Biosimilar accessible market: Size and biosimilar penetration

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About this document

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Background to the document

- The European Commission has set up a project group whose objective is to: “define what the necessary conditions within the pharmaceutical environment are to ensure informed and adequate access and uptake of biosimilar medicinal products”

- Members of the project include EFPIA, EGA and EuropaBio who are the trade associations representing the innovative, generic and biotechnology medicine sectors respectively

- The Commission project is composed of a number of work streams one asks that relevant data on the market penetration of Biosimilars is collated

- In this document IMS health a leading provider of data analysis and consultancy services to the health and pharmaceutical sector presents its data on the biosimilar accessible market in Europe
IMS’ brief

• EFPIA-EGA-EuropaBio have defined the constituents of a biosimilar competitive market. The market definition encompasses all products that compete along side biosimilars for each of the therapy areas concerned

• IMS was asked to apply this definition to its data and generate market size and penetration statistics for the three therapy areas in question and each country in the EU plus Norway and Switzerland
European legislation\(^1\) set out provisions for biological medicines and associated biosimilars and defines a biological medicine as:

“A *biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and for which a combination of physico-chemical-biological testing and the production process and its control is needed for it characterisation and the determination of its quality."

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\(^1\) Annex I to Directive 2001/83/EC, Part I, paragraph 3.2.1.1, point b, which defines a biological medicinal product and Article 10(4) of Directive 2001/83/EC provides the legal basis for biosimilar medicinal products.
Differences between biological medicines and their small molecule counterparts mean biologics require a special regulatory approach

<table>
<thead>
<tr>
<th>Biological Medicine</th>
<th>Small molecule Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complex molecule 20,000-200,000 daltons</td>
<td>• Small molecule 100-200 daltons</td>
</tr>
<tr>
<td>• Biological basis</td>
<td>• Chemically derived</td>
</tr>
<tr>
<td>• Spectrum of complexity, recombinant DNA, blood or blood plasma, immunologicals,</td>
<td></td>
</tr>
<tr>
<td>gene, cell therapy etc)</td>
<td></td>
</tr>
<tr>
<td>• Recombinant technology, for example, gene, via vector to synthesis by cell line</td>
<td>• Chemical synthesis</td>
</tr>
</tbody>
</table>

- **Nature**
  - Recombinant technology, for example, gene, via vector to synthesis by cell line
  - Chemical synthesis

- **Manufacture**
  - Innovation rewarded with a period of market exclusivity
  - At loss of exclusivity biosimilars launched by referencing an original product and proving comparability
  - Innovation rewarded with a period of market exclusivity
  - At loss of exclusivity generics are launched. Assay is sufficient to prove similarity

- **Example**
  - **Monoclonal antibody**
    - ~25,000 atoms
    - 150,000 Mol Wt
  - **acetylsalicylic acid (Aspirin)**
    - 21 atoms
    - 180 Mol Wt
The EMA has developed market authorisation processes for the special needs of the biosimilar market

- Emphasis is proving biosimilarity to original (ref.) product
- EMA committee for medicinal products for human use issues biosimilar guidelines
- Marketing authorisation regulation in place since 2005
  - Requires compilation of a dossier
    - Demonstration of similarity
    - Comparability studies
      - Quality
      - Safety
      - Efficacy
    - Form strength should be the same as the reference product, any change/development requires protracted discussion with the EMA
The evolution of a biologically based therapy area has distinct phases

**Innovation 1**
Innovation: research and development process culminates in the first ever biological medicine to market. Originator is rewarded with a period of market exclusivity.

**Later Innovation**
Other manufacturers develop and launch biological medicines for the same therapy area.

**Loss of exclusivity**
Loss of exclusivity: Original product loses exclusive rights, continues to market the product but that product can now be referenced by other manufacturers.

**Further Innovation**
Innovation process continues to generate new biological treatments.

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**European exclusivity**

**Innovation Track**

**Competitive Development**
All manufacturers are now able to reference the original product and bring competitors to market after satisfying comparability requirements.

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**Reference of original product**

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**Epoetin Alpha**  **Epoetin Beta**  **Biosimilar Epoetin Alpha**  **Darbepoetin Alpha**
The different phases mean that four product types are present on the market at any given time:

- **European exclusivity**
- **Innovation 1**
- **Innovation 2**
- **Loss of exclusivity**
- **Further Innovation**

**Referenced Product**

**Non-referenced Products**

**Patent protected products**

- **Epoetin Alpha**
- **Epoetin Beta**
- **Biosimilar Epoetin Alpha**
- **Darbepoetin Alpha**

**Reference of original product**

**Biosimilar**

**Competitive Development**
The different product types can be classified as follows:

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Definition</th>
<th>Participant in the biosimilar accessible market (in scope?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Reference Product</td>
<td>Original product, granted market exclusivity at the start of its life, exclusivity is now expired and the product has been referenced</td>
<td>Yes</td>
</tr>
<tr>
<td>2  Non-referenced product</td>
<td>Original product, granted market exclusivity at the start of its life, exclusivity is now expired and the product has never been referenced or may have been referenced but the referencing biosimilar has not launched</td>
<td>Yes</td>
</tr>
<tr>
<td>3  Biosimilar</td>
<td>Product launched with reference to the original product and after proving biosimilarity</td>
<td>Yes</td>
</tr>
<tr>
<td>4  Patent Protected Products</td>
<td>Product currently granted market exclusivity</td>
<td>No</td>
</tr>
</tbody>
</table>
A biosimilar accessible market applies to three molecules in 2011

**The European biosimilar competitive market for each therapy area, MAT to Month 6 2011**

<table>
<thead>
<tr>
<th>Therapy area</th>
<th>Molecule</th>
<th>Reference Product</th>
<th>Non-reference products</th>
<th>Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF</td>
<td>Filgrastim Lenograstim</td>
<td>Neupogen (Amgen)</td>
<td>Granocyte (Sanofi A.) Myelostim (Italafarmaco) Neutrogin (Roche) Euprotin (Almiral)</td>
<td>BIOGRASTIM (Teva) RATIOGRASTIM (Teva) ZARZIO (Sandoz Nov.) TEVAGRASTIM (Teva) FILGRAST. HEXAL (Hexal Nov.) FILGRASTIM TEVA (Teva) NIVESTIM (Hospira) FILGRASTIM MEPHA (Cephalon)</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>Somatropin</td>
<td>Genotropin (Pfizer)</td>
<td>Norditropin (Novo Nord.) Nutropina (Ipsen) Saizen (M. Serono) Zomacton (Ferring) Humatrope* (Lilly)</td>
<td>OMNITROPE (Sandoz Nov.)</td>
</tr>
<tr>
<td>Short Acting &quot;Epo&quot;</td>
<td>Epoetin Alpha, Beta, Delta, Theta and Zeta</td>
<td>Erypo/Eprex (J&amp;J)</td>
<td>NeoRecormon (Roche) Eporatio/Biopoin (Teva)</td>
<td>BINOCRIT (Sandoz Nov.) EPO A (Hexal Nov.) ABSEAMED (Medici) RETACRIT (Hospira) SILAPO (Stada)</td>
</tr>
</tbody>
</table>

NOTE: In this table IMS records the name and manufacturer of products in the biosimilar accessible market with significant sales. Some products have been withdrawn from the market, for example, Dynepo (shire). This product technically sold 6 DDD in the period concerned. This product has been excluded from the analysis above as it is immaterial. For full explanation and market definition see appendix 1. *Humatrope technically this product has been referenced but no biosimilar has been launched.
13 biosimilars have sales MAT to month 6 2011, each biosimilar accessible market has a different number of biosimilars, non-reference products competing against the reference for MS.

### Count of the product types associated with each molecule (Europe total)

<table>
<thead>
<tr>
<th>Therapy area</th>
<th>Molecule</th>
<th>Reference Product</th>
<th>Non-reference products</th>
<th>Biosimilar</th>
<th>TOTAL Products Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Short Acting “Epo”</td>
<td>5 (inc all subtypes)</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>TOTAL Europe</td>
<td>8</td>
<td>3</td>
<td>11</td>
<td>14</td>
<td>28</td>
</tr>
</tbody>
</table>

**NOTE:** In this table IMS records the name and manufacturer of products in the biosimilar accessible market with significant sales. Some products have been withdrawn from the market, for example, Dynepo (shire). This product technically sold 6 DDD in the period concerned. This product has been excluded from the analysis above as it is immaterial. For full explanation and market definition see appendix 1.
Using IMS data to measure the European biosimilar market

- IMS data measures sales record in the market for any given period
- IMS audits all EU countries plus Norway and Switzerland with the exception of Malta and Cyprus
- Both the hospital and retail markets are audited except for the hospital markets in Luxembourg, Estonia, Greece and Portugal
- IMS’ collection methodology is specific to each country, however, in principle IMS collects volume information into or out of pharmacy
- In this analysis the volume information is converted to defined daily dose (DDD) and value in Euro
- DDD conversions are made by applying the standard DDD factors to the volume data
- Euro conversion are made by applying price information that IMS sources from each country. The source of the information varies by country. Rebates and discounts are often not included as IMS sources list price information. This is of particular relevance in the hospital channel where, in many countries, procurement takes place via a tender, a process that typically incorporates significant discounts. IMS data excludes these discounts. IMS market valuations are therefore indicative of the list price value of the market (regulated market value) and are not equal to a financial view of ex-manufacture transactions into the market.
The WHO has defined daily doses for the molecules in the biosimilar competitive market

- DDD are defined by the WHO and are a proxy for the dose an average adult is given on a daily basis for the main indication for the molecule

### WHO defined daily doses for biosimilar medicines

<table>
<thead>
<tr>
<th>Therapy area</th>
<th>Molecule</th>
<th>DDD</th>
<th>DDD unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-GSF</td>
<td>Filgrastim Lenograstim</td>
<td>0.35</td>
<td>Mg</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>Somatropin</td>
<td>2</td>
<td>IU</td>
</tr>
<tr>
<td>Short Acting “Epo”</td>
<td>Epoetin Alpha, Beta, Delta, Theta and Zeta</td>
<td>1000</td>
<td>IU</td>
</tr>
</tbody>
</table>

Source: [http://www.whocc.no/atc_ddd_index/](http://www.whocc.no/atc_ddd_index/)

NOTE: Defined daily dose is an analytical methodology whose objective is to allow the international comparison of products. It selects the lead diagnosis for a product and defines an average dose for that indication for an adult patient. Any given medicine may have multiple indications requiring different dosages. The actual prescribed dose in any given situation may be different from that defined by the WHO collaborating centre for drug statistics based in the Norwegian Institute of Public Health, Oslo, Norway.
Biosimilars are a small segment in the total pharmaceutical market but have growth rates greater than other market segments.
The biosimilar accessible market will grow as the patent for several biological medicines expire over the next 5+ years.

*The EU has defined a period of 10 years data exclusivity. However, during the latest review of pharmaceutical legislation EU legislation was revised, its exclusivity criteria were adjusted to: The following applies: 10 years if the reference product is centrally approved or application to the centralised procedure has been made before 20/11/05. Or 8 years data exclusivity + 2+ 1 formula if a full dossier is submitted on or after 30/10/05 via national procedure or 20/11/05 via centralised procedure. ** The US BPCI act provided 12 years exclusivity

NOTE: In general exact patent expiration dates are hard to establish as precise expected expiration dates are proprietary information to the company concerned. These dates are typically subject to change as patent details are discussed near the expiration date. The IMS objective in sharing this gabi data is to inform the reader that there are a number of significant biological expirations over the next 5+ years and that these expirations will mean the size of the biosimilar accessible market will grow. Dates are illustrative and use publically available data from the generics and biosimilar initiative.

Source: [www.gabionline.net](http://www.gabionline.net)
Market penetration calculations are based on biosimilar sales as a proportion of the accessible market and not biosimilar share of reference molecule.

**Market share calculation:** \( \frac{\text{Sales biosimilar (a)}}{\text{Sales of biosimilar accessible market (b)}} \)
The short acting Epo market is the largest biosimilar accessible market in Europe by volume (DDD)

<table>
<thead>
<tr>
<th></th>
<th>Epo</th>
<th>G-CSF</th>
<th>G. Hormone</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDD</td>
<td>125m</td>
<td>4.5m</td>
<td>45m</td>
<td>175m</td>
</tr>
<tr>
<td>Sales, €</td>
<td>€968m</td>
<td>€451m</td>
<td>€842m</td>
<td>€2,261</td>
</tr>
</tbody>
</table>

EU + NO, CH Biosimilar market by molecule, DDD, MAT to M6 2011

Source: IMS MAIDAS Q6 2011

NOTE: Epo, Growth Hormone and G-CSF are different products used to treat very different diseases. The average cost per DDD of both Epo and Growth Hormone are typically in the 10's of Euro per DDD. G-CSF is in the 100's of Euro. The exact cost per DDD depend on the strength, manufacturer and country sales and DDD shown here are aggregate values. IMS values the market at regulated list prices and does not typically include discounts or rebates. For analysis of which products align to ache of the molecules above please see appendix 1.
Each therapy area utilises a mix of biosimilars, referenced and non-referenced products.

**Source:** IMS MAIDAS Q6 2011
Biosimilar have a 12% volume share of the accessible Epo market, 7% share of the growth hormone market and 18% share of the G-CSF market.

Source: IMS MAIDAS Q6 2011
Each therapy area has its own market dynamics, however, aggregating three therapy areas: biosimilars have an 11% share of the accessible European market, share has grown steadily from launch.

**EU + NO, CH total biosimilar accessible market by product type, % of DDD, Mat to M6 2011**

- **Biosimilar**: 79, 84, 81, 81, 80
- **Non-Ref. Product**: 94, 96, 93, 86, 75
- **Ref. Product**: 0, 2, 7, 13, 19

**EU + NO, CH share of biosimilar accessible market by product type, % of DDD, Mat to M6 2011**

- **Biosimilar**: 46%, 46%, 45%, 45%, 46%
- **Non-Ref. Product**: 54%, 53%, 51%, 47%, 43%
- **Ref. Product**: 0%, 1%, 4%, 7%, 11%

*Source: IMS MAIDAS Q6 2011.*
Biosimilars volume has grown, non-referenced product volume has declined. Reference products have maintained volume but value has declined.
Conclusions (1): Size, Europe aggregated view

- The total biosimilar accessible market was 175m DDD MAT to M6 2011 worth €2,261m before rebates and discounts.

- By volume the Epo biosimilar accessible market is the largest in Europe. It is 35 times and three times bigger than the daily growth factor and growth hormone markets respectively on a volume (DDD) basis.

- By value the Epo market is €968m, twice as big as the daily growth factor market at €451m and of a comparable size to the growth hormone market at €842m.

- Each therapy utilises a different mix of product type:
  - Biosimilars make up 12% of the Epo market by volume, 7% of the Growth Hormone market and 18% of the G-CSF market, the most penetrated market.
  - The Epo and Growth Hormone markets have 42% and 44% of their markets made up of non-reference products on a volume basis. Where are the G-CSF market has 56% of volume sales made up of non reference product.
ITA is the largest biosimilar accessible market in Europe by volume and FRA the largest by value.

Source: IMS MIDAS Q6 2011 Note: * IMS data covers the retail channel only
On a per capita basis: FRE and ITA have the highest consumption rates, some smaller markets SWE, AUS, BEL, ROM and SLV have high usage by comparison with other European countries.

Source: IMS MIDAS Q6 2011 Note: * IMS data covers the retail channel only
GER is the highest volume and value market for biosimilars followed by FRA.

**Biosimilar Market Europe, Volume, DDD**

**Biosimilar Market, Europe, Value, €**

Source: IMS MIDAS Q6 2011 Note: * IMS data covers the retail channel only
GRE, SWE and AUS have a higher consumption per capita of biosimilar products than GER, UK is notably low along with several small European markets.

Source: IMS MIDAS Q6 2011 Note: * IMS data covers the retail channel only
The penetration of biosimilars into the Epo. market varies by country, the highest is GRE* with penetration of 54%.

Source: IMS MIDAS Q6 2011 Note: * IMS data covers the retail channel only
GER, GRE, NOR, SWE and AUS are where Epo biosimilar penetration exceeds 20% MAT to M6 2011

Biosimilar Share > 20% of accessible market MAT to M6 2011

Biosimilar Share <20%, MAT to M6 2011

Source: IMS MIDAS Q6 2011 Note: * IMS data covers the retail channel only
H. Growth hormone biosimilars have a mixed penetration across Europe the highest is in Poland with 17% share by value.
Growth hormone biosimilars first launched in GER in Q6 2006 the rate of uptake has been slow relative to the other biosimilar markets.
Daily growth factor biosimilar penetrations are higher than the Epo market, CEE countries have a notably high penetration.

Source: IMS MIDAS Q6 2011 Note: * IMS data covers the retail channel only
Daily growth factor biosimilars first launched in the UK and GER in Q12 2008 most countries have seen a rapid uptake

**Biosimilar Share > 20% of accessible market in Q6 2011**

**Biosimilar market share uptake, %**

**Biosimilar Share <20% in Q6 2011**

**Biosimilar market share uptake, %**

Source: IMS MIDAS Q6 2011 Note: * IMS data covers the retail channel only
Conclusions national analysis (1) Market size and rank

• Total biosimilar accessible market
  – Italy is the largest biosimilar accessible market in Europe by volume, followed by France, Germany, Italy and Spain, representing 72% of the total European market combined.
  – Consumption patterns vary, Italy and France have the highest consumption per capita rates in the biosimilar accessible market.
  – A number of smaller markets; Romania, Slovenia, Spain, Sweden, Denmark, Belgium and Austria also have high consumption per capita rates.

• Biosimilar market
  – Germany is the largest volume market followed by France, Italy, Spain Romania Sweden and Greece.
  – On a per capita basis Austria, Greece, Germany and Sweden are notably high users of biosimilar products.
Conclusions national analysis (2) Uptake

- **General**
  - Daily growth factor has the highest uptake rate of the three biosimilar therapy areas. On average, penetration in several countries is greater than 50% of the accessible market. By contrast uptake rates for growth hormone biosimilars are lower, where countries have a high penetration of growth hormone biosimilars penetration rates are in the 10-20% rage compared to >50% in the daily growth factor market.
  - For Epo, the uptake rate is most mixed. The biosimilar uptake rate for Epo in Germany and Poland is 45% and 48% respectively. Several countries, for example, Belgium and Denmark have no uptake but have relatively large biosimilar accessible markets.

- **Epo**
  - Germany, Greece, Poland, Sweden and Austria have relatively high uptake rates.
  - Denmark, Belgium, Switzerland, UK and Italy and other have no or very low uptake.

- **Daily growth factor**
  - Characterised by relatively high uptake rates for biosimilars relative to Epo and Growth hormone.

- **Growth hormone**
  - Characterised by low uptake rates relative to other biosimilar accessible markets.
  - Many countries in the EU have no sales of biosimilars at all.
As the size of the biosimilar accessible market decreases the number of products on the market decreases

**Count of biosimilar products with sales by country ranked by size of the current size of the biosimilar market**

14 the maximum number of biosimilar products counted in IMS data across the EU + No, CH

9 largest biosimilar accessible markets: average number of biosimilars 5.3

Next 9: average number of biosimilars 5.1

Smallest 9: markets average number of biosimilars 3

Source: IMS MIDAS Q6 2011 Note: * IMS data covers the retail channel only

NOTE: IMS defines products according to a specific classification. Please see appendix 1 for discussion of the product and market definitions.
Overall conclusion (1)

- The biosimilar accessible market is early in its life.
- There are three markets; Epo, Growth Hormone and G-CSF each has different volume, growth and clinical characteristics
- Differences between the three markets include
  - Different rates of biosimilar uptake at an aggregate European level
    - G-CSF has the highest volume penetration of biosimilars followed by Epo and Growth hormone
  - Non-referenced products, reference products and biosimilars have a different share of the biosimilar accessible market depending on the molecule
  - Nationally Epo has a very mixed uptake rate across Europe, daily growth factor has a relatively high penetration across many countries and Growth hormone is characterised by low biosimilar uptake rates
  - Smaller European markets are most likely to have fewer biosimilars launched than the large markets
End (appendices follow)

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Appendix 1

Market definitions
Market Definition: short acting Epo (Epoetin alpha, beta, theta, zeta)

NOTE: The market definition in this analysis is based on the EFPIA-EGA-EuropeBio definition of the biosimilar accessible market. Dynepo and Epokine are two products that have effectively been withdrawn from the market, Thy are not formally included in the FPPIA-EGA-EuropeBio definition of the biosimilar accessible market. IMS data show that both have very small residual sales in the period MAT to M6 2011, they have been included here for accuracy and so that data can be reconciled against other IMS data sources. IMS records very small sales for the product Epogen in Italy.

Biosimilars are not approved under an INN name. However, they occasionally appear with an INN description in IMS data. This is due to IMS data suppliers who do not supply the product names at source. The data is simply identified as a biosimilar IMS does not know exactly which product only that a biosimilar was supplied. Data presented in this way should not be misinterpreted; naming labels should not be erroneously counted to conclude how many biosimilars are present on the market. To identify how many products are marketed product registration information should be consulted.
Market Definition: Growth Hormone (somatropin)

NOTE: The market definition in this analysis is based on the EFPIA-EGA-EuropeBio definition of the biosimilar accessible market. The product Maxomat is not formally included in the FP1A-EGA-EuropeBio definition of the biosimilar accessible market. IMS data show Maxomat to have very small sales in the period MAT to M6 2011, it has been included here for accuracy and so that data can be reconciled against other IMS data sources. Ihumatrope has technically been referenced by a biosimilar product but that biosimilar product is yet to launch.

Biosimilars are not approved under an INN name. However, they occasionally appear with an INN description in IMS data. This is due to IMS data suppliers who do not supply the product names at source. The data is simply identified as a biosimilar IMS does not know exactly which product only that a biosimilar was supplied. Data presented in this way should not be misinterpreted; naming labels should not be erroneously counted to conclude how many biosimilars are present on the market. To identify how many products are marketed product registration information should be consulted.