th>
<th>Therapeutic area</th>
<th>2013 sales (US$ billion)</th>
<th>No. of biosimilars in development</th>
<th>Biosimilar front runner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avastin</td>
<td>bevacizumab</td>
<td>Roche</td>
<td>Bowel/breast/co lon cancer</td>
<td>7.0</td>
<td>15</td>
<td>Amgen</td>
</tr>
<tr>
<td>Enbrel</td>
<td>Etanercept</td>
<td>Amgen/Pfizer</td>
<td>Arthritis Psoriasis</td>
<td>8.3</td>
<td>27</td>
<td>Sandoz/Samsung Bioepsis</td>
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<tr>
<td>Herceptin</td>
<td>Trastuzumab</td>
<td>Roche</td>
<td>Breast/stomach cancer</td>
<td>6.8</td>
<td>21</td>
<td>Amgen</td>
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<tr>
<td>Humira</td>
<td>Adalimumab</td>
<td>AbbVie</td>
<td>Arthritis Ulcerative colitis Crohn’s disease Ankylosing spondylitis</td>
<td>10.7</td>
<td>13</td>
<td>Amgen</td>
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<tr>
<td>Rituxan</td>
<td>Rituximab</td>
<td>Roche</td>
<td>Arthritis Non-Hodgkin lymphoma (NHL) Leukaemia</td>
<td>8.6</td>
<td>35</td>
<td>Boehringer Ingelheim</td>
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<tr>
<td><strong>Total</strong></td>
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<td><strong>49.8</strong></td>
<td><strong>125</strong></td>
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</table>

Source: GABI
Barriers to effective biosimilar penetration vary but will be higher for Mabs than recombinants

**Barrier**

- **New to repeat Rx opportunities** (high = attractive to biosimilars)
- **Indication extrapolation** (high = attractive to biosimilars)
- **Efficacy/safety acceptance** (High = attractive to biosimilars)
- **Market acceptance of biosimilars** (High = attractive to biosimilars)
- **Number of innovative competitors** (Low = attractive to biosimilars)

**Implications**

- Oncology Mabs will have higher new patient opportunities than autoimmune
- Significant indication extrapolation for many oncology products and autoimmune
- Very high level of efficacy and safety scrutiny for Mabs
- Market creation will mean higher investment and harder for Mabs than recombinants

△ Mab  ▶ Recombinant protein
The top players are major generic companies such as Teva, Sandoz along with specialists Hospira.

*Existing biosimilars competitive arena*

*Market share, 2008-14*

(*) it includes bio-comparables abbreviated approval of Omnitrope in North America

Source: IMS MIDAS MAT Sep 2014
But many other companies have recently confirmed and expanded biosimilar development programmes

Nov 2014, Gabi.net
– **Amgen** expands biosimilar programme. In addition to the existing six biosimilar programmes, Amgen has also initiated three additional biosimilar programmes, bringing its **total biosimilar programmes to nine**.

Sep 2014 – **Baxter and Coherus** to collaborate on biosimilars

Sep 2014 – **Merck KGAA plans to step up investments in biosimilars during 2015.** The company plans to invest an additional US$130–150 million in biosimilars for 2015 (on top of €100 million for 2014).

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...who’s next?

Apr 2014 – **Boehringer ingelheim** annual conference. Chairman Andreas Barner confirmed that all these compounds are in advanced stages of development. “We see **biosimilars** as a future **growth field**”

Feb 2014 – **Merck and Samsung Bioepis have expanded their collaboration** with an agreement to develop, manufacture and commercialize MK-1293 (biosimilar glargine)

*Source: Web research. IMS Health. List not exhaustive*
4 categories of players will mean very different go-to-market strategies, pricing and competitive behaviour.

Is there going to be space for everyone?

<table>
<thead>
<tr>
<th>Innovator companies</th>
<th>Generics companies</th>
<th>Other players</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer, Merck, Lily, Baxter, Boehringer Ingelheim</td>
<td>Sandoz, Hospira, Mylan, Teva, Actavis, Cipla, Dr. Reddy’s, Gedeon Richter</td>
<td>Fujifilm (Fujifilm Kyowa Kirin Biologics), Samsung, GE Healthcare</td>
</tr>
</tbody>
</table>

CRAMS* providers / Emerging market domestic players

*CRAMS, Contract Research and Manufacturing Services ** Based on press release news
Success and speed of biosimilar uptake will also be dependent on the strategy employed by originators. Many R&D companies have launched or will launch next generation biologics.

**Originators**
- Remicade® (Infliximab)
- MabThera® (Rituximab)
- Erbitux® (Cetuximab)
- Lantus® (Insulins)
- Enbrel® (ETANERCEPT)
- Herceptin®
- Humira® (Adalimumab)
- Avastin® (Bevacizumab)

**Biosimilars**
- Adalimumab
- Cetuximab
- Infliximab
- Interferon beta
- Rituximab
- Bevacizumab
- Etanercept
- Trastuzumab
- Insulins

**New biologics (future generation)**
- New modern insulins
- Gazyva (Obinutuzumab)
- Perjeta (Pertuzumab)
- Lonquex (Lipegfilgrastim)
- Kadcyla (Trastuzumab-drug conjugate)
- SC Herceptin
Payers and policy-makers are rising as biosimilar advocates

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

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

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

**Impact on biosimilars market**

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

- **EU, 2013**
- **EU, 2018**
Conclusions

• Biopharmaceuticals represent many of the future new clinical advances

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

• Payers are looking for cost savings but also low risks

• The first wave of mAb biosimilars has come from a new market player with a different go-to market strategy, competitive behaviour and expectations

• Many companies are competing to enter, with potentially just one lever to use: PRICE

• Plan for the unexpected!
Thank you!

- For further information please contact:
  - Doug Long dlong@us.imshealth.com