Succeeding on the French Biosimilars Market

Smart Pharma Consulting

Everything you wanted to know!

Position Paper

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This position paper provides key information and analyses to evaluate the French biosimilars market dynamics and the key success factors for pharma companies

Context & objectives

- Sandoz, Teva or Hospira (Pfizer), which have pioneered the biosimilars market in France, have placed great hopes in its development
- However, 12 years down the road, the achievement of these precursors and of the followers can be regarded as somewhat below expectations
- ***Smart Pharma Consulting***, which has developed a robust experience at analyzing and advising pharma companies on the biosimilars market, proposes to:

1. Analyze the biosimilars market structure and dynamics
2. Review the French regulatory environment
3. Share insights regarding customers behaviors
4. Evaluate the competitive landscape and the key success factors
5. Estimate 2018 – 2023 market growth

The biosimilars development on the French market is driven by the prescription of physicians who are encouraged by health authorities and certain hospital managers

Stakeholders involved in the French biosimilars market

Health Authorities & Payers[1]

- Health authorities and payers have introduced a series of measures to convince hospital and office-based physicians to prescribe more biosimilars, either as an initial treatment or as a switch
- The Ministry of Health has set the objective of achieving 80% biosimilar penetration by 2022

Office

Hospital | Pharmacists | Physicians

Rx → Patients ← Dispensation

Retail pharmacists

- Physicians prescription of biosimilars is very different according to the product considered
- Hospital pharmacists play a role in purchasing

- Patients and PAGs are still wary regarding the prescription of biosimilars
- They want to be informed in a transparent manner

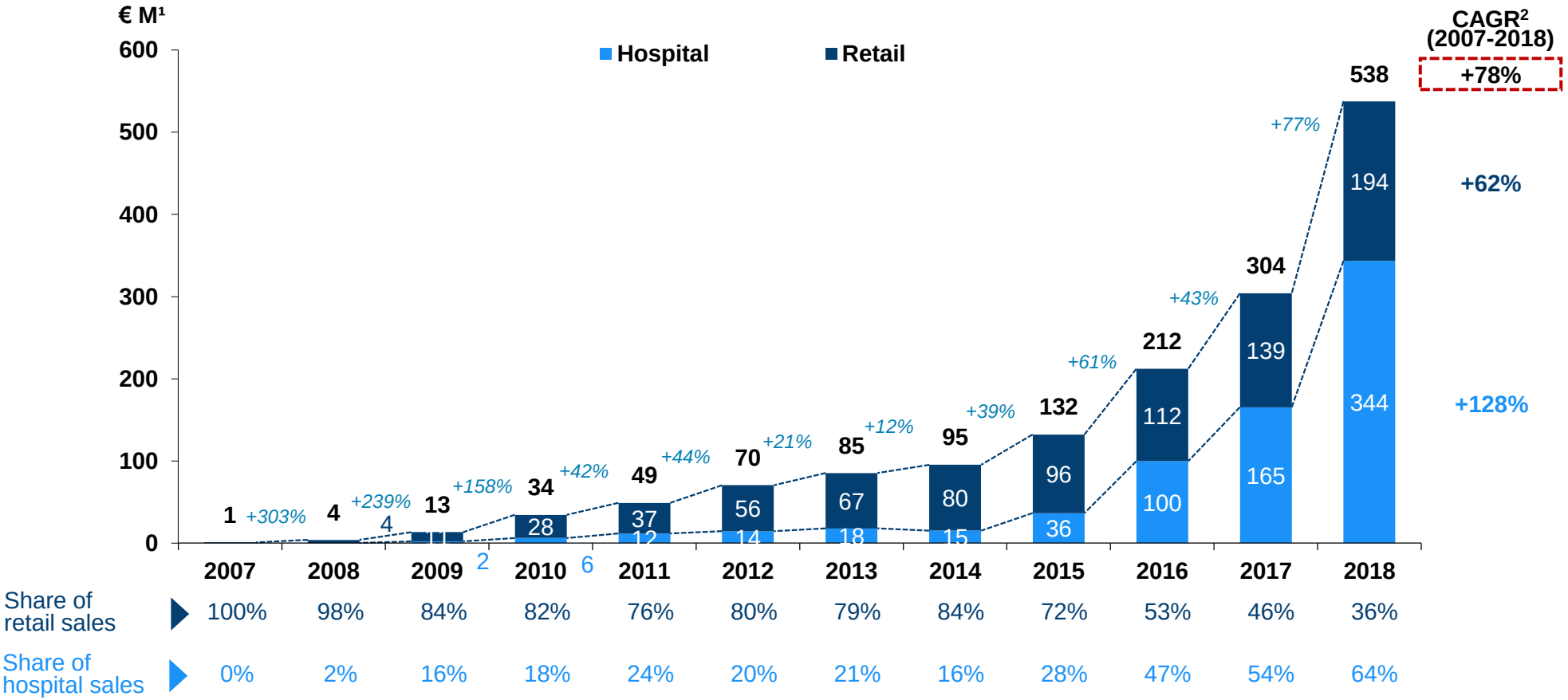
- Retail pharmacists are divided regarding the substitution of biological drugs

Smart Pharma Consulting analyses

[1] *National Health Insurance Fund*

Biosimilars, whose first products were launched in France in 2007, accounted for a total of € 538 M in 2018, based on ex-factory prices excluding rebates and taxes

Evolution of the biosimilars market (2007 – 2018)

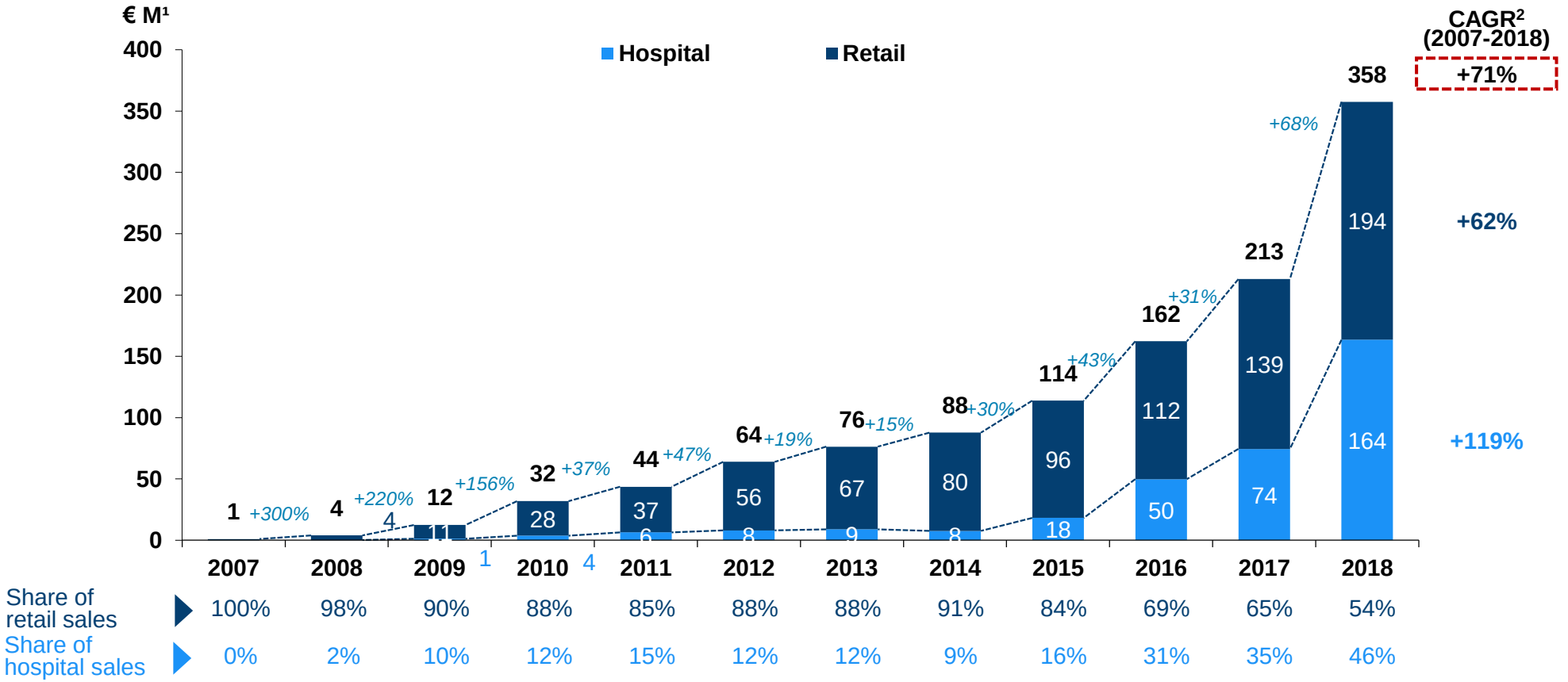


Sources: GERS – Smart Pharma Consulting analyses

¹ Ex-factory prices excluding rebates and taxes – ² Compound annual growth rate

When considering the rebates granted to hospitals on list prices, the 2018 biosimilars market reached € 358 M and the hospital sales are reduced to 46% of the total

Evolution of the biosimilars market (2007 – 2018) – Net prices



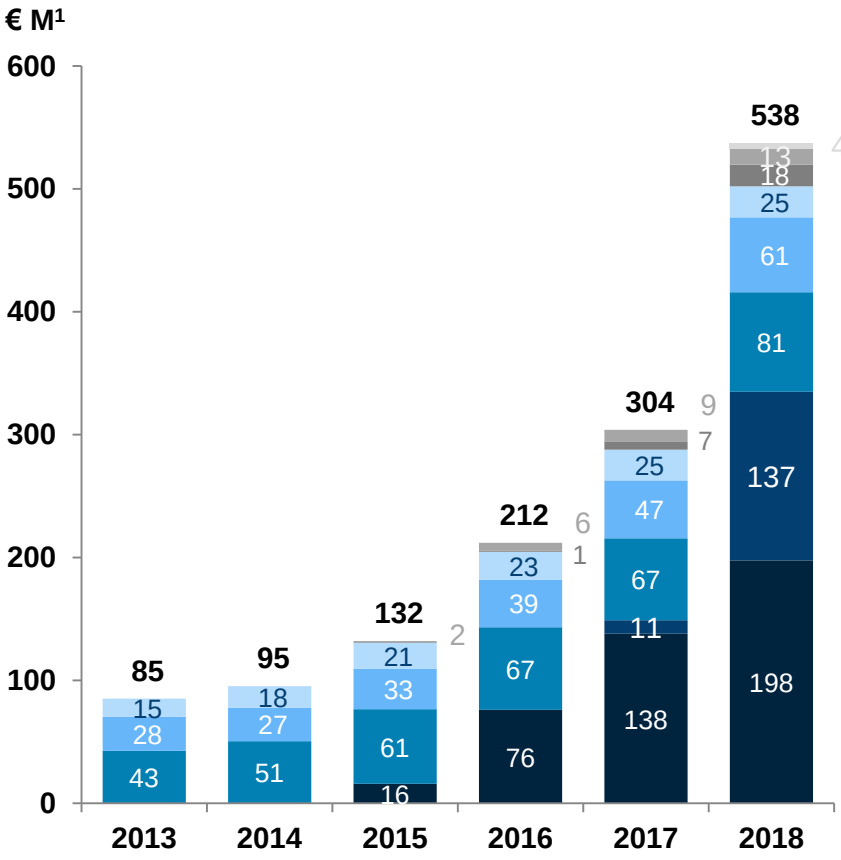
Note: In 2016, 2017 and 2018, the net prices were respectively 50%, 55% and 52% lower than the ex-factory prices excluding taxes and rebates (mainly through tenders) on the hospital market. The rebates granted in the retail market are considered as negligible

Sources: GERS – Smart Pharma Consulting analyses

¹ Net prices = Ex-factory prices excluding taxes and including rebates – ² Compound annual growth rate

In terms of therapeutic classes, anti-TNFs dominate the French biosimilars market, followed by monoclonal antibody antineoplastics and colony-stimulating factors

Distribution of the biosimilars market by therapeutic class (2013 – 2018)



	CAGR[2] 2013-2018	2017-2018 growth	Market share 2013	Market share 2018
Total market	**+44.5%**	**+76.9%**		
Fractionated heparins[3]	N/A	N/A	0.0%	0.8%
Gonadotrophins[4]	N/A	+39.6%	0.0%	2.5%
Human insulins[5]	N/A	+161.9%	0.0%	3.3%
Growth hormones[6]	+11.2%	+1.9%	17.6%	4.7%
Erythropoiesis-stimulating agents[7]	+17.1%	+29.0%	32.4%	11.3%
Colony-stimulating factors[8]	+13.7%	+21.5%	50.0%	15.0%
Monoclonal antibody antineoplastics[9]	N/A	N/A	0.0%	25.5%
Anti-TNFs[10]	N/A	+43.3%	0.0%	36.8%

Sources: GERS – Smart Pharma Consulting analyses

[1] Ex-factory prices excluding rebates and taxes – [2] Compound annual growth rate – [3] Enoxaparin sodium – [4] Follitropin alfa – [5] Insulin glargine – [6] Somatropin – [7] Epoetin – [8] Filgrastim and pegfilgrastim – [9] Rituximab and trastuzumab – [10] Adalimumab, etanercept and infliximab

With 3 biologic originators whose patent has expired, 7 biosimilars launched by 5 pharma companies, anti-TNF biosimilars sales reached € 198 M in 2018

Anti-TNF biosimilar drugs marketed in France (2018)

INN[1] (Originator)	Product name	Pharma company	Launch date	Hospital sales[2]	Retail sales[2]	Total sales[2]	Biosimilars penetration[3]
Infliximab (Remicade, MSD)	▪ Inflectra	▪ Pfizer	▪ Feb. 2015	€ 95.8 M	€ 0.0 M	€ 95.8 M	69.6%
	▪ Remsima	▪ Biogaran	▪ Feb. 2015	€ 52.0 M	€ 0.0 M	€ 52.0 M	
	▪ Flixabi	▪ Biogen	▪ Mar. 2017	€ 27.6 M	€ 0.0 M	€ 27.6 M	
	3 products	3 companies		€ 175.5 M	€ 0.0 M	€ 175.5 M	
Etanercept (Enbrel, Pfizer)	▪ Benepali	▪ Biogen	▪ Oct. 2016	€ 0.1 M	€ 19.0 M	€ 19.1 M	20.3%
	▪ Erelzi	▪ Sandoz	▪ Nov. 2017	€ 0.0 M	€ 2.2 M	€ 2.2. M	
	2 products	2 companies		€ 0.1 M	€ 21.2 M	€ 21.3 M	
Adalimumab (Humira, AbbVie)	▪ Amgevita	▪ Amgen	▪ Oct. 2018	€ 0.0 M	€ 0.5 M	€ 0.5 M	2.3%
	▪ Imraldi	▪ Biogen	▪ Oct. 2018	€ 0.0 M	€ 0.3 M	€ 0.3 M	
	2 products	2 companies[4]		€ 0.0 M	€ 0.8 M	€ 0.8 M	
Total	7 products	5 companies		€ 175.6 M	€ 22.0 M	€ 197.6 M	

Sources: GERS – Smart Pharma Consulting analyses

[1] International Non-propriety Name – [2] Ex-factory prices excluding rebates and taxes – [3] Biosimilar penetration in volume in December 2018 – [4] As of June 2019, two more biosimilars have entered the market: Hulio (Mylan) and Hyrimoz (Sandoz). An additional biosimilar, Idacio (Fresenius Kabi) is expected in the coming months

With 2 biologic drugs from Roche whose patent has expired, 5 biosimilars launched by 4 companies, rituximab & trastuzumab biosimilars sales reached € 137 M in 2018

Monoclonal antibody antineoplastics biosimilar drugs marketed in France (2018)

INN[1] (Originator)	Product name	Pharma company	Launch date	Hospital sales[2]	Retail sales[2]	Total sales[2]	Biosimilars penetration[3]
Rituximab (MabThera, Roche)	▪ Truxima ▪ Rixathon	▪ Biogaran ▪ Sandoz	▪ Sep. 2017 ▪ Jan. 2018	€ 104.8 M € 18.1 M	€ 0.0 M € 0.0 M	€ 104.8 M € 18.1 M	82.2%
	2 products	2 companies		€ 122.8 M	€ 0.0. M	€ 122.8 M	
Trastuzumab (Herceptin, Roche)	▪ Herzuma ▪ Ontruzant ▪ Kanjinti	▪ Biogaran ▪ MSD ▪ Amgen	▪ Jul. 2018 ▪ Sep. 2018 ▪ Aug. 2018	€ 10.7 M € 2.4 M € 1.4 M	€ 0.0 M € 0.0 M € 0.0 M	€ 10.7 M € 2.4 M € 1.4 M	62.3%
	3 products	3 companies		€ 14.5 M	€ 0.0 M	€ 14.5 M	
Total	5 products	4 companies		€ 137.3 M	€ 0.0 M	€ 137.3 M	

Sources: GERS – Smart Pharma Consulting analyses

[1] International Non-propriety Name – [2] Ex-factory prices excluding rebates and taxes – [3] Biosimilar penetration in volume in December 2018

With 2 biologic drugs from Amgen whose patent has expired, 5 biosimilars launched by 5 pharma companies, G-CSF biosimilars sales reached € 81 M in 2018

Colony-stimulating factors biosimilar drugs marketed in France (2018)

INN[1] (Originator)	Product name	Pharma company	Launch date	Hospital sales[2]	Retail sales[2]	Total sales[2]	Biosimilars penetration[3]
Filgrastim (Neupogen, Amgen)	▪ Zarzio	▪ Sandoz	▪ Oct. 2009	€ 10.7 M	€ 36.4 M	€ 47.1 M	94.1%
	▪ Nivestim	▪ Pfizer	▪ Jun. 2011	€ 4.9 M	€ 18.6 M	€ 23.5 M	
	▪ Tevagrastim	▪ Teva	▪ Mar. 2010	€ 1.5 M	€ 5.1 M	€ 6.7 M	
	▪ Accofil	▪ Arrow	▪ Feb. 2016	€ 2.6 M	€ 0.8 M	€ 3.3 M	
	4 products	4 companies		€ 19.7 M	€ 60.9 M	€ 80.6 M	
Pegfilgrastim (Neulasta, Amgen)	▪ Pelgraz	▪ Accord Healthcare	▪ Nov. 2018	€ 0.0 M	€ 0.2 M	€ 0.2 M	2.5%
	1 product	1 company		€ 0.0 M	€ 0.2 M	€ 0.2 M	
Total	5 products	5 companies		€ 19.7 M	€ 61.1 M	€ 80.8 M	

Sources: GERS – Smart Pharma Consulting analyses

[1] International Non-propriety Name – [2] Ex-factory prices excluding rebates and taxes – [3] Biosimilar penetration in volume in December 2018

Epoetin and somatropin biosimilars, whose first products were launched ~10 years ago, reached penetration rates of almost 50% in December 2018

Other biosimilar drugs marketed in France (2018)

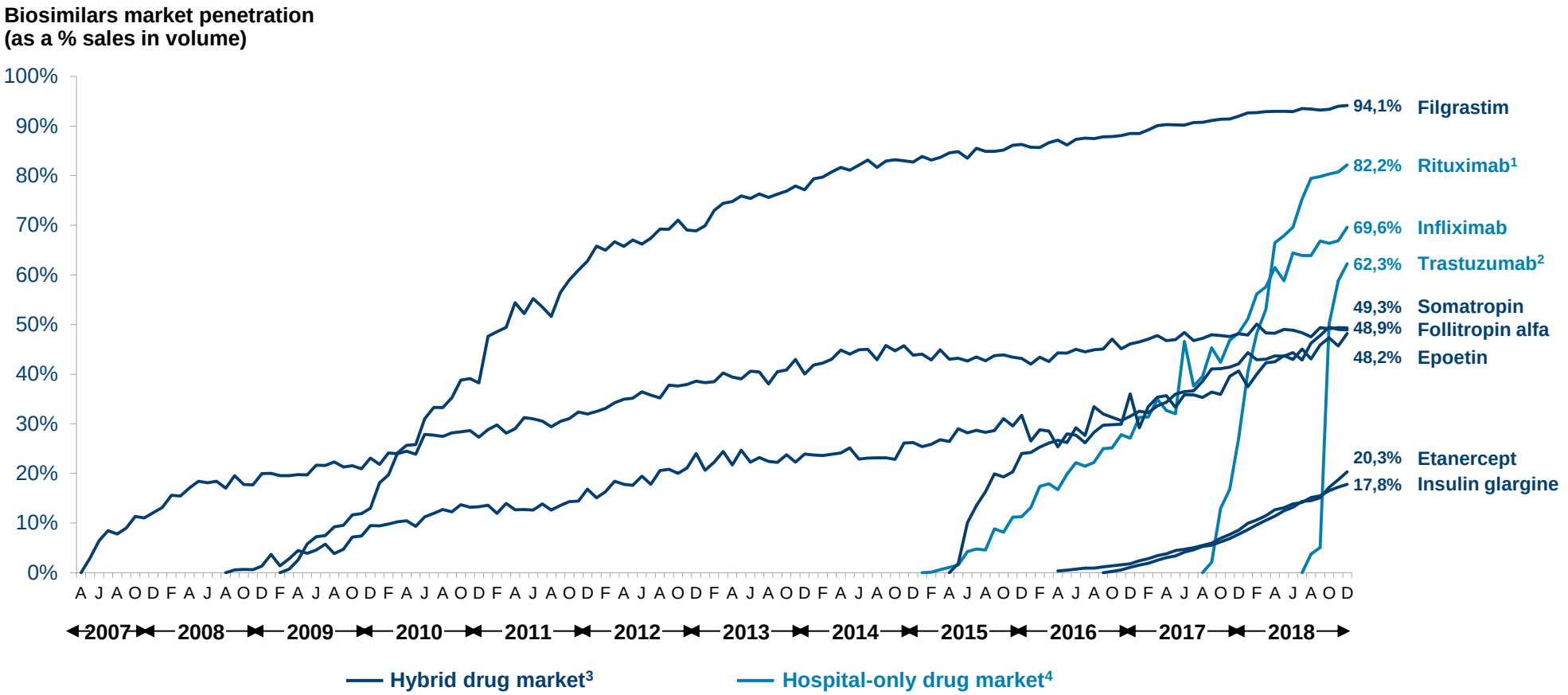
EPhMRA 4 therapeutic class	INN[1] (Originator)	Product name	Pharma company	Launch date	Hospital sales[2]	Retail sales[2]	Total sales[2]	Biosimilars penetration[3]
Erythropoiesis-stimulating agents	Epoetin (Eprex, Janssen)	▪ Binocrit ▪ Retacrit ▪ Eporatio[4]	▪ Sandoz ▪ Pfizer ▪ Teva	▪ Jul. 2008 ▪ Mar. 2009 ▪ May 2010	€ 7.1 M € 0.8 M € 0.6 M	€ 29.3 M € 16.5 M € 6.6 M	€ 36.4 M € 17.3 M € 7.2 M	48.2%
		3 products	3 companies		€ 8.5 M	€ 52.4 M	€ 60.9 M	
Growth hormones	Somatropin (Genotonorm, Pfizer)	▪ Omnitrope	▪ Sandoz	▪ May 2007	€ 0.0 M	€ 25.4 M	€ 25.4 M	49.3%
		1 product	1 company		€ 0.0 M	€ 25.4 M	€ 25.4 M	
Human insulins	Insulin glargine (Lantus, Sanofi)	▪ Abasaglar	▪ Lilly	▪ Jan. 2016	€ 2.3 M	€ 15.5 M	€ 17.8 M	17.8%
		1 product	1 company		€ 2.3 M	€ 15.5 M	€ 17.8 M	
Gonadotrophins	Follitropin alfa (Gonal-F, Merck)	▪ Bemfola ▪ Ovaleap	▪ Gedeon Richter ▪ Theramex	▪ May 2015 ▪ May 2016	€ 0.0 M € 0.0 M	€ 10.0 M € 3.2 M	€ 10.0 M € 3.2 M	48.9%
		2 products	2 companies		€ 0.0 M	€ 13.2 M	€ 13.2 M	
Fractionated heparins	Enoxaparin sodium (Lovenox, Sanofi)	▪ Enoxaparine Crusia	Biogaran	▪ Sept. 2018	€ 0.1 M	€ 4.4 M	€ 4.5 M	8.0%
		1 product	1 company		€ 0.1 M	€ 4.4 M	€ 4.5 M	

Sources: GERS – Smart Pharma Consulting analyses

[1] International Non-propriety Name – [2] Ex-factory prices excluding rebates and taxes –[3] Biosimilar penetration in volume in December 2018 – [4] Eporatio is not a biosimilar per se but rather a "me-too" product

Biosimilar penetration is faster and faster, notably in the hospital market where it ranged from ~62% (for trastuzumab) to ~82% (for rituximab) in December 2018

Biosimilars market penetration



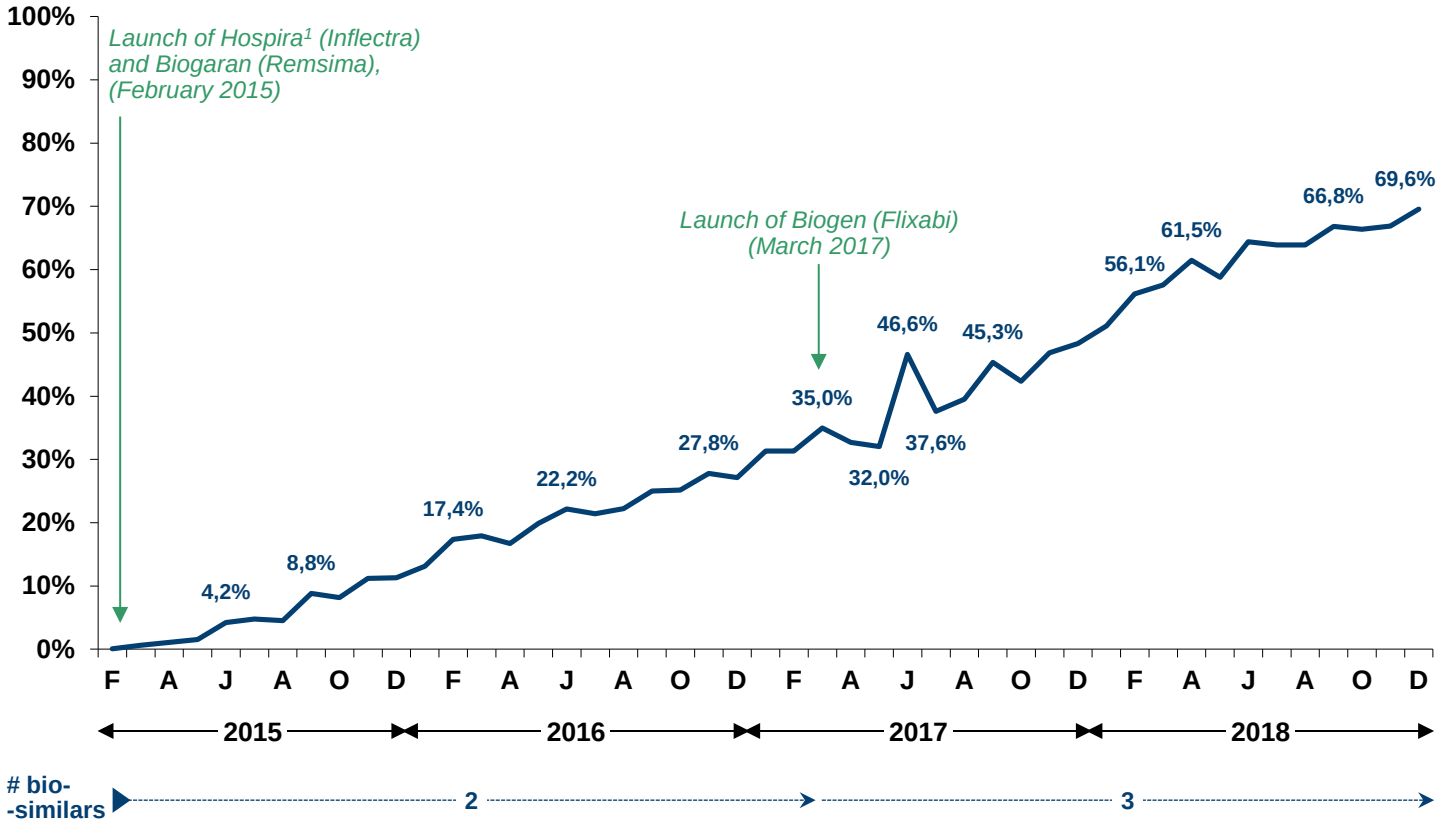
Sources: GERS – Smart Pharma Consulting analyses

[1] Excluding the 1,400 mg subcutaneous form, that is not yet subject to biosimilars competition – [2] Excluding the 600 mg subcutaneous form, that is not yet subject to biosimilars competition – [3] Products bought and/or delivered at hospitals and retail pharmacies – [4] Products exclusively bought and delivered at hospitals

Infliximab biosimilars penetration reached ~70% of the market in volume, ~4 years after biosimilar entry, despite MSD competitive price offering

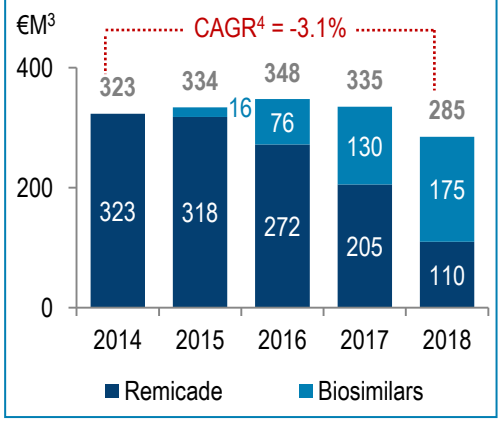
Penetration rate in volume – Infliximab case study

Biosimilars penetration as a % of infliximab sales in standard units



Comments	
Originator	Remicade (MSD)
Status	On-top of T2A[2] biologic drug
EPHMRA class	Anti-TNFs (L04B)
Indications	Ulcerative colitis, Crohn's disease, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis

Sales dynamics (2014 – 2018)



Sources: GERS – Thériaque – Smart Pharma Consulting analyses

[1] Acquired by Pfizer in September 2015 – [2] Activity-based costing – [3] Ex-factory price, excluding VAT and rebates – [4] Compound annual growth rate

The French biosimilars market is split in two different segments that require, from pharma companies, different strategies, tactics and organizational models to succeed

The biosimilars market segments

	Hospital-only market segment	Hybrid market segment
Definition	▪ Prescribed, purchased and delivered at hospitals (e.g. infliximab, rituximab, trastuzumab)	▪ Prescribed by hospital and/or office-based specialists, purchased and delivered by hospital and retail pharmacies (e.g. epoetin, filgrastim) or retail pharmacies only (e.g. follitropin alfa, somatropin)
Pricing	▪ Free pricing for drugs included in T2A system[1] ▪ Responsibility tariff set by the CEPS[2] for drugs on-top of the T2A list[3] (e.g. infliximab, rituximab)	▪ Ex-factory price set by the CEPS initially at -30% or -40% below the original biologic on the hospital and the retail market segments, respectively
Purchasing	▪ Mainly purchased through tenders and/or to a lower extent through negotiated agreements ▪ Possibility to grant rebates to hospitals ▪ Strong price pressure	▪ The level of rebates to retail pharmacies is limited to a maximum of 2.5% of the ex-factory price which is in general granted by wholesalers[4] ▪ Limited price pressure on retail sales
Medico-marketing activities	▪ Medical activity carried out by MSLs to reassure prescribers about the quality of the biosimilars ▪ Key account management activity carried out by KAMs to win tenders and set up a follow up plan	▪ Medical activity carried out by MSLs to reassure prescribers about the quality of the biosimilars ▪ Promotional activity carried out by marketers and medical reps to be prescribed to in- and out-patients
Market size & profit level	▪ Market size 2018: € 164 M (net price) ▪ Market growth 2007 – 2018: + 119% (net sales) ▪ Leading players profitability: medium to high	▪ Market size 2018: € 194 M (net price = price list) ▪ Market growth 2007 – 2018: + 62% (net sales) ▪ Leading players profitability: high

Sources: Smart Pharma Consulting analyses

[1] Activity-based costing system similar to a diagnosis-related group-based funding system – [2] Drug pricing committee – [3] Includes the most expensive drugs for which the CEPS sets a maximum reimbursed price called "Responsibility tariff" which is 30% (for hospital-only drugs) below the price of the original biologic before its price is cut, following biosimilars entry – [4] Pharma companies are not used to giving discounts to retail pharmacists for their biosimilars

Substitution of biosimilars by retail pharmacists, at treatment initiation, is legal since 2013, but the absence of the corresponding decree does not allow its implementation

Regulations specific to biosimilars

Biosimilar drugs[1]

- A biosimilar drug is any biological drug that has the **same qualitative** and **quantitative** composition of **active substance** and the same pharmaceutical **form** as a biological originator…
- … but does not fulfill the conditions for being regarded as a generic due to differences related in particular to **raw material variability** or **manufacturing processes** requiring the achievement of additional **preclinical** and **clinical data** under regulatory conditions…
- … demonstrating that the biosimilar:
  - Is similar to the biological originator
  - **Does not differ** significantly from the biological originator in terms of **quality**, **efficacy** and **safety**

Biosimilar register	▪ The ANSM[2] has created in 2017 **similar biologic groups**, each of them defined by a **reference biologic** and its corresponding **biosimilars**, listed by brand name
Biosimilar substitution right	▪ France was the first European country to **allow** the **substitution** of biosimilars, in **December 2013** ▪ Biosimilars substitution is only permitted if: – A **new treatment** is started – Within the **same** similar biologic **group** – The prescriber has not explicitly prohibited, in writing, the substitution of the prescribed drug – The pharmacist has **informed the prescriber**… – … and **recorded the details** of biosimilar dispensed ▪ In the **absence of a decree** defining the conditions of substitution, the **law has not yet been implemented**
Inter-changeability	▪ The ANSM has specified in **May 2016** that **inter-changeability** was **possible** between biologic drugs belonging to the **same similar biologic group**

Sources: Public Health Code – Official Gazette – ANSM – Smart Pharma Consulting analyses

[1] A specific legal framework for biosimilar medicines was introduced in Europe on March 31st, 2004 and the first biosimilar was authorized by the European Commission in April 2006 – [2] "Agence nationale de sécurité du médicament": National Agency for the Safety of Medicines and Health Products

The health authorities are strongly determined to accelerate the penetration of biosimilars, but remain relatively cautious to avoid any potential public health issue

Health authorities measures to boost biosimilars

LFSS 2018 – Focus on the CAQES

- Since January 2018, contracts between hospitals, health regional agencies and health insurance named CAQES[1], have set prescription targets for biosimilars

Objective

- Achieve **70%** penetration of hospital biosimilars in units, at **national level[2]**

Implementation

- Promotion of **biosimilars** prescriptions in the reference list
- Remuneration of hospitals: 20% of the price difference between reference and biosimilar products

2017 – Ministerial Order

- The DGOS[3], DSS[4], DGS[5] and the UNCAM[6] published an order on October 12th, 2017 to require the Regional Health Agencies (ARS) to promote the use of biosimilar drugs
- As a result, ARS are invited to promote the use of biosimilars by:
  - Informing patients
  - Harmonizing prescribers practices in favor of biosimilars
  - Helping hospitals organize tenders as soon as biosimilars are on the market
  - Developing financial tools to measure the savings related to biosimilars
- The DGOS has informed that physicians are authorized to switch one biological drug by another similar one during a treatment

LFSS 2018 – Article 51

- In August 2018, the Ministry of Health launched an experiment with 45 selected hospitals to stimulate their prescription of biosimilars delivered in retail pharmacies

Objective

- 15-points increase in biosimilar prescription rates vs. non-experimental hospitals

Implementation

- Duration: 3 years
- Scope: etanercept and insulin glargine at national level[7]
- Remuneration of hospital services: 30% of the price difference between reference and biosimilar products

ROSP

- This bonus program, which encourages physicians to comply with “best prescribing practices” for a better efficacy/cost ratio, includes, since 2017, the prescription of the insulin glargine biosimilar

Sources: Decree related to CAQES and setting quality and efficiency reference objectives – Smart Pharma Consulting analyses

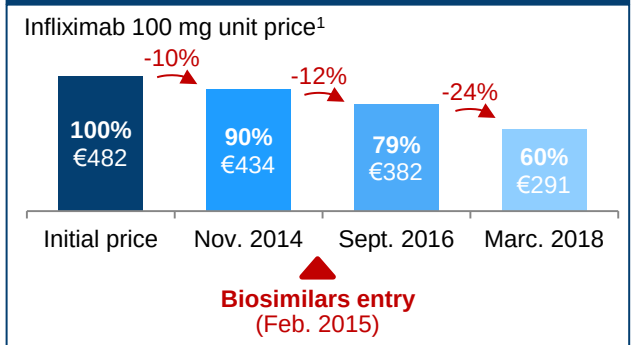
[1] CAQES: contract for healthcare quality and efficiency enhancement – [2] In December 2017, the government has set the global (hospital and retail markets) objective of 80% biosimilar penetration by 2022 – [3] Directorate of Health Care Supply – [4] Directorate of Social Security – [5] Directorate General for Health – [6] National Union of Health Insurance Funds – [7] Adalimumab has entered in the scope of the experiment in the second quarter 2019

Excepted for trastuzumab and etanercept, whose first biosimilars were launched in 2018 and 2016 respectively, the CEPS dropped all reference prices by ~40%

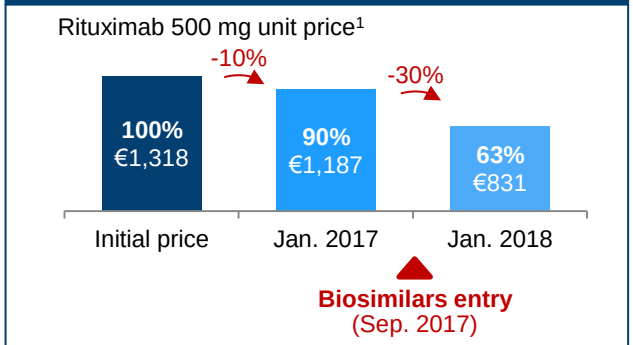
Historical imposed price cuts over time

Hospital-only products

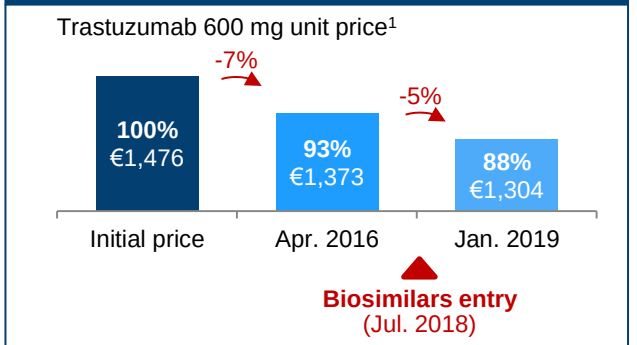
Infliximab (Remicade)



Rituximab (MabThera)

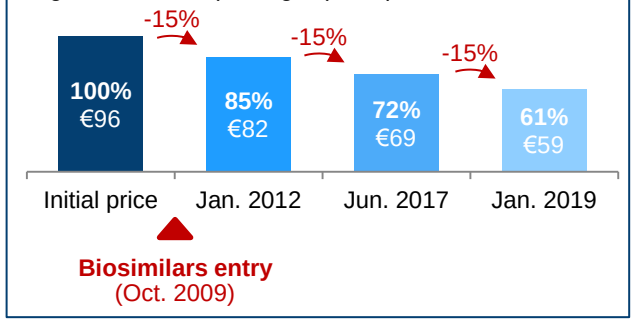


Trastuzumab (Herceptin)

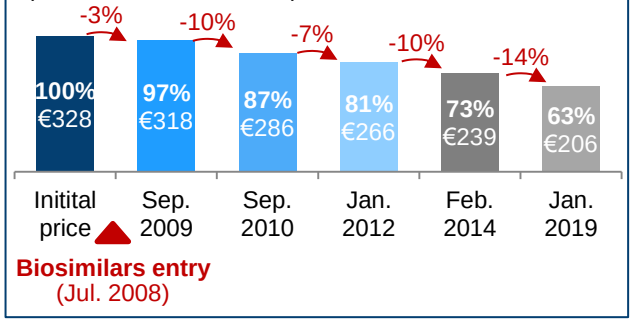


Hybrid products[2]

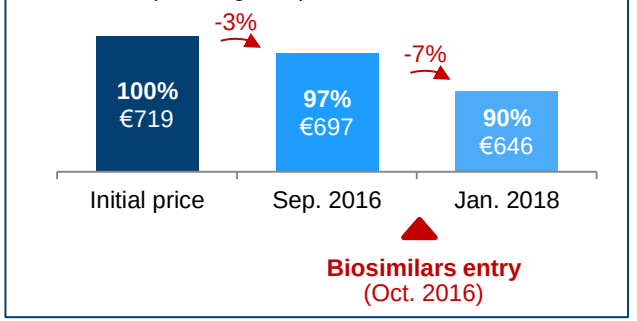
Filgrastim (Neupogen)



Epoetin (Eprex)



Etanercept (Enbrel)



Sources: French National Health Insurance prices database – Smart Pharma Consulting analyses

[1] Ex-factory price per standard unit, excluding rebates and taxes –
[2] Products with sales at hospital levels and retail pharmacies

Biosimilars prices on the hospital market are either free or set by the drug pricing committee (CEPS), while on the ambulatory market they are always regulated

Biosimilars price regulation – New Health Authorities Doctrine

Hospital market segment

- If the reference biological drug is **included in the T2A** (activity-based costing system), thus its price, as well as its corresponding biosimilars ones, will be **unregulated**
- If the reference biological drug is on:
  - **The top of T2A hospital drug list**[1] or
  - **The reassigned drug list**[2]

  the CEPS (drug pricing committee) applies the following pricing principles, when the first biosimilar enters the market:
  - A 30% price cut for the originator and its biosimilars
  - 24 months and 48 months later, 10% to 30% additional price cuts depending on difference observed between actual net prices and prices set by the CEPS

Ambulatory market segment

- **At the entry date of biosimilars:**
  - The CEPS sets the price of biosimilars **40% below** the price of the originator
  - The originator is imposed a price cut of **20%**
- **24 months and 42 months after the entry of the first biosimilar:**
  - Additional price cuts aimed at **price convergence**…
  - … and depending on the respective **market shares** of the originator and of its biosimilars

  will be imposed

Sources: CEPS Activity Reports – LEEM – IRDES – Decree of March 25th, 2016 regarding modalities of inscription to the on top of T2A list – Smart Pharma Consulting analyses

[1]This list includes expensive products which are funded on top of the hospital service tariffs (hospital budget) to improve patients access to innovation – [2] These products, which are on the retrocession list, can be sold to outpatients by the hospital pharmacies and, in such a case, are funded by the National Health Insurance Fund

Cost containment policies tend to make hospital prescribers increasingly concerned about the costs induced by their prescriptions, providing opportunities for biosimilars

Biosimilars and cost of hospital prescriptions

Drugs dispensed at hospitals

- Since 2007, hospital expenditures are covered by the National Health Insurance Fund according to their activity level, based on a fixed fee-for-service model, called T2A[1]
- As a result, hospitals have a strong incentive to pay the lowest price, as possible, for drugs and for the other goods they purchase, to achieve a balanced budget
- For drugs on "the top of T2A" and/or on the reassigned list, hospitals are reimbursed by the National Health Insurance Fund, at the reference price set by the CEPS[2]
- However, hospitals may obtain a lower price and, in such a case, the saving will be equitably distributed between hospitals and the National Health Insurance Fund

Biosimilars may contribute to reduce hospitals costs, but in a relatively limited proportion, knowing that drugs account for ~6% of total hospital budget[3]

Drugs dispensed at retail pharmacies

- The article 47 of the Social Security Act for 2010 introduced a new measure to contain the cost of drugs dispensed in retail pharmacies, but prescribed at hospitals, as this cost was increasing much faster than that related to primary care prescriptions
- This measure sets an annual maximum growth rate (+4.0% for 2018 and +3.3% for 2019) of drug expenditure related to hospital prescriptions that are bought at retail pharmacies by patients
- If exceeded, the ARS[4] may place the offending hospital under its supervision to compel it to improve prescribing practices, and may possibly demand financial penalties

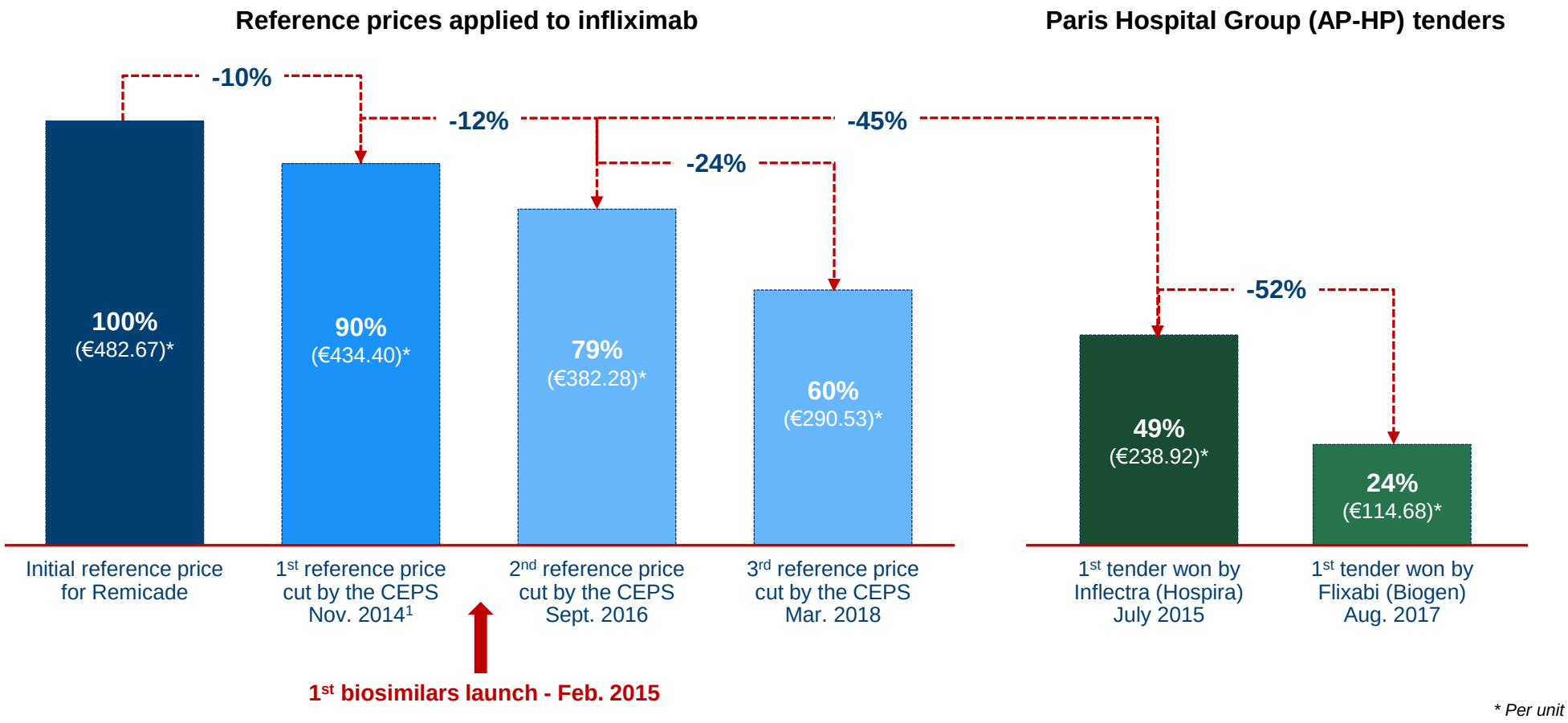
Prescription of biosimilars may help better control the cost evolution of drugs prescribed in hospital and dispensed in retail pharmacies

Sources: www.sante.gouv.fr/tarification-a-l-activite.html – Article 47, "LFSS 2010" Official Gazette, (December 27th, 2009) – Smart Pharma Consulting analyses

[1] Tarification à l'activité – [2] Drug pricing committee – [3] Salaries account for ~70%, general & administrative expenses for ~18% and medical devices for ~6% – [4] Regional health agency

2.5 years after biosimilars entry, the net price of infliximab (ex-factory price minus hospital rebates) has been reduced by ~76%

Hospital pricing evolution – Infliximab case study



** Per unit*

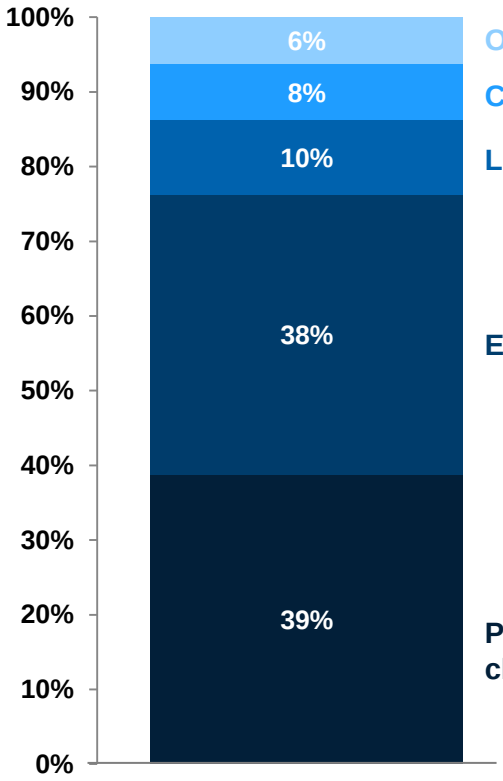
Sources: Desk research – APM News – Interviews – Smart Pharma Consulting analyses

[1] Applied to all infliximab brands, including biosimilars

The main criteria that will determine biosimilars listing in hospitals are product characteristics and economic aspects according to this pilot study

Listing procedures and protocols in hospitals

Criteria driving preference to list drugs subject to biosimilars competition at hospitals



Other services

- *"**Could be of interest** (e.g. **support during the implementation of treatments**, **help in organizing the services of hospitals**)" (2)*

Corporate reputation

Logistics aspects

- *"We have **more confidence in the most reputable pharmaceutical companies** because **we know the quality of their products and their ability to meet their commitments in terms of delivery times**" (2)*

Economic aspects

- *"**Are to be considered** even when the volumes of drugs in hospitals remain low such as for G-CSF" (2)*
- *"**Important** criterion **given the current context of willingness to control health expenditure**" (2)*
- *"One of the **most important criteria for biosimilars**" (2)*

Product characteristics

- *"The **methods of conservation** of the products are important. For example, products which do not need the respect of the cold chain are favoured" (2)*
- *"**The ease of use and the safety of injection** of the device is important" (1)*
- *"**The bioequivalence studies** are essential to adopt a biosimilar" (1)*

(X): Number of quotes

Source: Interviews with 4 hospital pharmacists (October 2018) – Smart Pharma Consulting analyses

HCPs would adopt biosimilars provided their bioequivalence to the originator is proven and their pricing generates savings

Expectations from HCPs for biosimilars

"What factors might convince you to prescribe a biosimilar once the molecule has fallen into the public domain?"

(+)

- *"**A drop in pricing**" (10)*
- *"**Bioequivalence to the original brand**" (2)*
- *"An optimal presentation of the product: **no reconstitution, already packaged in the syringe!**" (1)*
- *"That the treatment is **in adequacy with the challenges and prescription goals of the CAQES[1] plan**" (1)*
- *"**That the treatment be listed within the Unicancer[2] market**" (1)*

"What would be the barriers to use a biosimilar?"

(-)

- *"If there is an **uncertainty about the true biosimilarity of the product due to fewer clinical studies** and a lack of perspective on its use" (4)*
- *"**If it is not listed within my hospital**" (3)*
- *"**If the packaging is less convenient to use**" (2)*

"What would you recommend pharma companies to do to reinforce your preference?"

- *"To offer competitive prices where the savings made by the healthcare facility are substantial" (4)*
- *"To perform clinical bioequivalence trials for biosimilar products with follow-up over time, and injection site tolerance tests" (2)*
- *"To provide field monitoring services to ensure proper use of products" (2)*
- *"To develop long-acting forms and to target product conservation issues" (2)*
- *"To stop focusing on medico-economics only and to invest in clinical studies too" (1)*

Number of respondents: 10

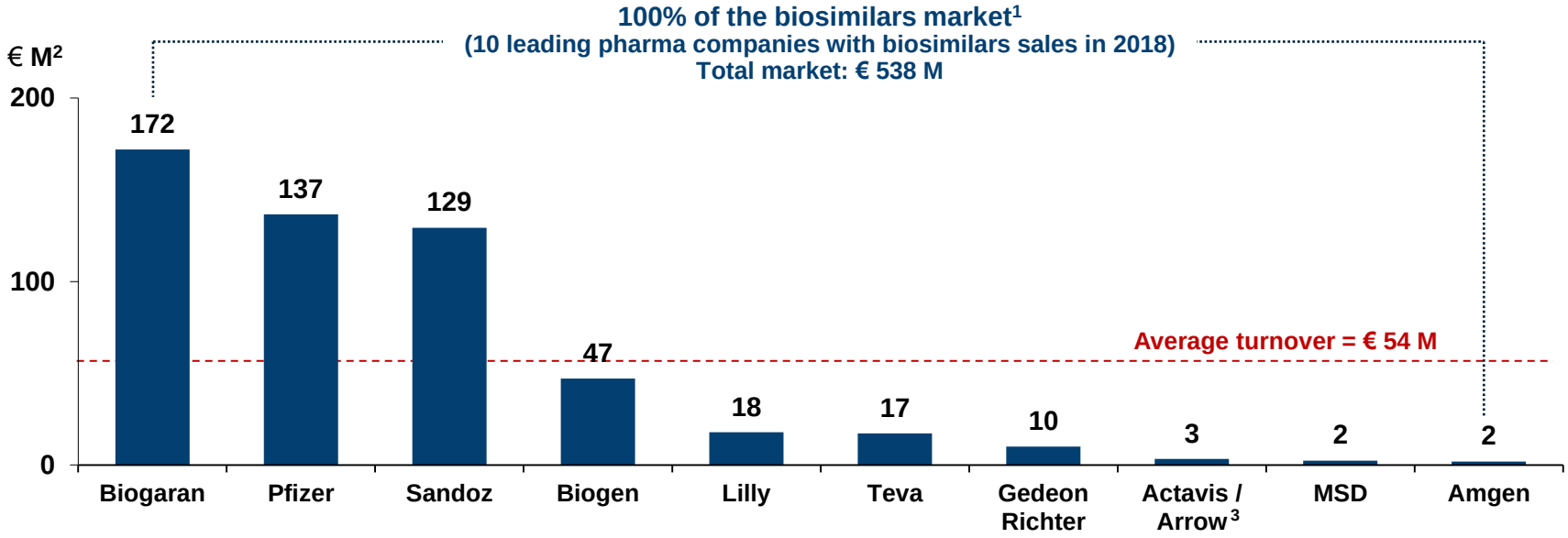
(X): Number of quotes

Source: Interviews with 6 hospital physicians and 4 hospital pharmacists (October 2018) – Smart Pharma Consulting analyses

[1] Contract for the improvement of quality and efficiency of care – [2] Hospital network regrouping the 18 regional centers for the fight against cancer (CRLCC) entirely dedicated to oncology and including a national purchasing unit

In 2018, Biogaran, Pfizer and Sandoz generated individually more than € 100 M sales and represented together ~82% of the French biosimilars market in value terms

Top 10 companies on the biosimilars market – In value[1] (2018)



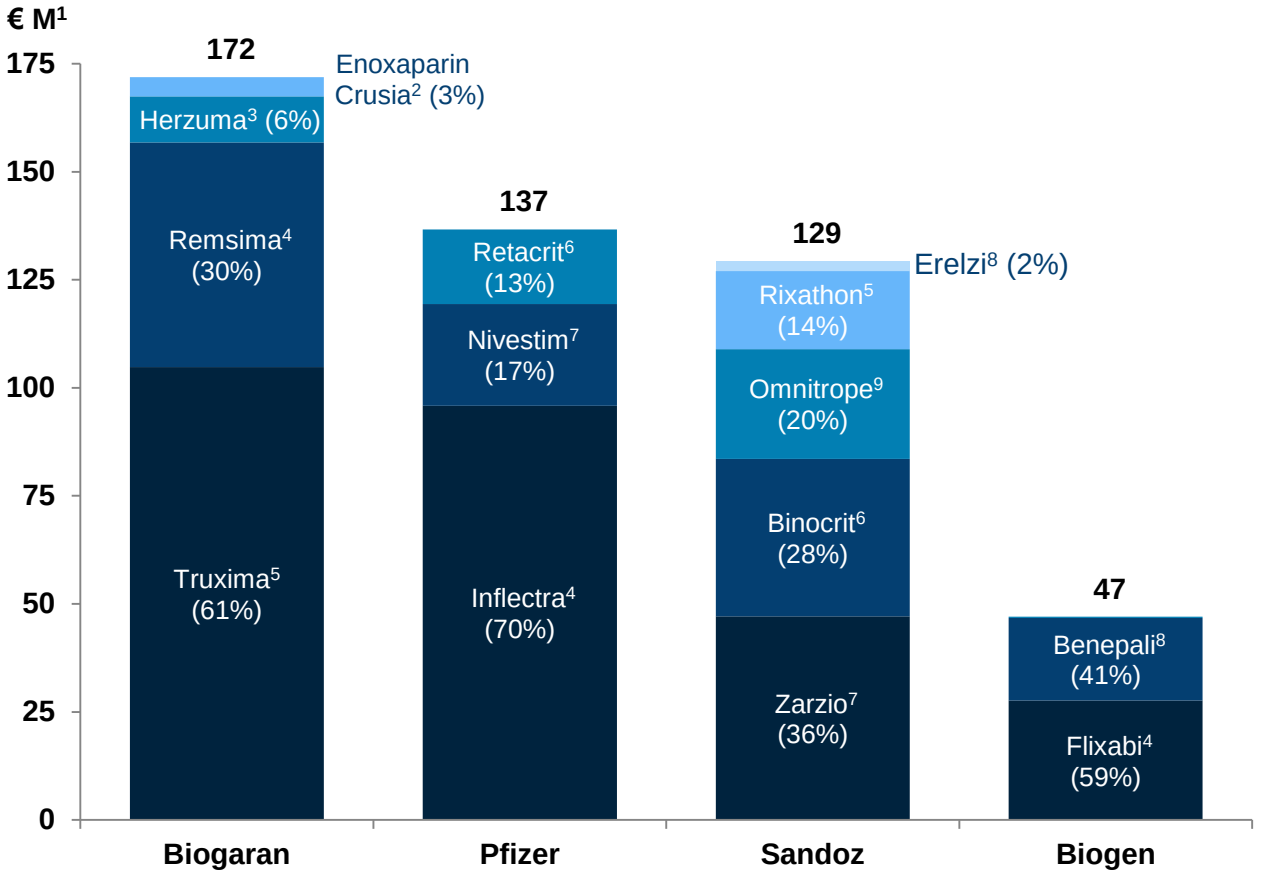
	Biogaran	Pfizer	Sandoz	Biogen	Lilly	Teva	Gedeon Richter	Actavis / Arrow[3]	MSD	Amgen
Market share	32.0%	25.4%	24.1%	8.7%	3.3%	3.2%	1.9%	0.6%	0.4%	0.4%
Biosimilars weight in the portfolio	14.2%	10.0%	19.2%	12.3%	5.0%	2.5%	66.9%	0.7%	0.2%	0.3%
2017-2018 evolution	+277.5%	+7.2%	+46.4%	+277.4%	+161.9%	+11.3%	+38.6%	+311.4%	N/A	N/A

Sources: GERS – Smart Pharma Consulting analyses

[1] Both retail and hospital sales – [2] Ex-factory price, excluding taxes and rebates – [3] Part of Aurobindo, since its acquisition of Actavis in 2014

In 2018, the top 4 companies operating on the French biosimilars market had from 2 to 5 brands, and sales split on the hospital and retail market segments

Top 4 companies on the biosimilars market – Portfolio structure (2018)



- **Biogaran:**
  - ~97% of prescriptions and sales come from hospital-only drugs (i.e. Truxima, Remsima and Herzuma) which are prescribed and dispensed at hospital
- **Pfizer:**
  - All biosimilars are either prescribed or initiated by hospital physicians
  - 26% of the corresponding sales are purchased at retail pharmacies
- **Sandoz:**
  - All biosimilars are either prescribed or initiated by hospital physicians
  - ~72% of Sandoz sales are generated at retail pharmacies
- **Biogen:**
  - All biosimilars are either prescribed or initiated by hospital physicians
  - ~40% of sales are bought at retail pharmacies

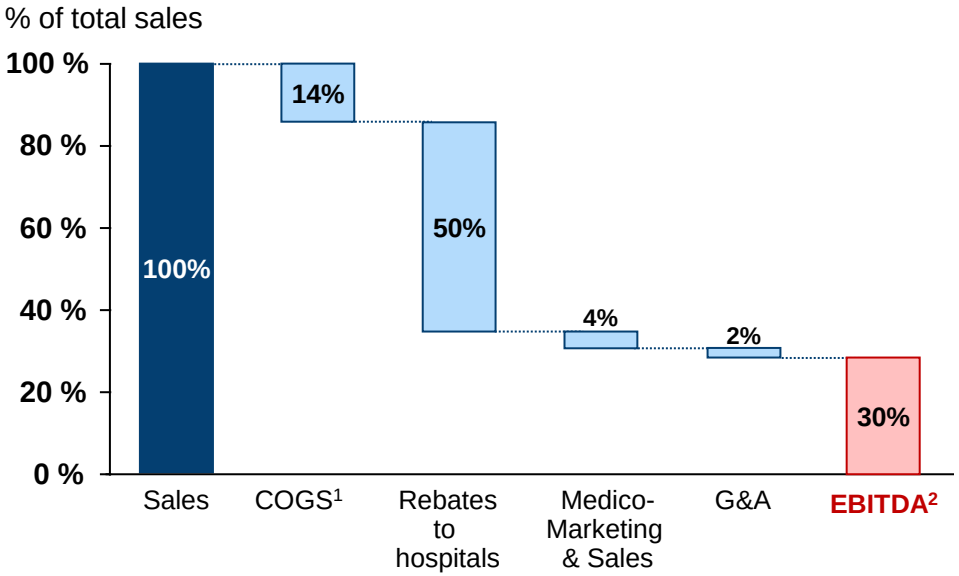
Sources: GERS – Smart Pharma Consulting analyses

[1] Both retail and hospital sales, in ex-factory price, excluding taxes and rebates – [2] Enoxaparin sodium – [3] Trastuzumab – [4] Infliximab – [5] Rituximab – [6] Epoetin – [7] Filgrastim – [8] Etanercept – [9] Somatropin

The hospital-only biosimilar model appears to be less profitable than the hybrid one due to a much higher level of rebates granted by pharma companies

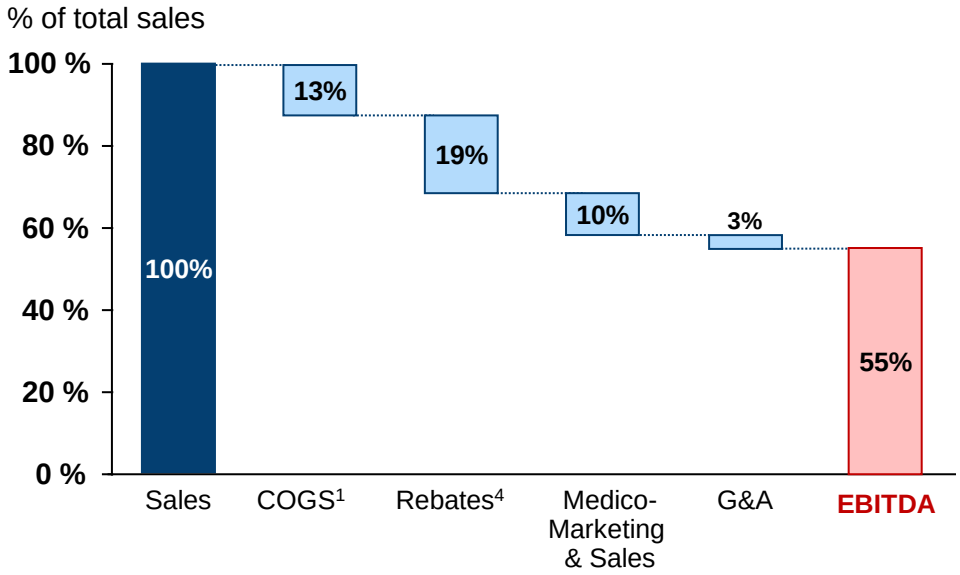
Estimated profitability of leading pharma companies on the biosimilars market (2018)

Hospital-only biosimilar model



- Estimates based on annual sales of € ~150 M generated by hospital-only biosimilars, with an average price list of 30% below the price of original brands before they enter the market
- Average discounts to hospitals: -50% on price list (ex-factory price)
- Medico-marketing and sales costs, incl.: 5 KAMs and 5 MSLs
- All other costs included in G&A[3]

Hybrid biosimilar model



- Estimates based on total annual sales of € ~130 M of which € ~90 M (72%) sold on the retail market, with an average price list of 40% below the price of original brands before they enter the market
- Average discounts to hospitals: -50% to -90% on price list [4]
- Medico-marketing and sales costs, incl.: 3 KAMs, 40 Reps and 4 MSLs
- All other costs included in G&A

Sources: Smart Pharma Consulting interviews with 5 General Managers of companies operating in the biosimilars market – Smart Pharma Consulting estimates

[1] Cost of goods sold, including licensing fees and distribution costs – [2] Earnings before interest, taxes, depreciation and amortization – [3] Registration costs, head office costs, management costs, support functions – [4] ~50% to hospital-only drugs, ~90% to non hospital-only drugs. No significant rebates granted to retail pharmacies

The most important success factor on the biosimilars market is to be the 1st market entrant and have the opportunity to remain the only biosimilar, for several months

Key success factors on the biosimilars market

#1 – Be the 1st entrant

- The historical analysis of the French market shows that the first entrants have a bigger market share than the followers (see p. 7 to 10)
- When a biosimilar benefits from a temporary period of monopoly, the probability it wins hospital tenders vs. the originator is very high
- Once a market has been won, it is locked for two to three years and the following biosimilars have to wait

#2 – Offer the best price

- The lowest the price offer, the highest the probability to win the tenders, especially for hospital-only products for which the savings for the hospital can be important, unlike for the biosimilars which are mainly bought at retail pharmacies
- Superior product attributes and/or services may help a biosimilar win a tender, in certain cases, only if its price offer is not superior to 5% to 10% than the lowest bidder

Key Success Factors

#4 – Develop services

- Services proposed to hospital pharmacists, physicians, nurses and patients to facilitate the procurement, the prescription, the patient education and the drug usage may play a significant role to get preferred by hospital HCPs[4]
- The market insight (knowledge and understanding) of in-field collaborators is a prerequisite to deliver highly valued services
- The quality of services will reinforce the reputation of the biosimilars company and preference of HCPs for its products

#3 – Propose a better product

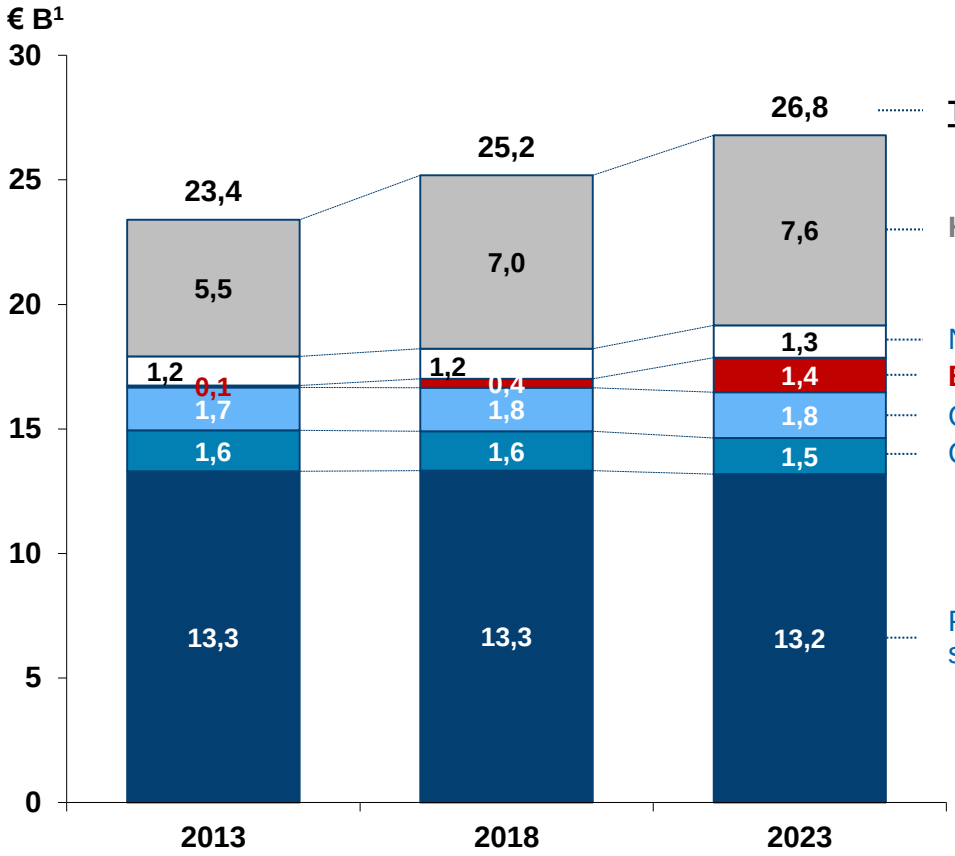
- There are possibilities to differentiate biosimilars amongst themselves and vs. the corresponding original biologic:
  - Amgevita (Amgen) and Hulio (Mylan) propose a citrate-free version of adalimumab, as Humira (AbbVie)[1] does since 2018, associated with less injection site-related pain[2]
  - Benepali (Biogen), a biosimilar of etanercept, has shown in a European study[3] that its autoinjector was easier to operate and more intuitive to use compared with the Enbrel (Pfizer) one, according to 86% of the 149 nurses who had been interviewed

Sources: Smart Pharma Consulting interviews with 5 General Managers of companies operating in the biosimilars market – Smart Pharma Consulting analyses

[1] Which is not the case for Imraldi (Biogen) and Hyrimoz (Sandoz) – [2] Peter Nash, Rheumatol Ther (2016) 3:257-270 – [3] Kunal Thaku, Rheumatol Ther (2016) 3:77-89 – [4] Especially for products that are used in home care (e.g. subcutaneous anti-TNFs). It is essential at the launch phase to put in place observational studies in the key centers to boost the adoption of the biosimilar brand by the HCPs

The biosimilars market should reach € 1.4 B in net value in 2023, with 1/3 of the growth driven by new biosimilars and 2/3 by increasing penetration of existing ones

Drugs sales forecast by segment (2013 – 2018 – 2023) – Net price



	CAGR[5] 2013-2018	CAGR 2018-2023
Total Market (Net price)	**+1.5%**	**+1.2%**
Hospital sales[2]	+4.9%	+1.8%
Non reimbursed	+0.5%	+1.5%
Biosimilars (hospital & retail)	**+36.2%**	**+31.0%**
Generics[3]	+0.4%	+0.9%
Genericized originators	-0.9%	-1.5%
Patent-protected and other specific drugs[4]	+0.0%	-0.2%

Note: In 2023, The biosimilars sold on the retail market should account for 68% of the total vs. 54% in 2018. The growth will be driven by new biosimilars* for 1/3 and by increasing penetration of existing ones for 2/3

** Such as: teriparatide, secukinumab, eculizumab, belimumab, certolizumab, ipilimumab, bevacizumab, ranibizumab, liraglutide, cetuximab, natalizumab, abatacept, insulin lispro*

Sources: GERS dashboards – Smart Pharma Consulting estimates

[1] Constant ex-factory prices including estimated rebates to hospital and retail pharmacists– [2] Excluding hospital sales of biosimilars but including all other products on the hospital budget and products invoiced in addition of the hospitalization charges (on top of T2A) and reassigned medicine sales – [3] Reimbursable generics and quasi-generics – [4] Sales of drugs whose patents have not expired and of other specific products (calcium, sodium, potassium, paracetamol, etc.) – [5] Compound annual growth rate

The future growth of biosimilars will be mainly driven by health authorities measures introduced to boost HCPs[1] prescriptions and by LOE[2] of several high sales biologics

Drivers & limiters of the biosimilars market (2013 – 2018 – 2023)

	Drivers	Limiters
Health authorities & Payers	▪ Biosimilars can increase access to treatments by: – **Decreasing the overall treatment costs** and thus – **Increasing affordability** (treatment of larger populations) ▪ Increasing **body of evidence** showing the **reliability**, **efficacy** and **quality** of biosimilars	▪ "**Precaution principle**": high cautiousness due to major public health issues in the past (e.g. blood transfusions contaminated with HIV, growth hormone case, sudden increase of pure red cell aplasia (PRCA) with Eprex[3]) ▪ **Substitution** permitted by law since Dec. 2013 **but not implemented**, in the absence of the corresponding decree
Hospital HCPs	▪ They contribute to improve **hospitals financial balance** ▪ Objective of penetration set at hospital level (CAQES) ▪ **Financial incentives** proposed by heath authorities for prescribing biosimilars (i.e. insulin glargine, etanercept, adalimumab) through the "article 51" experiment ▪ For physicians, biosimilars are an **alternative to reference products** (in case of shortage for instance)	▪ **No** guarantee of **perfect equivalence** with the reference product ▪ **Physicians** generally have **close relationships** for many years **with original brand companies**, which may discourage them to use (extensively) biosimilars
Patients	▪ None, except in cases where patients might have to bear (totally or partially) the cost of biological drugs	▪ **Preference for originators**, on principle, especially in the case of serious and/or chronical diseases
Biosimilar companies	▪ **Increasing number of biosimilar** products per molecule **accelerates** market **penetration** and **reduces** hospital **prices** ▪ ~**13 biologics** with high sales levels **will lose** their market **exclusivity** and face biosimilar competition by the end of 2023	▪ **The intensification of** competition **drives** biosimilar **prices** down and **jeopardizes** biosimilar companies **profitability**… ▪ … rendering the **market** much **less attractive** for new players

Sources: IQVIA PharmaStat (as of February 2019) – Smart Pharma Consulting analyses based on external interviews

[1] Healthcare professionals – [2] Loss of exclusivity – [3] Increase in PRCA explained by an increase in the immunogenicity of Eprex following a formulation change in 1998, in which the human serum albumin stabilizer was replaced with polysorbate 80 and glycine

The market of biosimilars will benefit from the launch of new products in existing classes and in new classes by 2023

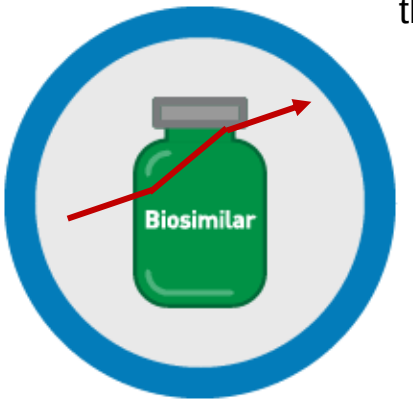
The French biosimilars market in a nutshell

1. The market structure and dynamics

- Since 2014, the market has increased four-fold[1]
- The penetration of hospital-only biosimilars is must higher than the one of biosimilars which are also delivered on the retail market

2. The French regulatory environment

- Since 2017, health authorities have multiplied the initiatives to boost the biosimilars market
- They have also developed a doctrine defining the decrease of biosimilars price over time



3. The customers behaviors

- Hospital listing and prescribing depend mainly on product attributes and price
- The absence of authorization for retail pharmacists to substitute biosimilars[2] makes physicians the main driver

4. The competitive landscape

- The top 3 leading players[3] have generated more than € 100 M gross sales in 2018, accounting for ~82% of the market in value
- They have generated EBITDA[4] rates ranging from 30% to 60% of gross sales

5. The key success factors

- Enter first the market
- Be the lowest-priced bidder…
- … and/or offer superior services
- Offer a better product than competitors

6. The 2018 – 2023 market growth

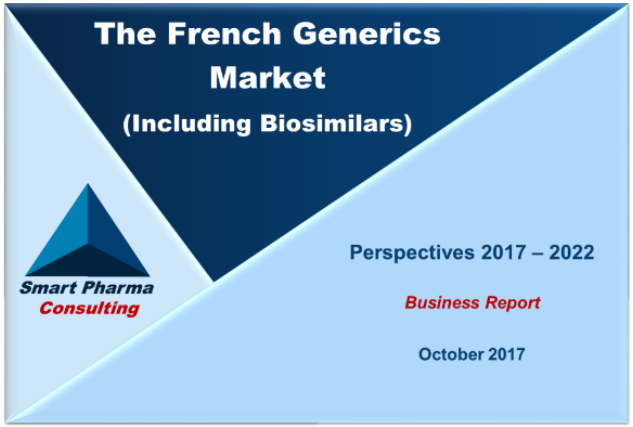
- The market should increase by € 1 B, thanks to the LOE of blockbusters (e.g. Avastin, Lucentis) and the increasing market penetration of recent biosimilars (e.g. Humira, Herceptin)

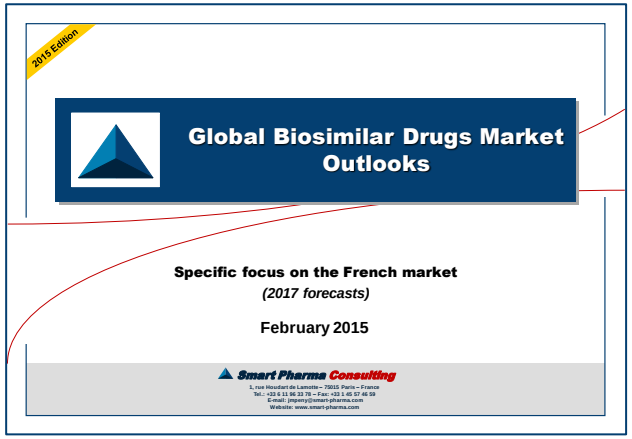
Sources: Smart Pharma Consulting analyses

[1] In net value – [2] The implementation decree which is required to apply the law voted in December 2013 is still pending. No change is expected in the short term. The health authorities are not in favor of substitution at retail level for public health security and responsibility reasons – [3] Biogaran, Pfizer and Sandoz – [4] Earning before interest, taxes, depreciation and amortization

Smart Pharma Consulting has published several analytical reports and carried out consulting projects on biosimilars market attractiveness and key success factors

Selected publications & consulting projects on biosimilars





Examples of recent consulting projects

- **2019** Training of a biosimilar sales forces on the healthcare system at national, regional and local levels
- **2018** Assessment of the market potential for a biosimilar version of pegfilgrastim
- **2018** Assessment of the market potential for a biosimilar version of adalumimab
- **2018** Analysis and forecasting of the original and biosimilar versions of infliximab
- **2017** Assessment of the French biosimilars market potential for a leading generics player
- **2017** Development of an economic simulation tool for hospital KAM managers of a biosimilar company
- **2017** Set up of coordinated action plans for in-field collaborators of a company marketing biosimilars
- **2017** Training of hospital sales forces of a biosimilar company
- **2017** Assessment of potential sales for biosimilar versions of teriparatide and pegfilgrastim for a European mid-size pharma company

Sources: Smart Pharma Consulting

Smart Pharma Consulting

Consulting firm dedicated to the pharmaceutical sector operating in the complementary domains of strategy, management and organization

The Smart Pharma Business Papers

- Our business papers have in common to:
  - Be well-documented with recent facts and figures
  - Highlight the key points to better understand situations
  - Propose in-depth analyses
  - Determine the business implications for stakeholders

Succeeding on the French Biosimilars Market Everything you wanted to know!

- In this position paper, Smart Pharma Consulting:
  - Analyzes the biosimilars market structure and dynamics
  - Reviews the French regulatory environment
  - Shares insights regarding customers behaviors
  - Evaluates the competitive landscape
  - Identifies the key success factors for pharma companies offering biosimilars
  - Estimates the 2018 – 2023 market growth potential
- This position paper is available, free of charge, on the Smart Pharma Consulting website, as all our other position papers

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  - Teaching and training activities
  - Publication of articles, booklets, books and business reports
- **Since 2012**, we have published **18 business reports** covering the following topics:
  - French healthcare system and pharma market (2019, 2017, 2015, 2014, 2013, 2012)
  - Market access and drug valuation (2016)
  - French generics market (2017, 2016, 2014, 2012)
  - Global biosimilars drugs market (2015, 2012)
  - Best pharma performers (2015)
  - French pharma distribution (2015, 2012)
  - Digital marketing (2012)
  - French OTC market (2012)…
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- We expect that this new position paper will be helpful

Best regards,

Jean-Michel Peny

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