What future for biosimilar drugs?

Specific focus on the French market (2013-2016 forecasts)

- Short Version -

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1. Introduction

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

Context & objective of the report

- **With the approaching patent expiry of several key biologic products, such as MabThera[1], Herceptin or Remicade, biosimilars are often heralded as the next big opportunity for biopharmaceutical companies**
- **However, biosimilars presently account for only 0.5% 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
  - The corresponding level of original brand sales (addressable market)
  - The general biosimilar regulation (interchangeability and substitution policy) and guidelines for each class of biosimilar products
- **In addition, the profitability of biosimilars remain 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 the French market over the 2012-2016 period**

Sources: Smart Pharma Consulting

[1] Also named Rituxan

1. Introduction

Although the size of the biosimilar market is still limited, prospects are positive given the success encountered by originator biologics

Introduction

- **Sandoz** was the first company to compete on the biosimilar market with the **growth hormone Omnitrope**, authorized in **Europe in April 2006** and approved in the **USA a month later**
- Since then, only a small number of companies (Teva[1], Hospira, Stada, etc.) have launched biosimilars in those markets
- In Europe, products currently pertain to **three therapeutic classes**: erythropoiesis stimulating agents (ESA), human growth hormones (HGH) and granulocyte colony-stimulating factors (G-CSF)
- As opposed to that of generics, the **development of biosimilar drugs remains quite low** in most countries
- The penetration of biosimilars has been slowed by a number of different limiters, such as their much **higher cost of development compared to generics**, the **uncertainty surrounding substitution** and the **reluctance of physicians to adopt those "copies"**
- However, several **drivers** are emerging, such as the **expiration of many key biologics patents over the next few years**, the **pressing need of healthcare systems** to contain costs and the **potential for the development and approval of biosimilar monoclonal antibodies**
- The biosimilar market is perceived as attractive enough that most **big pharmas** (e.g. Pfizer, Merck, Boehringer Ingelheim, AstraZeneca, etc.), but also **new comers like technology and electronics conglomerates** (Fujifilm, LG and Samsung), have announced plans or have already started to invest in biosimilars

Sources: European Medicines Agency "Guideline on similar biological medicinal products (CHMP / 437 / 04)" – Smart Pharma Consulting

[1] In 2010 Teva acquired Ratiopharm, which had also launched several biosimilars

2. Definitions

The variability of biopharmaceuticals and biosimilars is greater than that typically observed for conventional pharmaceuticals

Differences between generics and biosimilars

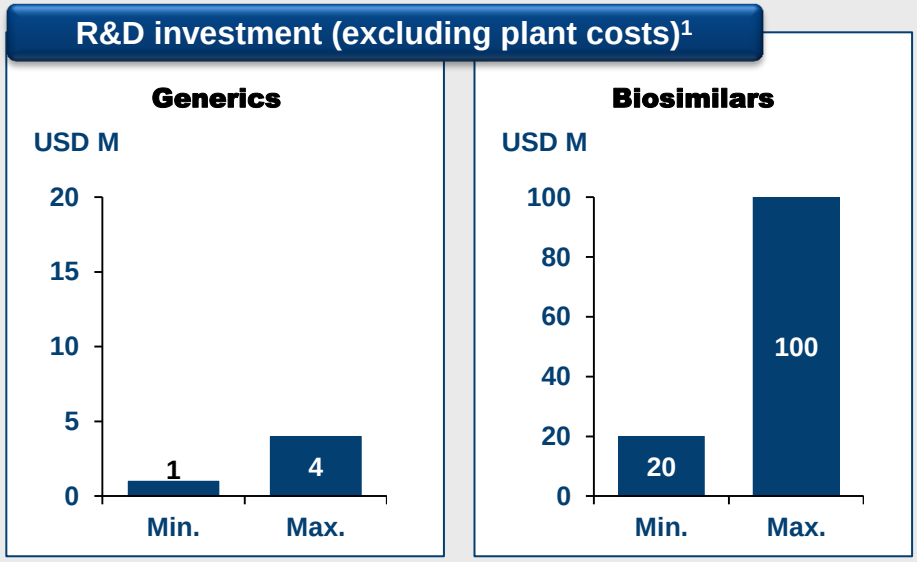
	Generics	Biosimilars
Composition	Generics have **simple chemical structures** and are considered to be **identical** to their **reference medicines**	Biosimilars and biopharmaceuticals are inherently **variable** due to the fact that they are **produced from living organisms**
Substitution	**Authorized**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

Sources: Smart Pharma Consulting Analyses

3. Drug development process

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

Biosimilar development



Comments

- **Biosimilars** are significantly **more expensive to develop** than are conventional generics
- On average, it takes **three times longer to develop a biosimilar medicine** compared with a generic one (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 **biosimilar** development programs is usually around **50-75%** while it is around **90%** for **generics** programs

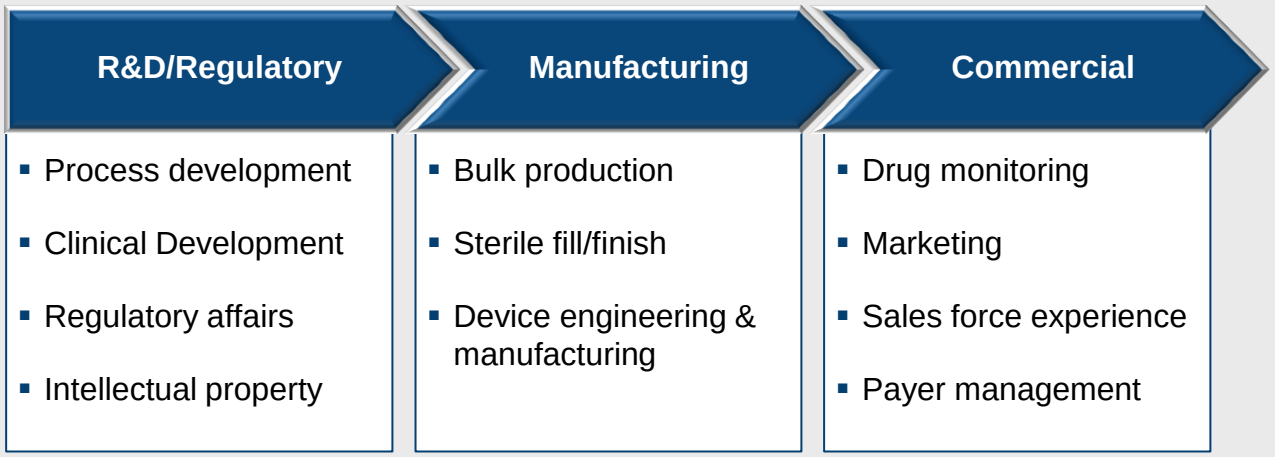
Sources: Sandoz – Teva – Lonza – Smart Pharma Consulting Analyses

[1] Plan costs are estimated at USD 150 M to USD 200 M

The capabilities necessary to develop biosimilars lie between those required for developing generics and those for developing biologics

Required capabilities for biosimilars

Capabilities overview



Comments

- Several **companies lacking important capabilities** have chosen to **partner** to penetrate the biosimilars market (e.g. Teva and Lonza, Merck Serono and Dr. Reddy's, Hospira and Celltrion, Samsung and Quintiles, Amgen and Actavis[1], etc.)
- A **partnering** or **network strategy** may offer a **competitive advantage** by bringing together **complementary capabilities** or **mutualizing investments** in development or marketing

Sources: Hospira Education Forum – http://www.egagenerics.com – Smart Pharma Consulting Analyses

[1] Previously Watson Pharmaceuticals

4. Marketed biosimilars

As of February 2013, only one biosimilar is marketed in the USA vs. 13 in Europe (based on 3 different active substances)

Authorized biosimilar drugs in Europe vs. USA

	Therapeutic classes	Date of authorization	Product name	Company	Indications
Europe	Erythropoiesis stimulating agents (ESA)	18/12/2007	Retacrit Silapo	Hospira Stada	*Symptomatic anemia associated with chronic renal failure, anemia in cancer, increase of the yield of autologous blood from patients in a predonation program, reduction of the exposure to allogeneic blood transfusions in adult non-iron deficient patients*
		28/08/2007	Epoeitin Alfa Hexal Abseamed Binocrit	Hexal Medice Sandoz	
	Growth hormones	24/04/2006	Valtropin	Biopartners	*Pituitary dwarfism, Turner syndrome*
		12/04/2006	Omnitrope	Sandoz	*Pituitary dwarfism, Prader-Willi syndrome, Turner syndrome*
	Granulocyte-colony stimulating factors (G-CSF)	08/06/2010	Nivestim	Hospira	*Cancer, hematopoietic stem cell transplantation, neutropenia*
		06/02/2009	Filgrastim Hexal Zarzio	Hexal Sandoz	
		15/09/2008	Ratiograstim[1] Tevagrastim Filgrastim ratiopharm[1,2] Biograstim	Teva Pharma Teva Pharma Teva Pharma CT Arzneimittel GmbH	
	3 active substances	7 applications	14 drugs		
USA	Growth hormones	30/05/2006	Omnitrope	Sandoz	*Pituitary dwarfism, Prader-Willi syndrome, Turner syndrome*
	G-CSF	29/08/2012	Tbo filgrastim[3]	Teva Sicor Biotech	*Cancer, hematopoietic stem cell transplantation, neutropenia*
	2 active substances	2 applications	2 drugs		

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

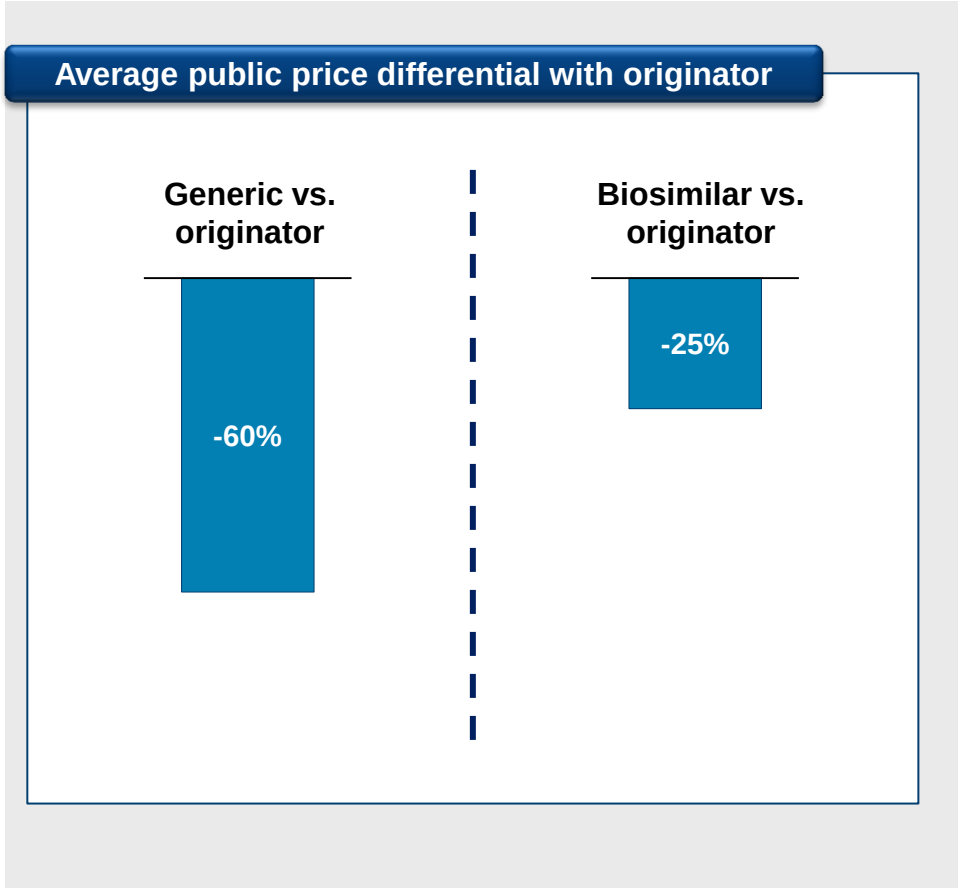
Sources: European Medicines Agency – FDA – Smart Pharma Consulting Analyses

[1] Formerly owned by Ratiopharm, which was later acquired by Teva in March 2010 – [2] Product withdrawn – [3] Teva is prohibited by court order from marketing this product in the U.S. prior to November 10, 2013

4. Marketed biosimilars

In Europe, biosimilar drugs are 20% to 30% cheaper than originators, which can lead to substantial economies for healthcare systems given the cost of biotech treatments

Biosimilars price differential in Europe



Comments

- Across **Europe** the average **price differential** by country ranges from **20% to 30%**
- In **Italy,** the initial price reductions applied range from **15% to 22%** of the initial price while a further price reduction is set once a predefined volume threshold is achieved
- In **Spain**, biosimilars are priced **30%** below the reference biological medicine price, as agreed with the Interministerial Commission for Pricing
- In the **UK**, there are no special arrangements for pricing and reimbursement of biosimilars. The relative price discounts between the reference product and biosimilar prices are generally around **20%-25%**
- In **France**, the average price discount is **20%**
- In **Germany** the discount range extends from **25% to 30%**
- Those **price reductions** can lead to **substantial economies for healthcare systems**. For instance, the ESA biosimilar introduction in Germany resulted in € 60M annual savings in its first year on the market

Sources: "The impact of biosimilars' entry in the EU market", EMINET, European commission (Jan. 2011) – GaBI Journal – ANSM – http://www.egagenerics.com – Smart Pharma Consulting Analyses

4. Marketed biosimilars

The situation regarding the attitudes of key stakeholders towards biosimilars varies across the five major European markets

Stakeholder attitudes towards biosimilars in the EU5

	Adoption of biosimilars	Authorities	Hospitals	Physicians	Patients
	**High**	▪ Government actively encourages biosimilars ▪ Regional prescription quotas requirements (20% to 40% of Rx)	▪ Hospitals are driven to use biologicals by cost reduction policies, regional authority pressures and contracts with health insurance funds	▪ Favorable view of biosimilars	▪ High acceptance of generics and biosimilars
	**High**	▪ NICE[1] issued guidance recommending to indifferently choose the least costly option	▪ 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[2], and thus prescribe according to NICE[1] requirements	▪ No opposition from patients towards biosimilars
	**Medium**	▪ No specific public policy encouraging the use of biosimilars	▪ Due to financial constraints, hospitals have a strong incentive to buy biosimilars rather than originators	▪ Physicians are not incentivized to prescribe biosimilars	▪ Reluctance to use similar drugs for serious diseases ▪ No advantages for using biosimilars
	**Low**	▪ In early 2013, the Italian Medicines Agency should take position in favor of biosimilars, but against substitution	▪ Hospitals are not incentivized to prescribe biosimilars	▪ Prescribing decisions depend on physicians, who have close relationships with originator companies	▪ Population mainly reluctant towards biosimilars
	**Low**	▪ Biosimilars are classified as hospital-only medicines ▪ 'Patents of use'[3] can keep certain indications protected	▪ Biosimilars are generally welcomed by the hospital pharmacotherapeutic committees	▪ Prescribing decisions depend on physicians ▪ Few incentives to prescribe generics or biosimilars	▪ General patients reluctance due to the legacy of counterfeit products

Sources: http://gabionline.net – IGAS – Agenzia Italiana del Farmaco – Smart Pharma Consulting Analyses

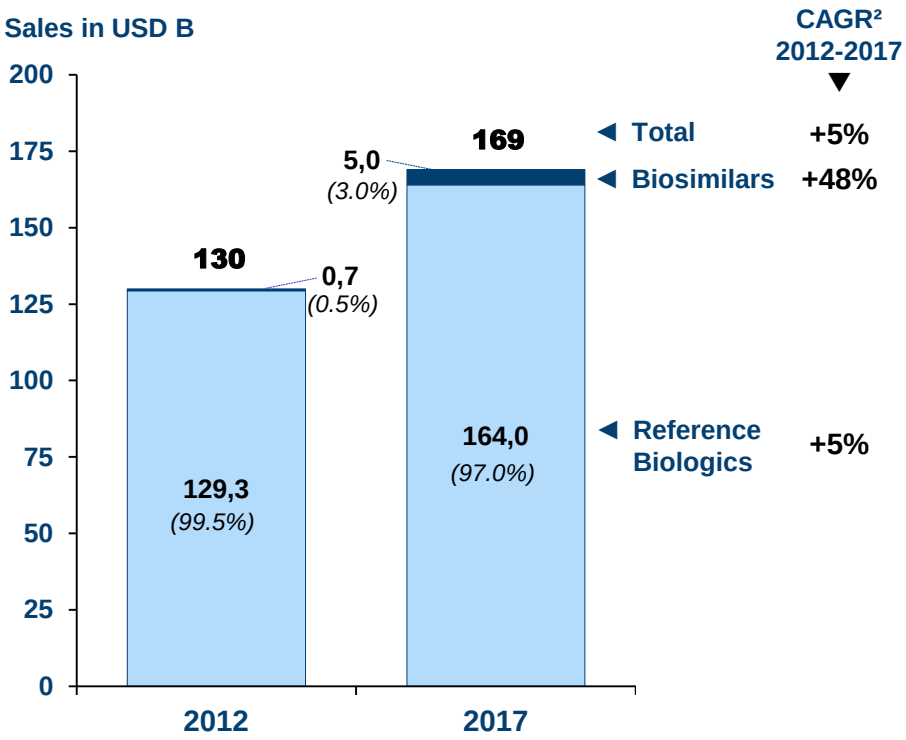
[1] National Institute for Clinical Excellence – [2] National Health System – [3] Patents covering the use in specific indications (most recent) of a drug, whose patent has expired for other indications

5. Market potential

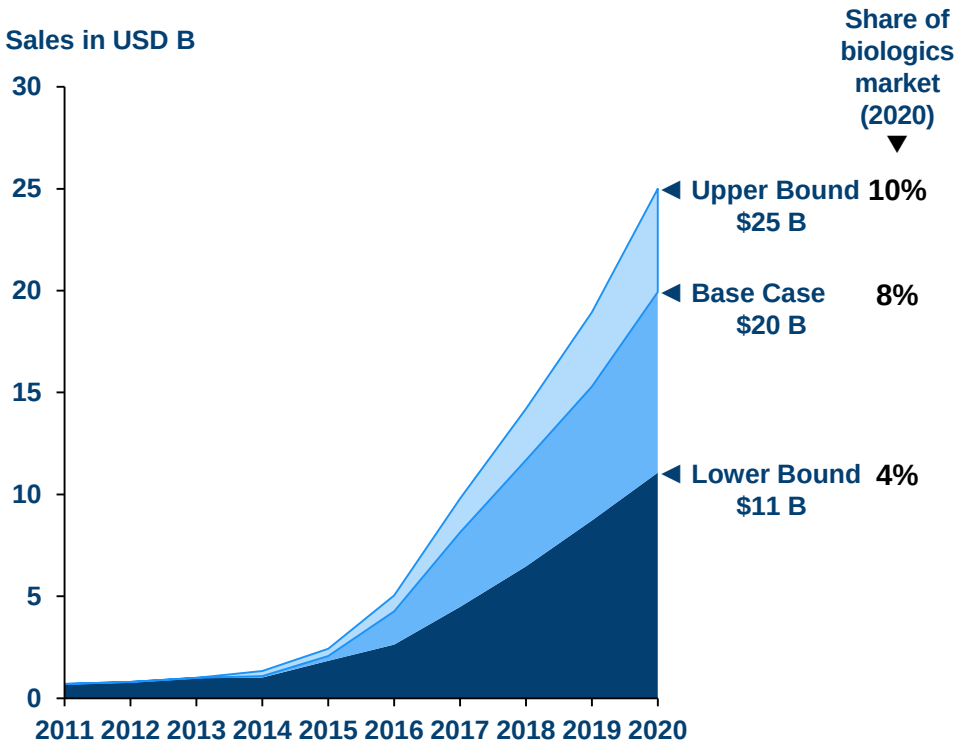
The biosimilar market is expected to grow significantly, driven by patent expiries and measures introduced by governments and payers, but its size will still remain limited

Worldwide biosimilars development forecasts

Biologics sales forecast 2012-2017[1]



Biosimilars sales forecast 2011-2020



Sources: IMS Medicines Outlook Through 2016 (July 2012) – Evaluate Pharma – European Medicines Agency – FDA – Pharmaceutiques, September 2009 – Smart Pharma Consulting Analyses

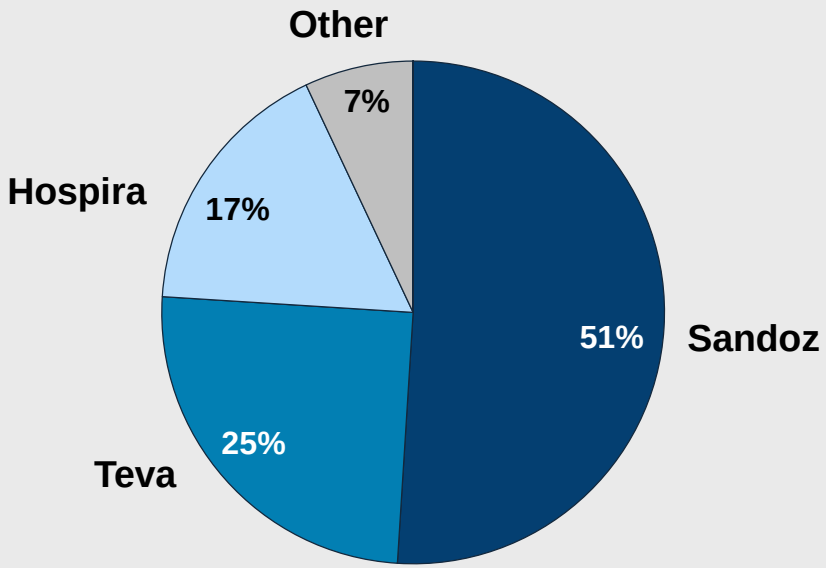
[1] Excluding vaccines –[2] Compound annual growth rate

6. Biosimilar market players

Sandoz dominates the biosimilar market – with one product marketed in each existing therapeutic class – and boasts the largest product offering

Current biosimilar players in highly regulated markets[1]

Market share in highly regulated markets[1] (2011)



Comments

- **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 fourth of the market** with currently **two products** in the G-CSF[2] therapeutic class (i.e. Ratiograstim and Tevagrastim)
- **Hospira** is the **third largest player** with products in **two therapeutic classes** (i.e. Retacrit in the ESA[3] therapeutic class and Nivestim in the G-CSF class)
- The **"Other"** category includes **smaller competitors** such as Medice, Stada and Biopartners

Sources: IMS Dec 2012 – Annual company financial reports – Sandoz analysis

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

6. Biosimilar market players

Big pharmas, biotechs and new entrants such as technology and electronic giants have the financial resources to fund biosimilar research and development programs

Players in the biosimilar market (1/2)

1 Big pharmas

- Big pharma companies have been rather late entrants in the biosimilar market
- Given their large financial resources and experience with patented products, they are more likely to work on developing improved versions of innovative biologics (patentable)
- They will benefit from their reputation with stakeholders for registration, marketing and sales of follow-on biologics
- Strategies are diverse for big pharmas:
  - With Sandoz, Novartis internally built the current leader in the biosimilar market
  - Some of them are working to develop products internally, such as Pfizer and Boehringer Ingelheim
  - Others, like Merck Serono and Baxter, have partnered with generics companies or services providers
  - Finally, Sanofi purchased Shanta Biotech in India to grow in emerging markets, thanks to its vaccines and ESA products

2 Biotechs

- Amgen – with its blockbuster drugs Neulasta/Neupogen ($5.4B sales in 2012), Embrel ($4.2B), Aranesp ($2.0B) and Epogen ($2.0B) – and Biogen Idec – with its blockbuster drugs Avonex ($2.7B in 2011) and Tysabri ($1.5B) – are developers of original biologics
- The two US biotechs face potential competition from copycat versions, especially in Europe
- In 2011, Amgen signed a collaboration deal with Actavis[1] to conjointly develop biosimilar anti-cancer antibodies and in 2012 with clinical research organization PRA to carry out clinical trials for its own pipeline of biosimilars
- In 2011, Biogen Idec created a joint venture with Samsung Biologics to develop, manufacture and market biosimilars

3 Technology and electronic conglomerates

- Samsung plans to invest $2.1 billion for its biopharmaceutical business by 2020. While Samsung BioLogics (joint-venture with Quintiles) will first focus on contract manufacturing, Samsung also set up a joint venture with Biogen Idec to develop, manufacture and market biosimilars (Samsung Bioepis)
- Fujifilm and Kyowa Hakko Kirin set up a joint venture with 50-50 capital participation for the development of biosimilars. In 2011, Fujifilm had purchased Merck BioManufacturing Network, a leading provider of contract manufacturing and development services for the biopharmaceutical industry

Sources: Websites – Press releases – Smart Pharma Analyses

[1] Previously Watson Pharmaceuticals

Generics companies often lack key capabilities along the value chain to develop, manufacture and market biosimilars on their own

Players in the biosimilar market (2/2)

4 Generics companies from developed countries

- Leading generics companies from developed countries are trying to leverage their generics know-how to develop and market biosimilars
- Sandoz (Novartis), Teva, Stada and Hospira were among the early entrants on the European market. They have gained experience with first-generation products[1] and are now working on the next generation of monoclonal antibodies
- Apart from Sandoz, all early entrants worked with partners, API producers or contract manufacturing organizations
- Actavis[2] and Mylan have not yet launched any product but are working on development projects with partners (Amgen and Itero Biopharmaceuticals for Actavis and Indian biotech leader Biocon for Mylan)

5 Generics companies from emerging countries

- In emerging countries with less stringent market access regulation and weak patent protection, such as India and China, the market for off-patent biological medicines is more developed than in Europe
- Several manufacturers sell biosimilars outside their home countries, but most exclusively in emerging markets for now
- Some Indian producers such as Biocon and Dr. Reddy's have already stated their intentions to market their products in Europe and in the USA
- China is expected to issue its first set of regulatory standards for companies developing biosimilars, with the aim of speeding up drug registration

6 Service providers

- Contract research organizations (CROs) such as Quintiles and Parexel provide clinical development services including drug development and regulatory consulting, clinical pharmacology, clinical trials management, medical education and reimbursement
- A player worth mentioning is South Korean Celltrion, a CRO for companies such as Hospira and HIKMA that expanded its playing field with the recent launch in South Korea of the first antibody biosimilar, a copy of infliximab (Remicade)
- Contract manufacturing organizations (CMOs) such as Lonza can use their resources and expertise from early development through commercial manufacturing to help companies achieve their strategic goals

Sources: Websites – Press releases – Smart Pharma Analyses

[1] ESA = Erythropoiesis-stimulating agent / G-CSF = Granulocyte-colony stimulating factor / HGH = Human growth hormone – [2] Previously Watson Pharmaceuticals

7. Biosimilar drugs drivers and limiters

The actual growth of biosimilars will depend on several factors, in particular, cost pressure might push health authorities to promote substitution

Biosimilar drugs drivers and limiters

Drivers

- **Cost pressure** on health authorities, exacerbated by an aging population, the economic slump, and gradually reduced savings from generics, might favor cheaper biologicals
- **Patent expirations** of top biological drugs (in Europe within five years: MabThera, Remicade, Herceptin, Erbitux, Embrel, Aranesp, etc.) will increase potential market size
- Limited budgets in **pharmerging markets** already favor biosimilars as cheaper and cost-effective alternatives to biologicals

Limiters

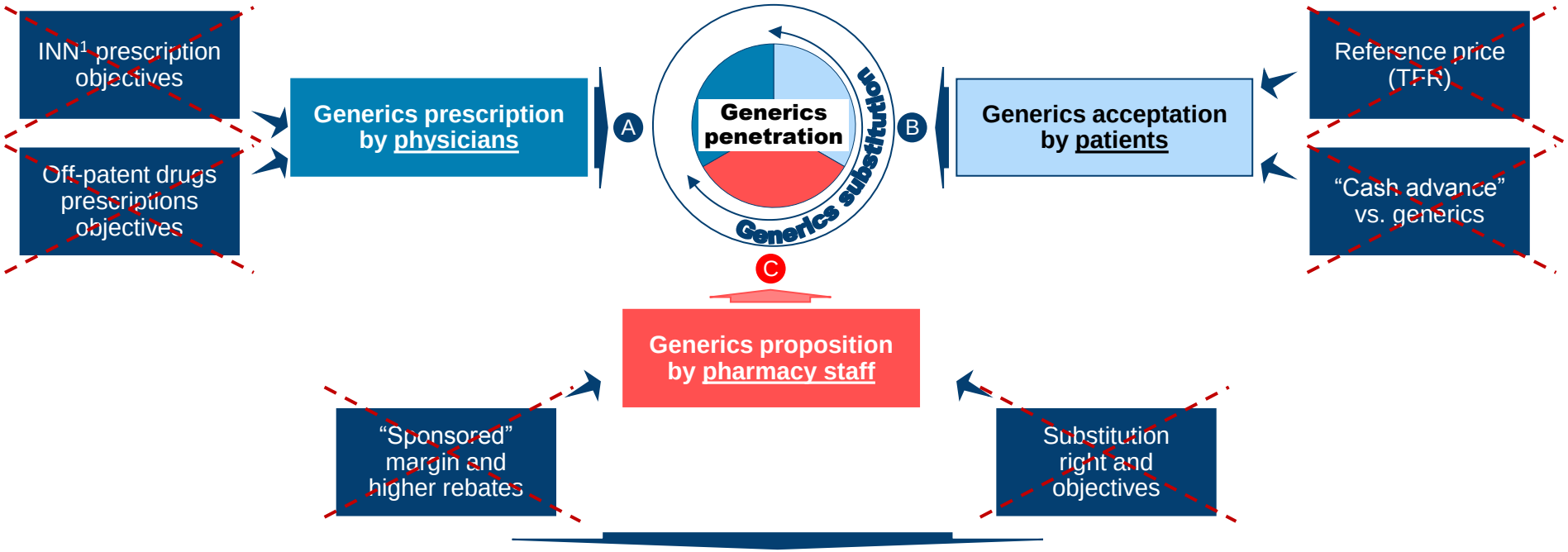
- **Uncertainty of regulatory frameworks** might keep investors from betting on biosimilars
- **Lack of experience** and **newness of guidelines** might slow down the uptake of biosimilars by prescribers
- **Limited price reduction** (i.e. 20 to 30%) might **limit the penetration** of biosimilars
- **Enhanced defense strategies for patents**
- **High development costs** and **manufacturing issues**

Sources: IMS Health – Smart Pharma Consulting Analyses

The “traditional” measures introduced by health authorities to boost generics sales do not apply to biosimilars

Barriers to transposition of the generics model to biosimilar drugs

Key drivers of generics penetration



- **Biosimilar drugs cannot be legally substituted to brands**
- **As a result, their sales and penetration trends are driven by physicians’ prescriptions**

Measures introduced by Health authorities

Sources: Smart Pharma Consulting Analyses

[1] International non-proprietary name

8. Case study: France

To evaluate the potential sales of biosimilar drugs in France by 2016, Smart Pharma Consulting has built three different scenarios based on three key dimensions

Development scenarios of biosimilars in France by 2016 – Assumptions

	Market volume	Biosimilar penetration	Biosimilar price
Scenario #1 "Progressive"	▪ Actual biosimilar classes trends in volume should continue "as is"[1] with: – 1 new filgrastim in January 2014 – 1 new pegfilgrastim in January 2015 – 1 lipegfilgrastim in January 2015 ▪ New classes of biologics should be concerned by biosimilars: – 2 biosimilars of **Remicade** (infliximab) in January 2015 – 1 biosimilar of **MabThera** (rituximab) in January 2015 – 1 biosimilar of **Herceptin** (trastuzumab) in January 2015 – 1 biosimilar of **Gonal-F** (follitropin alfa) in January 2014, 1 in January 2015 – 1 biosimilar of **Betaferon** et **Extavia** (interferon β 1b) in June 2014	▪ Penetration trends should continue "as is" for classes with biosimilars ▪ Limited penetration (<25%) by the end of year 2 for new biosimilar drugs[2]	▪ Authorities price drops depending on the date of launch and the number of biosimilar competitors
Scenario #2 "Dynamic"		▪ **Substitution right allowed in January 2015, boosting biosimilar penetration in retail market** ▪ No impact on hospital market	
Scenario #3 "Disruptive"		▪ **Lower biosimilar penetration on the retail market due to a reference price applied by therapeutic area** (e.g. all GCS-F products) ▪ No impact on hospital market	▪ **In January 2015 reference price application for all therapeutic areas in which biosimilars are marketed, irrespective of their penetration rate**

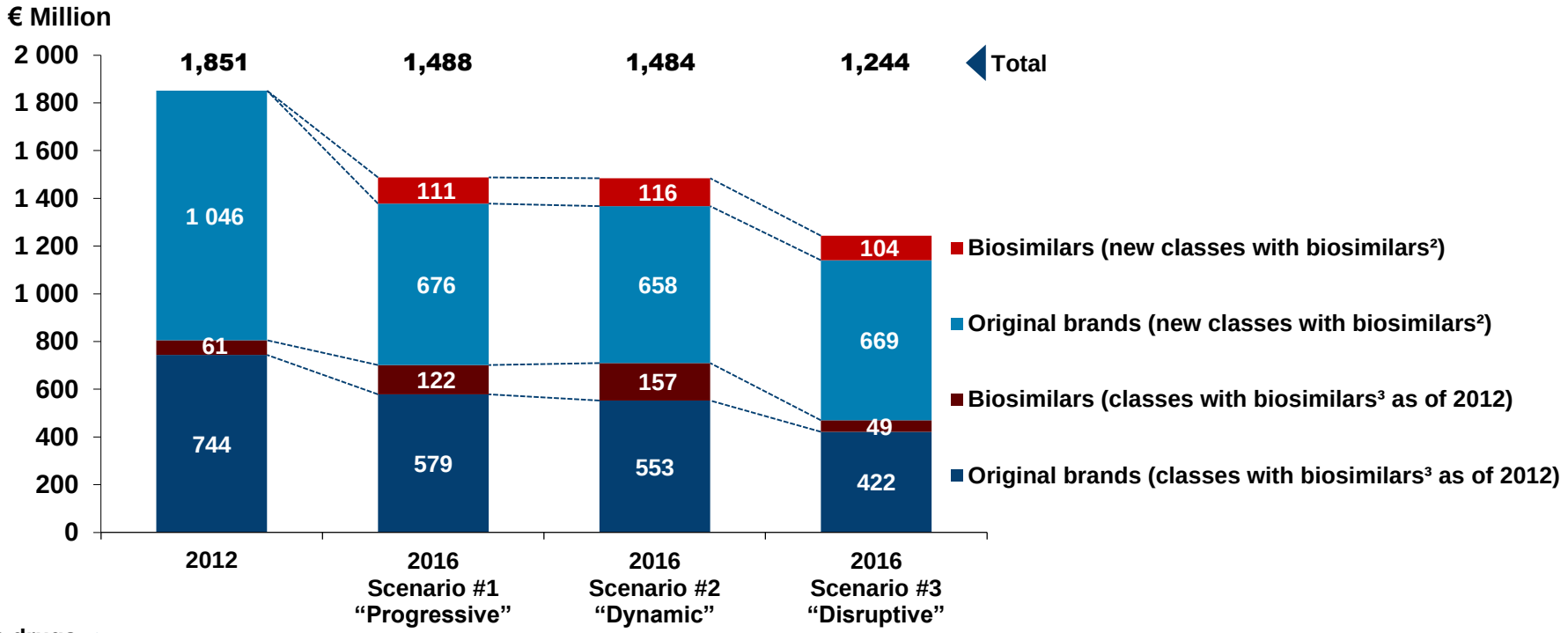
Sources: Smart Pharma Consulting analysis based on external interviews

[1] Higher biosimilar penetration in classes with several biosimilar players – [2] Infliximab (Remicade), rituximab (MabThera/Rituxan), trastuzumab (Herceptin), interferons β 1b (Betaferon & Extavia) and follitropin α (Gonal-F)

8. Case study: France

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



	2012	2016 Scenario #1 "Progressive"	2016 Scenario #2 "Dynamic"	2016 Scenario #3 "Disruptive"
Reference drugs sales (M€)	1,790	1,255	1,211	1,091
Biosimilars sales (M€)	61	233	273	153
Biosimilars penetration rate	8%[1]	19%	23%	14%

Note: Hospital sales include discounts

Sources: GERS retail – Smart Pharma Consulting analysis

[1] The penetration rate in 2012 only takes into account the classes where biosimilars are already marketed – [2] Infliximab (Remicade), rituximab (MabThera/Rituxan), trastuzumab (Herceptin), interferons β 1b (Betaferon & Extavia) and follitropin α (Gonal-F) – [3] Growth hormones, erythropoiesis stimulating agents, and granulocyte colony-stimulating factors

9. Conclusion

- The **size of the global biosimilar market should remain limited by 2016** ($ 5 billion expected vs. $ 205 billion for original biologics)
- Whether biosimilars will take hold in **the USA** is the single **most important factor** in biosimilars' global success and, in any cases, only a **limited number** of key **players** is **expected to emerge**
- The **biosimilars opportunity** is **unlikely to be attractive enough** to **justify the entry**, and **ensure the success**, **of many drug makers** (whether generic companies or big pharmas) as well as new players such as electronic and technology conglomerates and service providers on the market:
  - **Significant capabilities** are required to develop an integrated biosimilar business (e.g. highly specialized plant, technical know-how differing from chemical drugs, necessity for biosimilars to invest significantly in medical, marketing and sales, etc.)
  - **Biosimilars** currently face a major limiter in that they **cannot be successful on price discounts alone**
  - The **price differential** between biosimilars and originators is currently **not wide enough** to compensate for biosimilars' shorter track record, reliability and experience; besides reference products are free to decrease their price so that they can narrow down the price gap with biosimilars
  - The penetration of biosimilars is slowed down by the fact that in most countries, **patients and physicians remain reluctant** to adopt them; in addition, biosimilars are **not subject to substitution** in the USA and EU (except Bulgaria and Romania), leaving the decision power in the hands of prescribers
  - **Risks of immunogenicity** inherent to biologics products make physicians reluctant to switch prescribed reference drugs in favor of their biosimilars
- The **biosimilars** market in **France** should remain **modest** and **reach sales** between **€ 153 M** and **€ 273 M in 2016,** depending on the **considered scenario,** compared to **€ 61 M** in **2012**

Sources: Smart Pharma Consulting