Biosimilars: Revolutionizing Patient Care

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Biologics have revolutionized modern medicine – and will continue to do so

- “Borrowed from nature”, very complex
- Highly specific and powerful medicines
- Treat serious diseases

Source: Company websites and annual reports / Note: All trademarks, logos and pictures are the property of the respective owner
Biologics are representing a growing portion of the overall pharmaceutical market

Global pharmaceutical market, 2005-2017
USD billion

- Biologics sales are expected to grow to ~USD 170 bn by 2017
  - ~30% of industry pipeline in biologics
  - Monoclonal antibodies (mAbs) are largest and fastest growing segment
- By 2017, 7 of the top 10 pharmaceuticals worldwide are expected to be biologics

\(^1\)Vaccines not included
Source: Evaluate Pharma, May 2012; Sandoz analysis
Biologics are more complex than small molecules…

<table>
<thead>
<tr>
<th>Bacteria, Yeast</th>
<th>Mammalian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptide</td>
<td>Glycoprotein (with sugars)</td>
</tr>
<tr>
<td>protein</td>
<td>Protein (no sugars)</td>
</tr>
</tbody>
</table>

- acetylsalicylic acid: 0.18 kDa
- calcitonin: ~3.5 kDa
- filgrastim: ~19 kDa
- somatropin: ~22 kDa
- epoetin: ~30 kDa
- Monoclonal antibody: ~150 kDa

1x 19x 105x 122x 170x 833x
...and are produced from living organisms

Modify host cells (e.g., bacteria, yeast, mammalian) to produce recombinant proteins

Grow cells under controlled conditions (fermentation)

Extract, refold, purify (downstream) – generate drug substance

Formulate to stable finished drug product (vial, syringe, cartridge)
What is a biosimilar (or follow-on biologic)?

Overview

- **Successor to a biologic** medicine that has lost exclusivity
- **Not a simple generic** due to complexity: size, structure and manufacturing

Regulatory definition

- A biologic approved via a stringent regulatory pathway demonstrating comparability

Comparability approach

- **Highly analogous structure** (via robust analytical characterization)
- **Comparable quality, safety and efficacy** (via clinical trials)
Biosimilar development needs more time and budget, and is more complex than standard Gx development.

**Generics**

**Biosimilars**

<table>
<thead>
<tr>
<th>Costs</th>
<th>US$ 2 – 3m</th>
<th>US$ 100 - 250m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to market</td>
<td>2 – 3 yrs</td>
<td>7 – 8 yrs</td>
</tr>
<tr>
<td>Clinical</td>
<td>Bioequivalence studies in healthy volunteers</td>
<td>Phase III pivotal studies in patients</td>
</tr>
<tr>
<td>Post approval</td>
<td>Pharmacovigilance (PV)</td>
<td>Phase IV studies Risk mgmt. plan (incl. PV)</td>
</tr>
</tbody>
</table>

Source: Sandoz analysis

Note: All pictures are the property of the respective owner.
Access to biologics is a growing issue around the world

Almost one-quarter of 46 European countries do not provide access to biologics for arthritis\(^1\)

Cancer patients twice as likely as general population to go bankrupt a year after their diagnosis\(^2\)

Canadian children with juvenile idiopathic arthritis may not receive "standard" care because pediatric coverage for biologic drugs is limited and inconsistent\(^3\)

Only 50% of severe RA patients receive biologics across EU5, US and Japan\(^4\)

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\(^1\) EULAR 2012: Annual Congress of the European League Against Rheumatism  
\(^2\) Cancer diagnosis as a risk factor for personal bankruptcy, ASCO 2011  
\(^3\) Access to biologic therapies in Canada for children with juvenile idiopathic arthritis. J.Rheum, September 2012  
\(^4\) Stakeholder Insight: Rheumatoid Arthritis DMHC2592/ Published 09/2010
Biosimilars are recognized around the world as safe and effective medicines

EU draft general guidelines adopted

Sandoz Somatropin first biosimilar approved and launched in EU

Sandoz first EPO approved and launched in EU

Filgrastim* approved in EU

Sandoz Somatropin first biosimilar—type medicine approved in Australia

US Draft Guidelines

Japan regulatory guidelines

Sandoz Somatropin first biosimilar approved and launched in Japan & Canada


“...the product is as safe and effective as any other product authorized by the Commission.”

- Nicolas Rossignol, former administrator of EC pharma division

1 Source: Speech at EGA Biosimilars conference 2008, quoted in Scrip

* First competitor product (Sandoz product approved Feb 2009)
Biosimilars are well established in Europe, new mAb guideline will support next wave of biosimilars

- **Clear legal basis**, Directive 2001/83/EC as amended
- **Multiple general and product specific guidelines**, e.g. for monoclonal antibodies
- **Totality of evidence** approach
- **Extrapolation** across indications possible
- **Same INN**
- **No IP** provisions
- **Use of biosimilar reference medicines sourced outside European Economic Area** supports global development

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¹EMA press release Sep 28, 2012: *These changes will come into effect after the revision of the guideline on similar biological medicinal products. The Agency expects to release a draft version of this revised guideline for public consultation in early 2013.*
First wave of high-quality biosimilars are gaining acceptance

Biosimilars approved in EU

- Somatropin: 1
- Epoetin: 5
- Filgrastim: 6

Biosimilar % penetration rates in Daily G-CSF class market (Standard Units May 2012)

- Australia: 14
- Netherlands: 24
- France: 25
- Italy: 34
- Germany: 36
- Spain: 38
- **Average**: 56
- UK: 60
- Hungary: 61
- Finland: 62
- Poland: 63
- Greece: 67
- Bulgaria: 75
- Sweden: 86
- Czech Republic: 96
- Romania: 99

Source: IMS Health Standard Units May 2012

Sandoz biosimilars are marketed in over 50 countries and have over 50 million patient exposure days for the three marketed Sandoz products

1 Sandoz analysis / 2 Sandoz Risk Management Plan reports 2012
Introduction of filgrastim biosimilars in Sep 2008 has significantly increased uptake of G-CSF

G-CSF volume, MAT thru Sep
Number of syringes

2007 2008 2009 2010 2011 2012
Filgrastim 5,816 6,160 6,318 6,730 7,298 7,579
Lenograstim 3,259 3,302 3,329 3,773 4,394 4,855
Pegfilgrastim 2,186 2,397 2,461 2,370 2,263 2,083

This increase in filgrastim use could have potentially increased access for thousands of cancer patients across Europe

1 Compares Oct 11 - Sept 12 vs Oct 10 - Sept 11 from monthly database
Note: All values MAT thru September of respective year / Source: IMS Quarterly Database
Modest penetration of Biosimilars in the GCSF market, but still low levels in EPO and Growth Hormone segments

Spain

Market shares in value and absolute market size
USD (millions) : MAT Nov’12

Filgrastim

<table>
<thead>
<tr>
<th></th>
<th>Total Market</th>
<th>Short acting Market</th>
<th>Biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Long acting</td>
<td>Short acting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55%</td>
<td>41%</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>Short acting</td>
<td>45%</td>
<td></td>
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<tr>
<td>Hospira</td>
<td>29%</td>
<td>59%</td>
<td></td>
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<tr>
<td>Teva</td>
<td>15%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Sandoz</td>
<td>55%</td>
<td>41%</td>
<td>55%</td>
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</table>

EPO

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>Long acting</td>
<td>Short acting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>53%</td>
<td>18%</td>
<td>29%</td>
</tr>
<tr>
<td>Hospira</td>
<td>47%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Teva</td>
<td>33%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>Sandoz</td>
<td>55%</td>
<td>41%</td>
<td>55%</td>
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</table>

Growth Hormone

<table>
<thead>
<tr>
<th></th>
<th>Total Market</th>
</tr>
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<tbody>
<tr>
<td>Pfizer</td>
<td>46%</td>
</tr>
<tr>
<td>Novo</td>
<td>8%</td>
</tr>
<tr>
<td>Merck</td>
<td>17%</td>
</tr>
<tr>
<td>Lilly</td>
<td>16%</td>
</tr>
<tr>
<td>Ipsen</td>
<td>3%</td>
</tr>
<tr>
<td>Ferring</td>
<td>9%</td>
</tr>
<tr>
<td>Sandoz</td>
<td>9%</td>
</tr>
</tbody>
</table>

- Attractive market with modest Biosimilar penetration
- Largest market overall, but low Biosimilar penetration
- Large market size, but low Biosimilar penetration

Source: IMS Nov’12
Biosimilars expected to save between €11.8 to 33.4 bn between 2007-2020 in 8 EU countries

Source: EGA
International Symposium London, April 19th, 2012 / Bertram Häussler IGES Institut, Berlin Germany

• EU8 = Germany, France, the UK, Italy, Spain, Sweden, Poland and Romania
• All compounds = Epoetin, Filgrastim, mAbs
• BS = biosimilar
• Market entry: immediate at IP expiry or 2 years later
Genuine competition – with a “level playing field” for all biologics – will lead to increased innovation.

*Competition and innovation are inextricably linked – a “virtuous circle”*

- Originators should be able to realize fair profit and return on investment.
- Indefinite monopolies lead to stagnation.
- Biosimilars will increase competition and encourage “next wave” of biologics innovation.
Conclusion

- Biologics have revolutionized medicine and will continue to do so.
- Access to biologics is an increasingly important health care issue around the world.
- High-quality, affordable biosimilars can dramatically increase access to important medicines and can help make health care systems more sustainable.
- The EU uptake of biosimilars has been variable between product class, between EU countries and within countries.
- Biosimilars penetration in Spain is still low for EPO and Growth Hormone and moderate for GCSF - measures to increase the penetration could be the following:
  - Appropriate incentives at the government level.
  - Improved awareness and understanding of biosimilars within the healthcare community – support from health authorities.
  - Realistic expectations in terms of pricing for monoclonal antibodies.