Global Biosimilar Drugs Market
Outlooks

Specific focus on the French market
(2017 forecasts)

February 2015
Introduction

This document presents an analysis of the current state of the biosimilar market as well as its perspectives of evolution, with a particular focus on the French market.

Context & objective of the report

- With the recent patent expiry of several key biologic products, such as Remicade, MabThera\(^1\), Herceptin or Lovenox, biosimilars are often heralded as the next big opportunity for biopharmaceutical companies.
- The first biosimilars of Remicade are expected to be launched in February 2015.
- However, biosimilars presently account for only 1% of the biologics market at a global level and their growth remains highly dependent on a number of factors:
  - The date of patent expiry of biologics
  - Their level of sales (addressable market)
  - The general biosimilar regulation (interchangeability and substitution policies) and guidelines for each class of biosimilar products
- In addition, the profitability of biosimilars remains uncertain: although the required investments in development and manufacturing are well known, there is a common lack of visibility on biosimilars’ acceptance by authorities, physicians and patients.
- In this context, Smart Pharma Consulting has reviewed and analyzed the specificities of the biosimilar market to help stakeholders better understand its key success factors and has estimated the perspectives of evolution of the French market over the 2015-2017 period.

\(^1\) Also named Rituxan.
The variability of biopharmaceuticals and biosimilars is greater than that typically observed for chemical drugs

### Differences between generics and biosimilars

<table>
<thead>
<tr>
<th>Composition</th>
<th>Generics</th>
<th>Biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Generics have <strong>simple chemical structures</strong> and are considered to be <strong>identical</strong> to their <strong>reference medicines</strong></td>
<td>Biosimilars and biopharmaceuticals are inherently <strong>variable</strong> due to the fact that they are <strong>produced</strong> from living organisms</td>
</tr>
<tr>
<td>Substitution</td>
<td><strong>Authorized</strong> and <strong>encouraged</strong> by health authorities of most countries</td>
<td><strong>Not formally authorized in most countries</strong> (exception of countries like Bulgaria and France(^1)) but physicians are allowed to interchange biopharmaceuticals with biosimilars and vice versa</td>
</tr>
<tr>
<td>Indications</td>
<td>Always the <strong>same as the originator’s</strong></td>
<td><strong>Same as the originator’s only when sufficient evidence</strong> have been <strong>provided</strong></td>
</tr>
<tr>
<td>European Marketing authorization</td>
<td><strong>Abridged procedure</strong> with simplified dossier reproducing original brand’s clinical outcome</td>
<td><strong>Full clinical dossier</strong> (excluding Phase 2 studies) <strong>centralized procedure</strong></td>
</tr>
<tr>
<td>USA Marketing authorization</td>
<td><strong>Abbreviated new drug application</strong></td>
<td><strong>Analytical, animal and clinical studies</strong></td>
</tr>
</tbody>
</table>

Sources: Smart Pharma Consulting Analyses

\(^1\) Substitution of an original biological medicine by a biosimilar is possible only at the time of initiation
Drug development process

It takes much longer to develop a biosimilar drug than a generic drug and the probability of success is much lower

Biosimilar development

Comments

- **Biosimilars** are significantly more expensive to develop than generics
- On average, it takes **three times longer to develop a biosimilar medicine** compared with a generic (7.5 years vs. 2.5 years)
- Biosimilars take much longer to develop because of the **intricate regulatory approval process** and the **stringent evidence requirements** (i.e. proofs of quality, efficacy and safety)
- **Clinical studies with ~500 patients** are required for biosimilars
- The **probability of success** of biosimilars development programs is usually around 50-75% while it is around 90% for generics programs

Sources: Sandoz – Teva – Lonza – Smart Pharma Consulting Analyses

\(^1\) Plant costs are estimated at USD 150 M to USD 200 M
Drug development process

USA and Europe remain the most dynamic regions in terms of biologics manufacturing but “bio-clusters” are emerging in Asia

Sources: BioPlan’s Top 1000 Global Biopharmaceutical Facilities Index, August 2014

Global Biosimilar Drugs Market Outlooks

February 2015
Registration guidelines

In Europe, the EMA and, above all, its expert committee – the CHMP – are the authorities in charge of evaluating and authorizing potential biosimilar drugs

Biosimilar drug registration in Europe

- Biosimilar medicines are assessed by the European Medicines Agency (EMA), which constitutes the scientific body of the European Commission responsible for the evaluation of medicines

- Afterwards, they are approved by the European Commission based on the positive scientific opinion issued by the EMA and its main expert committee, the Committee on Human Medicinal Products (CHMP)

- Unlike generics, biosimilars cannot benefit from the abridged procedure with mere bioequivalence studies to obtain a marketing authorization, but require a full clinical dossier:
  - Biosimilarity should be established at all levels (quality, safety and efficacy) using a reference medicinal product authorized in the Community on the basis of a complete dossier
  - The active substance should be similar to the reference medicinal product in molecular and biological terms
  - The pharmaceutical form, strength and route of administration should be the same as for the reference product
  - The specific medicinal product given to the patient should be identified in order to support drug monitoring

- The CHMP released “final regulatory guidelines” for G-CSF (granulocyte-colony stimulating factors), LMWH (low-molecular-weight heparins), IFN-β (interferon β), ESA (erythropoiesis stimulating agents), somatropin, mAbs (monoclonal antibodies) and recombinant human follicle-stimulating hormones (r-hFSH)

Sources: European Medicines Agency “Guideline on similar biological medicinal products (CHMP / 437 / 04)” – Smart Pharma Consulting
Biosimilars must be closely monitored after their approval, thus entailing higher drug monitoring costs and risks compared to generics

**Drug monitoring and risk management of biosimilars in Europe**

- The different production and purification processes of biosimilars vs. reference drugs can have important implications on their safety profile.

- Biosimilars may exhibit a different safety profile in terms of nature, seriousness or incidence of adverse reactions.

- The most critical safety concern relating to biosimilars, as well as other biologicals, is immunogenicity.

- In the European Union, biosimilars have the same drug monitoring requirements as their reference products; therefore, they have to submit a risk management plan (RMP) as part of their marketing application as well as safety update reports on a regular basis after approval.

- In the European Union, the marketing authorization for a biosimilar can also require post-authorization safety and efficacy studies.

**Risk Management Plan (RMP)**

- Safety specification
  - Epidemiology of the indication and target population
  - Non-clinical part of the safety specification
  - Clinical trial exposure
  - Populations not studied in clinical trials
  - Post-authorisation experience
  - Additional EU requirements for the safety specification
  - Identified and potential risks

- Plans for post-authorisation efficacy studies

- Pharmacovigilance plan

- Risk minimisation measures

The RMP should provide a detailed description of the drug monitoring system, and, where appropriate, of the risk management system that the applicant will put in place.

---

**Sources:**

- GVP Risk Management Systems. EMA (April 2014)
Registration guidelines

16 Member States of the European Union (and two other European countries) follow strict rules against automatic substitution by retail pharmacists

**Position of European countries regarding biosimilars substitution**

Croatia, Ireland, Finland, Hungary, Malta, **Norway¹**, Romania, Sweden

→ **Law against automatic substitution**

Belgium, Croatia, Denmark, Germany, Greece, Italy, The Netherlands, United Kingdom, Slovakia, **Switzerland¹**

→ **Guideline prohibits automatic substitution**

France → **Pharmacists are authorized to substitute an original biological product by its biosimilar provided it is an initial prescription and the prescriber is informed by phone** (decree to be published circa 2015)

Austria, Czech Republic, Lithuania, Portugal, **Serbia¹**

→ **No specific regulation / no specific guideline / insufficient information**

Bulgaria², Cyprus, Estonia, Latvia, Poland

→ **No law / guidance but automatic substitution happening**

Sources: “EBE Biosimilars Webinar on French Biosimilars Law” (February 2014), European Biopharmaceutical Enterprises – HAS

¹ Not part of the European Union –

² No interdiction but no promotion from authorities; in practice, pharmacists do not substitute
Registration guidelines

The guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues – is more detailed than other guidelines

**EMA Guidelines: Monoclonal antibodies (mAbs)**

| Draft agreed by Biosimilar Medicinal Products Working Party (BMWP) | October 2010 |
| Adoption by the Committee for medicinal products for human use (CHMP) for release for consultation | November 18th, 2010 |
| End of consultation (deadline for comments) | May 31st, 2011 |
| Agreed by BMWP | March 2012 |
| Adoption by CHMP | May 30th, 2012 |
| Date for coming into effect | December 1st, 2012 |

**Summary**

This guideline has been drafted with several “steps”:

- **Non clinical studies**
  - **Step 1: In vitro studies**, that “should be performed with an appropriate number of batches of product representative and should include relevant assays”
  - **Step 2: Determination of the need for non clinical in vivo studies**, “provided that a relevant in vivo model with regard to species or design is available”
  - **Step 3: In vivo studies**

- **Clinical studies**: “The number and type of studies might vary according to the reference product and should be justified based on a sound scientific rationale”
  - **Step 1: Pharmacokinetics (PK)** → This steps requires a study design, depending on safety, the PK characteristics of the antibody, etc. and sampling times
  - The guidelines also stresses on PK parameters of interest and on the timing of the PK evaluation
  - **Pharmacodynamics (PD)** using multiple PD markers as support to establish comparability and as pivotal proof of comparability
  - **Step 2: Clinical efficacy** → similar clinical efficacy between the similar and the reference product should be demonstrated in adequately powered, randomized, parallel group comparative clinical trial(s), preferably double-blind, normally equivalence trials
  - **Clinical Safety studies** are required, especially on immunogenicity

- A risk management plan/pharmacovigilance plan should also be presented
- Extrapolation of indications may be possible

---

Sources: “Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues”, EMA, May 30th, 2012

---

Global Biosimilar Drugs Market Outlooks

February 2015

Smart Pharma Consulting
Market access process

In France, the CEPS is in charge of setting biosimilars price; the probability of a reference price for biosimilars and the original biologic brand is low, by end of 2017

Market access considerations in France

**Pharma company**
- Dossier submission following marketing authorization granted by the ANSM (Drug Agency)\(^1\)

**Haute autorité de santé (HAS)**
- Provides recommendations of usage for medical products

**Economic committee for healthcare products (CEESP)**
- Responsibility for medico-economic assessment since October 2013…
- … for innovative/expensive drugs only

**Transparency commission (CT)**
- CT assesses clinical benefits of the drug vs. existing comparators
- Responsible for setting reimbursement rates

**Ministry of social affairs & health (MoH)**

**CEPS**
- Responsible for setting prices for reimbursable products, reference price list (TFR) for generics and hospital price list outside the fee-for-service payment scheme
- Gives a technical advice to the MoH, which will determine if the new drug will be added to a positive reimbursement list

Source: FirstWord 2013 – IMS – Smart Pharma Consulting Analyses

\(^1\) Under the responsibility of the ministry of health
The situation regarding the attitudes of key stakeholders towards biosimilars varies across the five major European markets

### Stakeholders attitudes towards biosimilars in the EU5

<table>
<thead>
<tr>
<th>Adoption of biosimilars</th>
<th>Authorities</th>
<th>Hospitals</th>
<th>Physicians</th>
</tr>
</thead>
</table>
| **High**                | - Government actively encourages biosimilars  
- Regional prescription quotas requirements | - Hospitals are driven to use biologicals by cost reduction policies, regional authority pressures and contracts with health insurance funds | - Favorable view of biosimilars |
| **Medium**              | - Biosimilars are classified as hospital-only medicines  
- ‘Patents of use’ can keep certain indications protected | - Biosimilars are generally welcomed by the hospital pharmacotherapeutic committees | - Prescribing decisions depend on physicians  
- No incentives to prescribe biosimilars |
| **Medium**              | - Government encourages biosimilars by allowing pharmacists to substitute a biosimilar when a new original biologic drug is initiated | - Due to financial constraints, hospitals have an incentive to buy biosimilars rather than originators (especially for hospital-only drugs) | - Physicians are not obliged nor incentivized to prescribe biosimilars |
| **Medium**              | - NICE issued positive recommendations towards biosimilars  
- The product choice is mostly based on price | - Trusts purchase medicines in tenders where price makes 50% in the equation, which should be favorable to biosimilars | - 95% of physicians are public employees of the NHS, and thus prescribe according to NICE requirements |
| **Low**                 | - No specific measure to ensure biosimilars penetration  
- Long and complex price and reimbursement process | - Hospitals are not incentivized to prescribe biosimilars | - Prescribing decisions depend on physicians, who have close relationships with originator companies |

Sources: NICE – AGEPS – AIFA – GABionline.net – Assessing biosimilar uptake and competition in European markets, IMS – Smart Pharma Consulting Analyses

1 Patents covering the use in specific indications (the most recent ones) of a drug, whose patent has expired for other indications  
2 The substitution right should be officially granted in 2015  
3 National Institute for Clinical Excellence  
4 National Health Service
In February 2015, 19 biosimilars were approved in Europe and one was waiting for an approval.

**Authorized biosimilar drugs in Europe**

<table>
<thead>
<tr>
<th>Therapeutic classes / Category</th>
<th>Date of authorization</th>
<th>Status</th>
<th>Product name</th>
<th>Company</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Growth hormones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12/04/2006</td>
<td>Authorized</td>
<td>Omnitrope (somatropin)</td>
<td>Sandoz</td>
<td>Pituitary dwarfism, Prader-Willi syndrome, Turner syndrome</td>
</tr>
<tr>
<td></td>
<td>24/04/2006</td>
<td>Withdrawn</td>
<td>Valtropin (somatropin)</td>
<td>Biopartners</td>
<td>Pituitary dwarfism, Turner syndrome</td>
</tr>
<tr>
<td><strong>Erythropoiesis stimulating agents</strong> (ESA)</td>
<td>28/08/2007</td>
<td>Authorized</td>
<td>Epoetin Alfa Hexal (epoetin alfa)</td>
<td>Hexal</td>
<td>Anemia, cancer, chronic kidney failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Authorized</td>
<td>Abseamed (epoetin alfa)</td>
<td>Medice</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Authorized</td>
<td>Binocrit (epoetin alfa)</td>
<td>Sandoz</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18/12/2007</td>
<td>Authorized</td>
<td>Retacrit (epoetin alfa)</td>
<td>Hospira</td>
<td>Anemia, autologous blood transfusion, cancer, chronic kidney failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Authorized</td>
<td>Silapo (epoetin zeta)</td>
<td>Stada</td>
<td></td>
</tr>
<tr>
<td><strong>Granulocyte-colony stimulating factors</strong> (G-CSF)</td>
<td>15/09/2008</td>
<td>Authorized</td>
<td>Ratiograsit1 (filgrastim)</td>
<td>Teva Pharma</td>
<td>Cancer, hematopoietic stem cell transplantation, neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Authorized</td>
<td>Tevagrasit (filgrastim)</td>
<td>Teva Pharma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawn</td>
<td>Filgrastim ratiopharm1,2 (filgrastim)</td>
<td>Teva Pharma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Authorized</td>
<td>Biograsit (filgrastim)</td>
<td>CT Arzneimittel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>06/02/2009</td>
<td>Authorized</td>
<td>Filgrastim Hexal (filgrastim)</td>
<td>Hexal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>08/06/2010</td>
<td>Authorized</td>
<td>Nivestim (filgrastim)</td>
<td>Hospira</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18/10/2013</td>
<td>Authorized</td>
<td>Grastofit (filgrastim)</td>
<td>Stada</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18/09/2014</td>
<td>Authorized</td>
<td>Accofit (filgrastim)</td>
<td>Accord Healthcare</td>
<td></td>
</tr>
<tr>
<td><strong>Anti TNF (monoclonal antibodies)</strong></td>
<td>10/09/2013</td>
<td>Authorized</td>
<td>Remsima (infliximab)</td>
<td>Celltrion</td>
<td>Arthritis, psoriatic arthritis, rheumatoid colitis, ulcerative crohn disease, psoriasis, ankylosing spondylitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Authorized</td>
<td>Inflectra (infliximab)</td>
<td>Hospira</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>SB4 (etanercept)</td>
<td>Amgen</td>
<td>Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, non-radiographic axial spondyloarthritis</td>
</tr>
<tr>
<td><strong>Recombinant human follicle-stimulating hormones</strong></td>
<td>27/09/2013</td>
<td>Authorized</td>
<td>Ovaleap (follitropin alfa)</td>
<td>Teva Pharma</td>
<td>Anovulation</td>
</tr>
<tr>
<td>(r-hFSH)</td>
<td>27/03/2014</td>
<td>Authorized</td>
<td>Bemfola (follitropin alfa)</td>
<td>Finox</td>
<td></td>
</tr>
<tr>
<td><strong>Insulins</strong></td>
<td>09/09/2014</td>
<td>Authorized</td>
<td>Abasaglar3 (insulin glargine)</td>
<td>Eli Lilly/Boehringer Ingelheim</td>
<td>Insulin glargine injection, which is indicated to improve glycemic control in adults with type 2 diabetes and in combination with mealtime insulin in adults and pediatric patients with type 1 diabetes</td>
</tr>
</tbody>
</table>

6 therapeutic areas

19 authorized drugs

Note: The epoetin zeta, Retacrit and Silapo are biosimilars of the reference product Eprex (epoetin alpha). The epoetin theta, Eporatio, launched by Ratiopharm is a “me-too” product, developed independently of any reference drug.

Sources: European Medicines Agency – FDA – Smart Pharma Consulting Analyses

1 Formerly owned by Ratiopharm, which was later acquired by Teva in March 2010 – 2 Product withdrawn – 3 Previously named Abasaria
Biosimilars penetration in volume is still low in most European countries but is growing faster every year

Biosimilar penetration in selected European countries (2013)

% of Treatment days

Epoetin  Filgrastim  Somatropin

0 10 20 30 40 50 60 70 80 90 100

Austria  Belgium  Bulgaria  Denmark  Finland  France  Germany  Hungary  Ireland  Italy  Norway  Spain  Sweden  Switzerland  UK

Comments

- Market shares for biosimilars are calculated as a percentage of treatment days or DDD (defined daily dose) in each product class.
- Product classes include biosimilars and originator products as well as me-too pharmaceuticals (second generation products are excluded).
- Biosimilar sales (in DDDs) are still a relatively small segment of the EU pharmaceutical market, but have strong annual growth.
- Uptake for epoetin biosimilars was highest in Bulgaria, Germany, Norway and Sweden.
- Market shares of filgrastim biosimilars are very high in Bulgaria, Hungary, Norway and Sweden.
- The uptake of somatropin biosimilar is generally lower than for filgrastim and epoetin. This may be related to the fact that somatropin is used for growth-hormone-related illness requiring long-term treatment whereas medicines containing epoetin and filgrastim are used for short-term treatments.
- The highest uptake for somatropin biosimilars was found in Denmark, Spain, Sweden and France.

Sources: “Assessing biosimilar uptake and competition in European markets”, IMS Health, October 2014
The biosimilar market is expected to grow significantly, driven by patent expiries and measures introduced by governments and payers, but its size will still remain limited.


<table>
<thead>
<tr>
<th>Reference Biotech drugs</th>
<th>Biosimilars</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 (99%)</td>
<td>12</td>
<td>222</td>
</tr>
<tr>
<td>210 (95%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>222</td>
<td>+5%</td>
<td></td>
</tr>
<tr>
<td>182</td>
<td>+57%</td>
<td></td>
</tr>
<tr>
<td>2 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Drivers**
- **Cost pressure** exacerbated by ageing population, economic slump and reduced savings from generics might favor biosimilars
- **Patent expirations** of top biological drugs (within five years: MabThera, Herceptin, Erbitux, Remicade, Enbrel, Neulasta, Synagis, Aranesp and Humira) will increase potential market size
- Limited budgets in pharmerging markets will favor biosimilars as cheaper and cost-effective alternatives to original biotech drugs

**Barriers**
- **Uncertainty of regulatory frameworks** might keep investors from betting on biosimilars
- **Lack of experience and biosimilar guidelines** might slow down the uptake of biosimilars by prescribers
- **Low price reduction** might limit biosimilars (i.e. ~25% in Europe and ~35% in the USA)
- **Enhanced defense strategies of patents**
- **High development cost** and **manufacturing costs** induced by specific manufacturing plants to be set up (USD 200 M to USD 300 M)

---

**Sources:**

¹ Compound annual growth rate – ² Also named Rituxan
Current and potential market

In the next years, the biotech segment will experience its own patent cliff as 13 original products that generated USD 73 billion in 2013 will face patent expiration

Top biologic patent expirations

<table>
<thead>
<tr>
<th>Product</th>
<th>Global Sales (FY 2013), USD billion</th>
<th>EU Expiry Date</th>
<th>US Expiry Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>11.0</td>
<td>2018</td>
<td>2016</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>8.8</td>
<td>2015</td>
<td>2028 (extended)</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>8.4</td>
<td>2015</td>
<td>2018</td>
</tr>
<tr>
<td>Insulin glargine (Lantus)</td>
<td>7.6</td>
<td>Expired</td>
<td>Expired</td>
</tr>
<tr>
<td>Rituximab (Mabthera)</td>
<td>7.5</td>
<td>Expired</td>
<td>2016</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>6.7</td>
<td>2019</td>
<td>2017</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>6.6</td>
<td>Expired</td>
<td>2019</td>
</tr>
<tr>
<td>Pegfilgrastim (Neulasta)</td>
<td>4.4</td>
<td>2015</td>
<td>Expired</td>
</tr>
<tr>
<td>Ranibizumab (Lucentis)</td>
<td>4.2</td>
<td>2016</td>
<td>2016</td>
</tr>
<tr>
<td>Interferon Beta-1A (Avonex, Rebif)</td>
<td>3.0</td>
<td>Expired</td>
<td>Expired</td>
</tr>
<tr>
<td>Insulin aspart (Novomix, Novorapid)</td>
<td>3.0</td>
<td>2015</td>
<td>2015</td>
</tr>
<tr>
<td>Palivizumab (Synagis)</td>
<td>1.1</td>
<td>Expired</td>
<td>2016</td>
</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>0.9</td>
<td>2015</td>
<td>2015</td>
</tr>
</tbody>
</table>

Comments

- These 13 listed compounds represented ~40 percent of the global biologic market and included such blockbuster brands as Humira, Enbrel, Remicade and Lantus

- This represents an opportunity for manufacturers of original biologics and of biosimilars

- Indeed, the first two biosimilars for infliximab (original brand: Remicade), were approved as Inflectra/Remsima by the EMA in September 2013 and have started to be launched in Europe in February 2015

Biosimilar market players

Sandoz was the sales leader in 2013, with products in each of the therapeutic classes that were existing until biosimilars of infliximab entered the market, early 2015

Current biosimilar players in highly regulated markets¹

Market share in highly regulated markets¹ (2013)

- **Sandoz** is the **global leader in biosimilars** with **three marketed products** in highly regulated markets (Omnitrope, Binocrit and Zarzio) and over 50% market share

- **Teva** accounts for **one sixth of the market** with currently **two products** in the G-CSF² therapeutic class (i.e. Ratiograsit, Tevagratstim in Europe) and **one** in the ESA³ therapeutic class (i.e. Eporatio which is an epoetin theta, and not developed as a biosimilar per se. It is rather a “me-too” product with a distinct clinical development). End of 2013, Teva has launched in the USA, Granix (Tbo-filgrastim), which is not considered as biosimilar a per se but as a “follow-on” proteins

- **Hospira**, which was acquired by Pfizer in February 2015, is the **third largest player** with products in **three therapeutic classes** (i.e. Retacrit in the ESA therapeutic class, Nivestim in the G-CSF class and Inflectra in the monoclonal antibody class, which is a biosimilar of infliximab)

- The “**Others**” category includes **smaller competitors** such as Medice, Stada, Biopartners, etc.

Sources: Sandoz analysis – External interviews – IMS

¹ North America, Europe, Japan and Australia – ² Granulocyte-colony stimulating factors – ³ Erythropoiesis stimulating agents

Global Biosimilar Drugs Market Outlooks 16 February 2015
Biosimilar market players

Six different profiles of players can be identified in the biosimilar market, on the basis of their level of innovativeness and biological capabilities

Segmentation of players in the biosimilar market

<table>
<thead>
<tr>
<th>Innovativeness</th>
<th>Biological capabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Big pharmas (e.g. Boehringer Ingelheim, Pfizer, Merck &amp; Co.)</td>
</tr>
<tr>
<td></td>
<td>Biotech (e.g. Amgen, Biogen Idec)</td>
</tr>
<tr>
<td>-</td>
<td>Technology and electronic conglomerates (e.g. LG, Samsung Biologics)</td>
</tr>
<tr>
<td></td>
<td>Service providers (e.g. Quintiles, Parexel, Celltrion)</td>
</tr>
<tr>
<td>1</td>
<td>Generics companies from developed countries (e.g. Sandoz¹, Teva, Stada, Hospira)</td>
</tr>
<tr>
<td>2</td>
<td>Generics companies from emerging countries (e.g. Biocon, Dr. Reddy's)</td>
</tr>
</tbody>
</table>

Sources: Smart Pharma Consulting

¹ Sandoz is the generics and biosimilars subsidiary of Novartis, but managed in a rather independent way
Biosimilar market players

Sandoz is the leading player in the biosimilar market in which it benefits from the resources and capabilities of Novartis

Sandoz

Sales (2014)

<table>
<thead>
<tr>
<th></th>
<th>Biosimilars</th>
<th>Sandoz</th>
<th>Novartis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sales (in M USD)</td>
<td>0.514</td>
<td>9,562</td>
<td>54,996</td>
</tr>
<tr>
<td>Growth (%)</td>
<td>5.4%</td>
<td>0.9%</td>
<td>-</td>
</tr>
</tbody>
</table>

Biosimilar ambitions

- Sandoz has been developing biosimilars since 1996
- The company aims to remain the global leader with three in-market products, a broad pipeline, and extensive capabilities

Marketed products

- Filgrastim: Filed (USA), Authorized in Japan
- Pegfilgrastim: Phase III completed for global registration, Filing in preparation
- Rituximab: Phase III ongoing for follicular lymphoma, Phase II ongoing for rheumatoid arthritis
- Adalimumab: Phase III ongoing
- Epoetin alfa: Phase III in subcutaneous use in nephrology indication / Phase III (USA & EU), patient enrolment completed
- Etanercept: Phase III patient enrolment completed

Acquisitions & Partnerships

- No significant acquisition, but Sandoz benefits from its unique position within the Novartis Group through:
  - Novartis modeling & simulation capabilities to develop innovative study design
  - Novartis clinical network & resources to enhance study execution
  - Strong commercial synergies with Novartis Pharma leading commercialization in selected markets and providing support for government affairs and market access

Sources: Biosimilars by Sandoz, Capturing the future opportunity – Novartis AG 2015, January 2015 – Smart Pharma Consulting Analyses

¹ Known pipeline as of February 2015

Global Biosimilar Drugs Market Outlooks

February 2015
The substitution right in the French retail pharmacies should apply soon to biosimilar drugs, but a decree is to be published circa 2015

The four status of “copies” in France

<table>
<thead>
<tr>
<th>Generics</th>
<th>Quasi-Generics</th>
<th>Essentially similar drugs</th>
<th>Biosimilar drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td><strong>Description</strong></td>
<td><strong>Description</strong></td>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Abridged procedure with simplified dossier reproducing original brand’s clinical outcome</td>
<td>Same as for generics Necessity to respect the modified form of the originator (i.e. prolonged, delayed or sequential)</td>
<td>Minimal clinical development to document safety/efficacy profile (e.g. with specific device used)</td>
<td>Complete clinical development (excluding phase 2 studies)</td>
</tr>
<tr>
<td><strong>Market approval requirements</strong></td>
<td><strong>Market approval requirements</strong></td>
<td><strong>Market approval requirements</strong></td>
<td><strong>Market approval requirements</strong></td>
</tr>
<tr>
<td>Copies of synthetic drugs Bioequivalence has been proven</td>
<td>Copies of oral modified release form drugs Bioequivalence (has not or) cannot be proven</td>
<td>Copies of synthetic drugs Bioequivalence (has not or) cannot be proven</td>
<td>Copies of biotech products Bioequivalence cannot be proven</td>
</tr>
<tr>
<td><strong>Substitution</strong></td>
<td><strong>Substitution</strong></td>
<td><strong>Substitution</strong></td>
<td><strong>Substitution</strong></td>
</tr>
<tr>
<td>Allowed</td>
<td>Allowed</td>
<td>To be allowed, circa 2015, only at treatment initiation²</td>
<td>To be allowed, circa 2015, only at treatment initiation</td>
</tr>
<tr>
<td>Examples of originators</td>
<td>Examples of originators</td>
<td>Examples of originators</td>
<td>Examples of originators</td>
</tr>
<tr>
<td>MOPRAL (Omeprazole)</td>
<td>INEXIUM (Esomeprazole)</td>
<td>TANAKAN (Gingko biloba)</td>
<td>EPREX (Epoetin alpha)</td>
</tr>
</tbody>
</table>

Sources: Legifrance – LFSS 2014 – Smart Pharma Consulting Analyses

¹ Substitution vs. original brand, generics and other essentially similar/biosimilar drugs, in retail pharmacies – ² For anti-asthmatic drugs only
Sales of biosimilars, which were launched in 2007, currently pertain to three therapeutic classes, and reached a total € 80 million on the retail market in 2014.

Global Biosimilar Drugs Market Outlooks

Sources: GERS retail – Smart Pharma Consulting analyses

1 Ex factory prices – 2 Compound annual growth rate – 3 Eporatio is not a biosimilar per se but is rather a “me-too” product. It was first launched by Ratiopharm, before to be acquired by Teva in March 2010.
The potential sales of biosimilars will depend on three key determinants: the addressable market size, the biosimilar penetration and their price.

**Determinants to biosimilar sales forecasts**

<table>
<thead>
<tr>
<th><strong>Addressable market size</strong></th>
<th><strong>Biosimilar penetration</strong></th>
<th><strong>Biosimilar price</strong></th>
</tr>
</thead>
</table>
| Hospital and retail prescribing trends of the addressable market including:  
  - The reference product (e.g. Neupogen)  
  - Original “me-toos” (e.g. Granocyte)  
  - Bio-betters (e.g. Neulasta)  
| Prescribers and patients safety and efficacy concerns  
  - Authorization of interchangeability and/or substitutability  
  - Extrapolation of indications based on overall evidence of biosimilarity  
  - Incentive schemes or coercive measures implemented by health authorities/payers to stimulate biosimilar prescription by physicians, acceptance by patients and/or substitution by pharmacists | Authorities/payers’ pricing mechanism regarding the price of biosimilars and of their reference product:  
  - Free pricing (e.g. tenders)  
  - Fixed price difference (e.g. -30%, -50%)  
  - Reference price per INN\(^1\) (e.g. for all filgrastim)  
  - Reference price per therapeutic class (e.g. for all G-CSF, including peg-filgrastim, lenograstim)  
  which might be influenced by the number of biosimilars competing |
| Application for, and authorization of, additional indications for current originator products  
  - Reimbursement policies of biologics  
  - Price evolution of innovative biologics |  

---

\(^1\) International Non proprietary Name

**Sources:** Smart Pharma Consulting Analyses

---

**Smart Pharma Consulting**

---

**Global Biosimilar Drugs Market Outlooks**

**February 2015**
Biosimilars’ penetration rate and value are expected to increase in all scenarios, even if the impact of reference price (scenario #3) would limit the growth in the retail market.

Biosimilar market sales forecast (value) – Hospital and retail markets

### 2017 (three scenarios)

<table>
<thead>
<tr>
<th></th>
<th>Hospital Sales (M€)</th>
<th>Retail Sales (M€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario #1 “Progressive”</td>
<td>1,771</td>
<td>898</td>
</tr>
<tr>
<td>Scenario #2 “Dynamic”</td>
<td>1,723</td>
<td>868</td>
</tr>
<tr>
<td>Scenario #3 “Disruptive”</td>
<td>1,694</td>
<td>876</td>
</tr>
</tbody>
</table>

### Sources:
- GERS retail – Smart Pharma Consulting analysis

**Note:** Hospital sales include discounts
Conclusion

- The **biosimilar market** is far **more risky** than the **generic market**, due to:
  - Higher investment required in R&D, manufacturing facilities, medical, marketing and sales activities
  - Lower probability to obtain a Marketing Authorization (MA)
- The **companies most likely to succeed** in the biosimilar market are those that can **combine biotech expertise with specific sales and marketing capabilities**, either alone or through partnerships
- With the **need for biosimilars to be promoted** directly to **prescribers, reputation** will matter considerably so that **big pharma companies will benefit from their higher profile**
- **Big pharma already involved in biotech**, like Amgen or Biogen Idec, may optimize their business by taking advantage of their technological platforms to develop "bio-betters":
  - Bio-betters differ from biosimilars in that they provide some advantages to the existing product
  - The improvement can be linked to changes in chemistry, alterations in formulation or innovative delivery method (e.g. Neulasta is a pegylated version of Neupogen, the latter compete directly with filgrastim biosimilars)
  - Bio-betters being an optimized version of an existing reference biological medicine, they involve higher development risk than biosimilars and same registration requirements, but they are both less risky and less costly to bring to market
  - Bio-betters compete on value more than on price and therefore are more successful on developed markets (e.g. USA, Europe) than on emerging markets (e.g. India, China, Mexico, etc.)
- The **future growth of biosimilars** will depend on **health authorities’ decisions** and **payers’ pressure** to encourage their use in the **major market across the world**
# Core capabilities

## 1 Strategy
- **Assessing the attractiveness of markets** (Hospital / retail innovative products - Vaccines - OTC - Generics)
- **Growth strategy**
  - Optimization of marketing / sales investments
  - Development of a company in the hospital market
    
  - Valuation for acquisition
  - Portfolio / franchise assessment
- **Extension of product life cycle performance**
  - Improvement mature products performance
  - Adaptation of price strategy
- **Defense strategies vs. new entrants**
- **Competitive strategies in the hospital market**
- **Strategic partnerships companies / pharmacies**

## 2 Management
- **Facilitation and structuring of strategic thinking for multidisciplinary product teams**
  - Key challenges identification
  - Strategic options formalization
  - Resource allocation optimization program
- **Training of marketing and market research teams to sales forecast techniques (modeling and scenarios development)**
- **Development and implementation of a "coaching program" for area managers**
  - Sales reps coaching
  - Regional action plans roll-out
- **Development and implementation of a "sales techniques program" for sales forces (STAR\(^1\))**

\(^1\) *Sales Techniques Application for Results* (training course)

## 3 Organization
- **Rethink of operational units organization**
- **Improvement of sales force effectiveness**
- **Improvement of the distribution channels covering the hospital and retail markets**
- **Development of a strategic planning process**