Biologica l & biosimilars; addressing the needs of patients and payers

The Role of Functioning Competitive Markets
Agenda

• Why do patients and payers need biosimilars?
• How can we increase the uptake of biosimilars?
• What role can biosimilars play?
Why do patients and payers need biosimilars?

- Savings
- Patient access
- Competition
- The increasing use of biologicals
In the absence of competition, cumulative spending in the EU5 is expected to reach €47 billion over the period 2016-2020.

The Addressable Biosimilar Medicines Market in the EU5 and the US, 2016-2020

Conversion rate: 1 USD = 0.916562 EUR (01/20/2016)

Source: IMS Health, MIDAS, IMS Health Market Prognosis, IMS Institute for Healthcare Informatics, Dec 2015

Notes: Addressable market is calculated based on projected growth of originator market without biosimilar entry. Growth rate is based on historical growth and analogue analysis.
The value of biologic products losing patent exclusivity between 2015 and 2020 is significant.

**EU5+US Sales of Key Biologics Scheduled to Lose Patent Protection in 2015-2020**

<table>
<thead>
<tr>
<th>Biologic</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>10.8</td>
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<tr>
<td>Insulin glargine</td>
<td>8.7</td>
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<tr>
<td>Etanercept</td>
<td>6.9</td>
<td></td>
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<tr>
<td>Infliximab</td>
<td>5.3</td>
<td></td>
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<tr>
<td>Rituximab</td>
<td>4.2</td>
<td></td>
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<tr>
<td>Peg-filgrastim</td>
<td>3.9</td>
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<tr>
<td>Trastuzumab</td>
<td>3.2</td>
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<tr>
<td>Follitropin alfa</td>
<td>0.3</td>
<td></td>
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</table>

Source: IMS Health, MIDAS, Dec 2015
Cumulative savings over the next five years (EU5 and US) could range from between €49 billion to as much as €98 billion.

Savings potential from 8 Key Products with LOE 2016-2020

Source: IMS Health, MIDAS, IMS Health Market Prognosis, IMS Institute for Healthcare Informatics, Dec 2015
How can we increase the uptake of biosimilars?

- Education and incentives
- Biosimilar first prescribing (all naïve patients)
- Quotas
- Tenders
- Pricing
- Interchangeability/switching/substitution
Payers need to ensure that stakeholders are sufficiently educated on the benefits of biosimilars medicines and are appropriately incentivised.

Unlocking the Potential of Biosimilar Medicines

Source: IMS Health, IMS Consulting Group, Jan 2016
Considerable variation across the EU exists in terms of payer policy approaches to biosimilars

**EU Payer Biosimilar Policies**

- **Most patients out of reach for manufacturers**
  - National management passive (i.e. fixed biosimilar price reduction)
  - No prescribing incentives
  - No prescription quota

- **Competition averse**

- **Foster competition**
  - Increased active management nationally (i.e. regular price adoption)
  - Education of physicians by payers
  - Biosimilar prescribing stimulated (quotas)

**Many patients available for manufacturers to compete for**

Source: IMS Health, IMS Consulting Group, Jan 2016
Germany (North Rhine): quotas for prescribing biosimilars

- Medicines agreement struck between German Health Insurance funds and statutory doctors’ associations
- EPO: Nephrologists expected to ensure at least 63% of the prescriptions are biosimilars
- TNF-alpha inhibitor class:
  - Gastroenterologists: 11,5%
  - Rheumatologists and dermatologists: 4,5%
Belgium: convention to increase uptake of biosimilar medicines

- Gentleman’s agreement between Belgian government, hospital pharmacists, physicians and pharmaceutical industry
- Physicians voluntarily commit to increasing uptake of biosimilar medicines
- Biosimilars have to be considered for bio-naïve patients
- If no sign of increased uptake by July 2016, government will implement additional (legislative) measures

Some Belgian physicians still sceptical about biosimilar medicines

**L’expert** « On doit mieux vérifier l’efficacité de ces médicaments »

L’expert: 

Some Belgian physicians still sceptical about biosimilar medicines

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Some Belgian physicians still sceptical about biosimilar medicines
In Europe, biosimilar penetration has only been incremental in non-tender systems. EU5 penetration 10-24% in under a year.

**Europe: Infliximab biosimilar market share**

- **Denmark**: 98%
- **Poland**: 94%
- **Norway**: 86%
- **Finland**: 49.9%
- **Croatia**: 47.2%
- **Hungary**: 30.1%
- **Czech Republic**: 23.9%
- **Italy**: 23.7%
- **UK**: 22.9%
- **Sweden**: 21.8%
- **Portugal**: 20.5%
- **Spain**: 20.1%
- **Germany**: 15.0%
- **Romania**: 12.9%
- **France**: 10.2%
- **Slovakia**: 7.3%
- **Austria**: 6.5%
- **Ireland**: 5.0%

**Source**: IMS MIDAS monthly Dec 2015; Denmark data from MIDAS Monthly Restricted database; Bulgaria, Latvia excluded because only biosimilar manufacturers present in market.
Presence on the market increases infliximab usage, and will eventually cut spending

Source: IMS Health MIDAD Monthly Jan 2016
In the EU5 markets, price reductions have varied considerably.

Global Spending and Growth, 2010-2020

Source: IMS Health, The Impact of Biosimilar Competition, Nov 2015
Note: Analysis based on publically available prices.
Interchangeability (EU)

- The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting on the initiative, or with the agreement of the prescriber. (1)

Interchangeability (USA)

The interchangeable product (determined by FDA) may be substitutable for the reference product without the authorization of the health care prescriber.


Switching (EU)

- Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment
- Hospital: decision is made by a multidisciplinary team always including the clinical community (therapeutic/formulary committee)
What role can biosimilars play?

- Create headroom for expenditure on new innovative medicines
- Stimulate innovation with existing molecules
- Treat more patients within the same financial budgeted levels
- Increase patient access to modern medicines
Over the period 2016-2020, some 225 new active substances (NAS) are expected to come to market globally.

Global New Active Substances Available Since 1996

- Cumulative Total Since 1996: 943
- 5 year NAS: 718
- Earlier NAS: 184


Note: Disease categories based on therapy areas and expected launches 2016-20. Orphan drugs are those to treat small populations with rare diseases, and are defined separately by U.S. FDA and the European Medicines Agency (EMA). Any medicine with an orphan designation for an approved use within the first year after global launch are categorized as Orphan. Half of designated orphan indications are granted more than a year after original approval.
Sovaldi only the first of several potential tsunamis

Are these innovations sustainable?

Hepatitis-C market 2012-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Historic sales (Bn US$)</th>
<th>Analyst forecast (Bn US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>$32 Bn</td>
<td>$18-22 Bn</td>
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<tr>
<td>2013</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>2014</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>2015</td>
<td>30</td>
<td>30</td>
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</table>

Immuno-Oncology

<table>
<thead>
<tr>
<th>Year</th>
<th>Analyst forecast (Bn US$)</th>
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</thead>
<tbody>
<tr>
<td>2014</td>
<td>0</td>
</tr>
<tr>
<td>2016</td>
<td>2</td>
</tr>
<tr>
<td>2018</td>
<td>5</td>
</tr>
<tr>
<td>2020</td>
<td>8</td>
</tr>
</tbody>
</table>

Respiratory biologics

<table>
<thead>
<tr>
<th>Year</th>
<th>Analyst forecast (Bn US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>0</td>
</tr>
<tr>
<td>2016</td>
<td>2</td>
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<td>2018</td>
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</tr>
<tr>
<td>2020</td>
<td>8</td>
</tr>
</tbody>
</table>

PCSK9 inhibitors?

<table>
<thead>
<tr>
<th>Year</th>
<th>Analyst forecast (Bn US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>0</td>
</tr>
<tr>
<td>2016</td>
<td>0.5</td>
</tr>
<tr>
<td>2018</td>
<td>2.5</td>
</tr>
<tr>
<td>2020</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Source: IMS Health Analytics Link consensus analyst forecast; Drug analyst consensus; IMS Health MIDAS Q4 2015;
Biosimilars provide access to modern treatments at lower costs as well as potentially creating headroom for use of new innovative treatments.

Opportunity to lower costs, e.g. price reductions of 30-60% generating significant savings

Make room for increased expenditure on innovative drugs reaching the market by 2020
Oncology and Autoimmune targeted by biosimilars

Biosimilar pipeline by phase 2015
*Pre-clinical to registration*

- Preclinical: 32
- Phase I: 23
- Phase II: 1
- Phase III: 23
- Pre-Reg/Reg: 12

35 biosimilars in late stage development

Biosimilar pipeline by therapy area 2015
*Pre-clinical to registration*

- Oncologics: 28
- Autoimmune: 25
- HGFs: 10
- Immunosuppr.: 7
- Erythropoietins: 3
- Sex Hormones: 3
- Antidiabetics: 3
- Growth Hormones: 3
- Dermatologics: 2
- Multiple Sclerosis: 2
- Others: 5

Source: IMS Health R&D focus Dec 2015; Not exhaustive
Several factors will influence the uptake of biosimilars in Europe

- 2nd/3rd Generation products may pose a major threat
- Therapy areas with chronic disease will be more dependent on switching existing patients
- Strategic pricing strategy
- Capitalization on the continuing patients if biosimilar approved as non interchangeable
- Switching patients to protected formulation / device enhancement
- Maintaining competitive promotional efforts
- Regulatory approval process still optimising
- Biologic substitution regulations left to the country member states
- 2nd/3rd Generation products may pose a major threat
- Therapy areas with chronic disease will be more dependent on switching existing patients
- Strategic pricing strategy
- Capitalization on the continuing patients if biosimilar approved as non interchangeable
- Switching patients to protected formulation / device enhancement
- Maintaining competitive promotional efforts

- Varying confidence in biosimilars, some being very open to use / others are more cautious
- Clinical results will be a key driver influencing the prescriber
- Greater willingness to experiment and learn from each other
- Greater interventionism
- Biosimilar tenders becoming increasingly competitive
- Diverse marketing strategies, emphasizing education around the quality, safety and efficacy
- Strategy not limited to promotion as a lower-cost option. Abasaglar
- Number of biosimilar competitors will influence discounts from the originator price
Three key outcomes from the use of biosimilars long-term

Market opportunity for biosimilar players

Huge financial incentive in pursuing this growing market

Cost Savings (~20-30% vs. Originator) and better patient healthcare management

Patients seeking access

Affordable Access to breakthrough therapies leading to better health outcomes
Thank you!
Science-driven conceptual approach - Science-driven knowledge-based approach

Biosimilar 2005 - Biosimilar 2015

Slide Dr. Peter Richardson EMA, DIA London Nov. 2015
Comparability exercise has become the scientific norm for biosimilar development

The role of clinical trials is to confirm biosimilarity

Quality – the foundation of biosimilars

EMA slide DIA London 2015, adapted

Comparability exercise has become the scientific norm for biosimilar development.

The role of clinical trials is to confirm biosimilarity.

Higher

Sensitivity to Differences

Lower

Clinical

PK/PD

Preclinical

Biological characterization

Physicochemical characterization

Quality – the foundation of biosimilars

Comparability exercise has become the scientific norm for biosimilar development.

The role of clinical trials is to confirm biosimilarity.

Higher

Sensitivity to Differences

Lower

Clinical

PK/PD

Preclinical

Biological characterization

Physicochemical characterization

Quality – the foundation of biosimilars
Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise. Extrapolation is a logical consequence of the biosimilar concept that has been successfully implemented in the EU.
Biosimilar Candidates under evaluation
January 2016

- 10 applications for biosimilar medicines under evaluation by CHMP
  - Enoxaparin sodium (2)
  - Insulin Glargine (1)
  - Etanercept (1)
  - Infliximab (1)
  - PEG-filgrastim (2)
  - Rituximab (1)
  - Adalimumab (2)

Source: EMA website (January 2016) & GaBI Online
# Key therapeutic areas covered by current and future biosimilars

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Key therapeutic areas covered by current biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatropin</td>
<td>Pituitary dwarfism, Prader-Willi syndrome, Turner syndrome</td>
</tr>
<tr>
<td>Epoetin</td>
<td>Anemia, Follow-up of cancer treatment, Consequences of chronic kidney failure</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Neutropenia, Follow-up of cancer treatment, Hematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Rheumatoid arthritis, Crohn's disease, Ulcerative colitis, Psoriasis, Psoriatic arthritis, Ankylosing spondylitis</td>
</tr>
<tr>
<td>Follitropin alfa</td>
<td>Anovulation</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Diabetes mellitus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Key therapeutic areas to be covered by future biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Crohn’s disease, Rheumatoid arthritis</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Colorectal cancer, Lung</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Colorectal cancer, Head and neck cancer</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Rheumatoid arthritis, Psoriatic arthritis, Plaque psoriasis, Ankylosing spondylitis</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Diabetes mellitus, Neutropenia</td>
</tr>
<tr>
<td>PEG-filgrastim</td>
<td>Follow-up of cancer treatment, Hematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>Macular degeneration</td>
</tr>
<tr>
<td>Rituximab</td>
<td>B-cell non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Breast cancer</td>
</tr>
</tbody>
</table>

Source: EMA website, April 2015
Review of switching between therapeutic proteins

- Review of switching studies of biological medicines (originator-originator or originator-biosimilar)
  - Somatropin: 13 studies, 415 subjects (adults & children)
  - Epoetin: 35 studies, 11,249 subjects
  - Filgrastim: 10 studies, 374 subjects

- Review 193 ADR reports for currently approved biosimilars
  - EPO – 46
  - Filgrastim – 118
  - Growth hormone – 29

  Data on frequency of switching is scarce, but no evidence that switching to and from different biological medicines leads to safety concerns

  No indication of safety issue resulting from switching between products

  → No signal of switch-related adverse effects

  → No data that switching induces increased immunogenicity
Interchangeability of biosimilar medicines – Supported by national authorities

Medicines Evaluation Board – MEB (The Netherlands)¹:
- Exchange between biological medicines (regardless of whether they are innovator products or biosimilar medicinal products) is permitted, but only if adequate clinical monitoring is performed and the patient is properly informed.

Finnish Medicines Agency – Fimea (Finland)²:
- Biosimilar medicines are interchangeable with their reference products under the supervision of a health care person.

Paul Ehrlich Institute (Germany)³:
- Biosimilars can be used in the same way as the reference products to which they have shown equivalence. This implicitly covers both patients who have not yet received biological therapy as well as patients who previously received the originator molecule.

² Interchangeability of biosimilars – Position of Finnish Medicines Agency Fimea (22/2/2015).
Pricing policies for biosimilar medicines

Description of biosimilar P&R pathway

<table>
<thead>
<tr>
<th>Country</th>
<th>Specified Price Discount</th>
<th>Key take-away</th>
</tr>
</thead>
<tbody>
<tr>
<td>France⁷</td>
<td>N</td>
<td>- Products are reviewed by the Transparency Commission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Biosimilar products will be given an ASMR rating of 'V', forming the basis of price negotiations with CEPS</td>
</tr>
<tr>
<td>Greece⁴</td>
<td>N</td>
<td>- Reimbursement is determined by the Ministry of Health and Social Solidarity with no dispensations for biosimilar products</td>
</tr>
<tr>
<td>Spain⁷,⁸,⁹</td>
<td>Y</td>
<td>- 2014 reform of the reference pricing system includes the creation of biosimilar groups; however, concerns have been raised regarding how this contradicts other biosimilar policy, for example on interchangeability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Biosimilar prices are set 30% below originator product price</td>
</tr>
<tr>
<td>Sweden¹⁰</td>
<td>N</td>
<td>- For reimbursement under the pharmaceutical benefit scheme, all products are reviewed by the TLV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- A cost minimisation model versus branded original is required</td>
</tr>
<tr>
<td>UK¹¹,¹²,¹３</td>
<td>N</td>
<td>- England: NICE will consider biosimilar products, usually in the context of an MTA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Scotland and Wales: SMC and AWMSG respectively require full submissions for all new biosimilar medicines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cost minimisation models are accepted</td>
</tr>
<tr>
<td>Belgium¹⁴,¹⁶</td>
<td>N</td>
<td>- Biosimilar products undergo review for reimbursement by the CRM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Guidelines for biosimilar submissions (filed under class 2) are available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- For biosimilar products filed under class 2, list price cannot exceed that of their comparator and is set through negotiations</td>
</tr>
<tr>
<td>Switzerland¹⁵,¹⁷</td>
<td>Y</td>
<td>- Products are reviewed by the BAG for inclusion on the specialty list</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Submission guidelines include specific section for biosimilar submissions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Biosimilars are required to have an ex-manufacturer price 10% below branded original to be considered cost-effective</td>
</tr>
<tr>
<td>Austria¹⁸,¹⁹</td>
<td>Y</td>
<td>- All drugs are reviewed for reimbursement by the HVB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Price caps implemented for generic products are applied to biosimilars</td>
</tr>
<tr>
<td>Germany⁵,⁸,¹⁹</td>
<td>N</td>
<td>- Biosimilars do not undergo early benefit assessment by the G-BA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Biosimilars and their originator drug can be included in the same level 1 reference price group (EPO and somatropin are included in the reference pricing system)</td>
</tr>
<tr>
<td>Italy²⁰</td>
<td>Y</td>
<td>- Faster access to market (60 days) achieved if a pre-specified price discount, dependent on sales of the reference product, is applied</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Otherwise, full AIFA P&amp;R negotiations are required (180 days) and, like generics, biosimilars are required to set their price at least 20% below the originator product price</td>
</tr>
<tr>
<td>Netherlands²¹</td>
<td>N</td>
<td>- Zorginstituut Nederland (formerly CVZ) regards biological medicines as therapeutically interchangeable if they have been deemed &quot;similar&quot; following registration by the EMA or CIBG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Biosimilars do not undergo standard P&amp;R assessment; they are allocated to same reference price group as originator</td>
</tr>
<tr>
<td>Poland²</td>
<td>Y</td>
<td>- P&amp;R approval process for biosimilars is the same as for generics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Mandatory price discount of 25% below originator is applied (if it's first to original)</td>
</tr>
</tbody>
</table>

NICE guidance on introducing a biosimilar infliximab

- Tips from the NHS for managing the introduction of biosimilars
  - Identify **clinical and pharmacy champions** to take the lead in introducing biosimilars
  - **Consult all stakeholders** (including patients) to ensure confidence in using biosimilars
  - **Provide information** on
    - EMA licensing process for biosimilars
    - Extrapolation and equivalence
    - Manufacturing process and intra-product manufacturing changes
  - Identify the potential **cost-saving and re-investment opportunities**
  - Seek **formal approval at the local formulary committee** once there is clinical consensus to include biosimilars on the formulary
  - **Collect baseline data** and agree metric to be collected during and after the introduction of biosimilars
  - **Submit data** to national audits and registries
  - **Prescribing should be done by brand name** to ensure that there is no unintended substitution of drugs at the pharmacy level