

The French Generics Market

(Including Biosimilars)

Excerpts



Smart Pharma
Consulting

Perspectives 2017 – 2022

Business Report

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This report describes and explains the dynamics of the French generics and biosimilars markets and evaluates their attractiveness by 2022

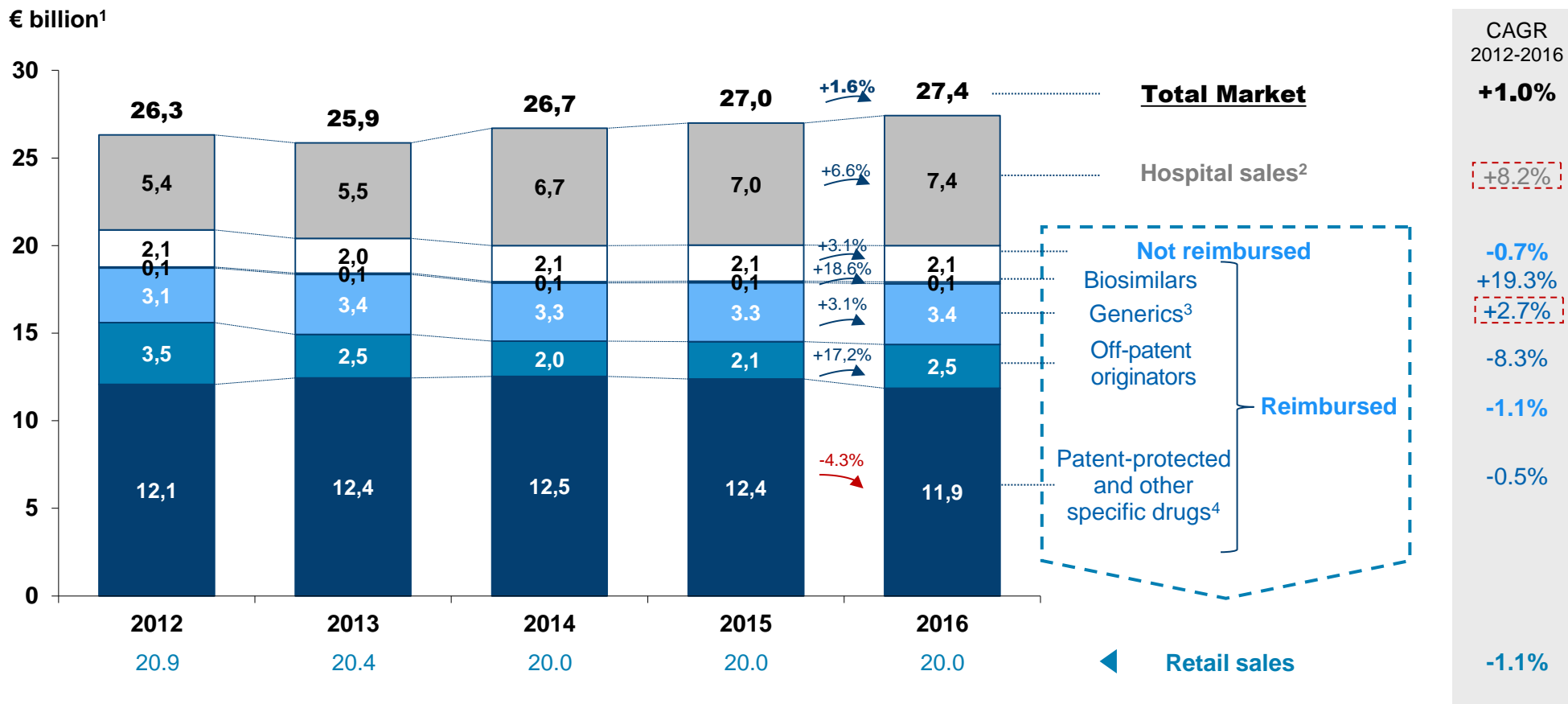
Context and objectives

- **In this report, Smart Pharma Consulting proposes to cover the following questions:**

- What is the definition and status of generic drugs in France?
- What are the recent dynamics, changes and trends on the retail generics market?
- What are the recent dynamics, changes and trends on the hospital generics market?
- What is the behavior of the different stakeholders towards generics and how should it evolve?
- What are essentially similar drugs and what is their performance?
- What are biosimilar drugs and what is their performance?
- Who are the major generics manufacturers?
- What are the main drivers to market generics?
- What would the French drugs market look like in 2022?

Spending on drugs is mainly driven by hospital sales and by generics sold in retail pharmacies

Evolution of drug sales by segment (2012 – 2016)



Sources: GERS and Top Pharma data – Smart Pharma Consulting analyses

¹ Constant ex-factory prices – ² Estimated rebated sales including hospital sales of biosimilars and products invoiced in 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.)

Substitution of biosimilars by retail pharmacists, at treatment initiation, is legal since 2014, but the absence of the corresponding decree does not allow its implementation

Characteristics of the four statuses of “copies” in France

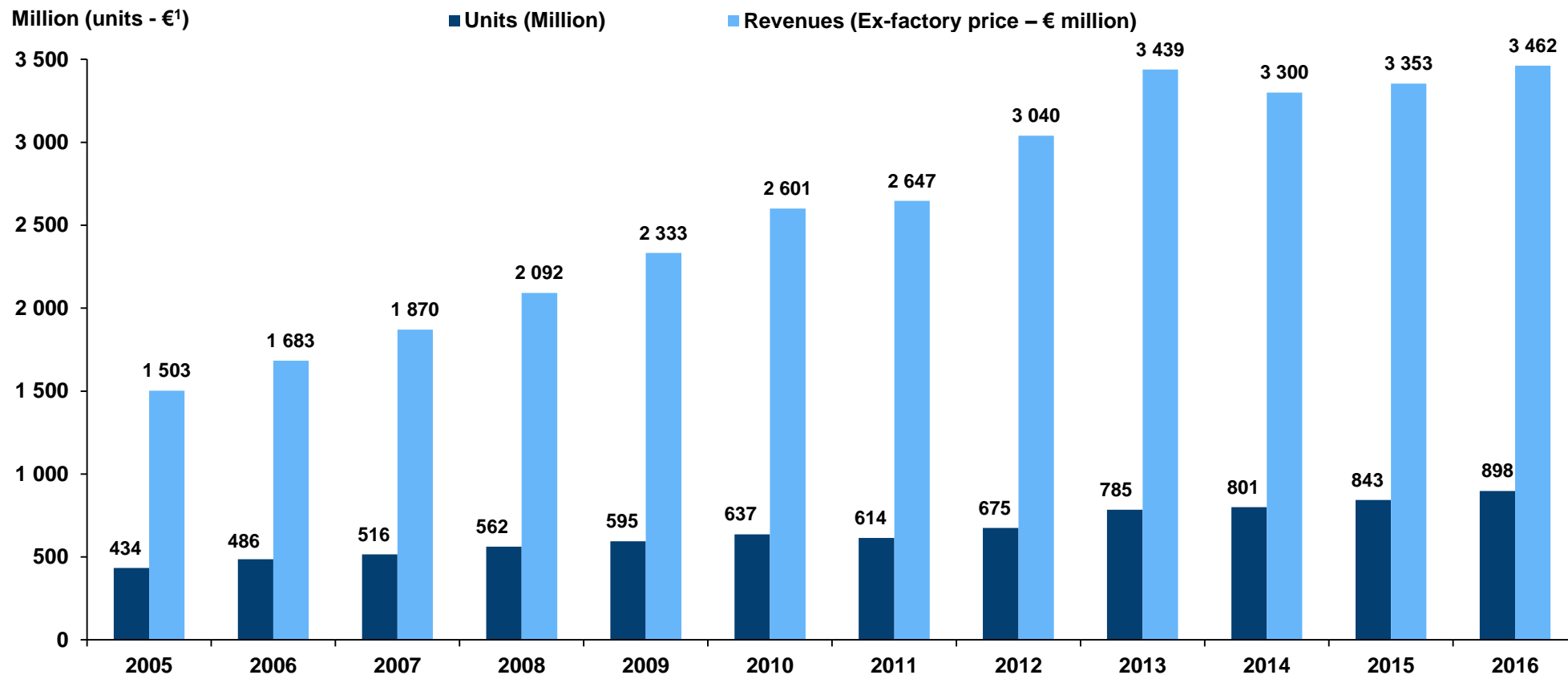
	Generics	Quasi-generics / Generic FOLM ¹	Essentially similar drugs	Biosimilar drugs
Description	<ul style="list-style-type: none"> Copies of synthetic drugs Bioequivalence has been proven 	<ul style="list-style-type: none"> Copies of oral modified release form drugs Bioequivalence (has not or) cannot be proven 	<ul style="list-style-type: none"> Copies of synthetic drugs Bioequivalence (has not or) cannot be proven 	<ul style="list-style-type: none"> Copies of biotech products Bioequivalence cannot be proven
Market approval requirements	<ul style="list-style-type: none"> Abridged procedure with simplified dossier reproducing original brand's clinical outcome 	<ul style="list-style-type: none"> Same as for generics Necessity to respect the modified form of the originator (i.e. prolonged, delayed or sequential) 	<ul style="list-style-type: none"> Minimal clinical development to document safety/ efficacy profile (e.g. with specific device used) 	<ul style="list-style-type: none"> Complete clinical development (excluding phase 2 studies)
Substitution ²	Allowed	Allowed	To be allowed only at treatment initiation, pending application decree ³	To be allowed only at treatment initiation, pending application decree
Examples	OMEPRazole MYLAN (generic of MOPRAL)	ESOMEPRazole BIOGARAN (Quasi-generic of INEXIUM)	VITALOGINK (Essentially similar of TANAKAN)	BINOCRIT (Biosimilar of EPREX)

Sources: Legifrance, Article L.5125-23 CSP – Senate, November 2016 – LFSS 2017 – Smart Pharma Consulting analyses

¹ “Formes orales à libération modifiée” = Modified-release oral forms – ² Substitution of original brands by their generic / essentially similar / biosimilar drug, in retail pharmacies – ³ For anti-asthmatic drugs only

In 2016, sales of reimbursable generics reached € 3,5 billion and 898 million units in the retail market...

Evolution of reimbursable generics' sales in the retail market (1/2)

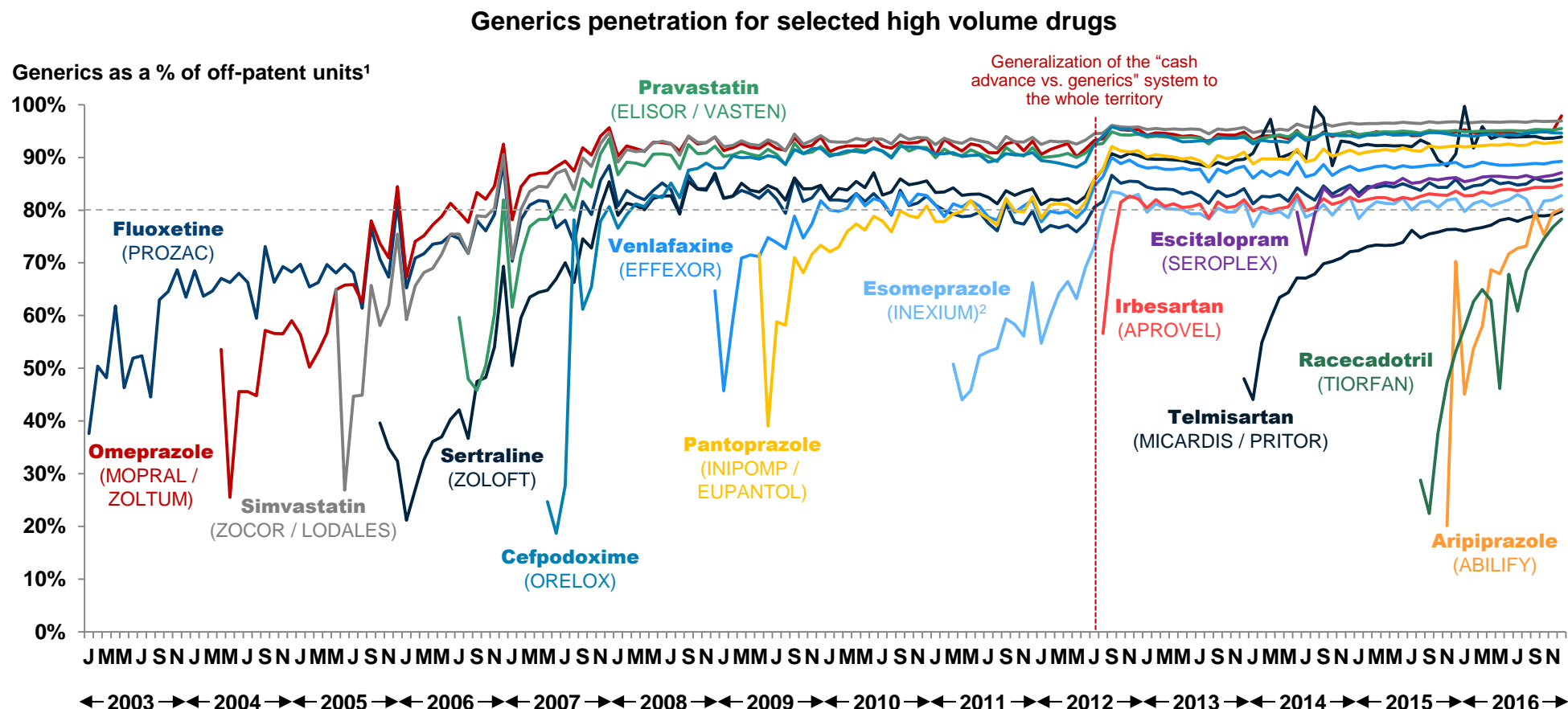


Sources: GERS dashboard (December 2016) – Smart Pharma Consulting analyses

¹ Ex-factory prices, excluding taxes

The speed of penetration has accelerated since 2003, reaching ~80% within a few months for brands with no particular barriers to substitution

Generics penetration trends on the retail market



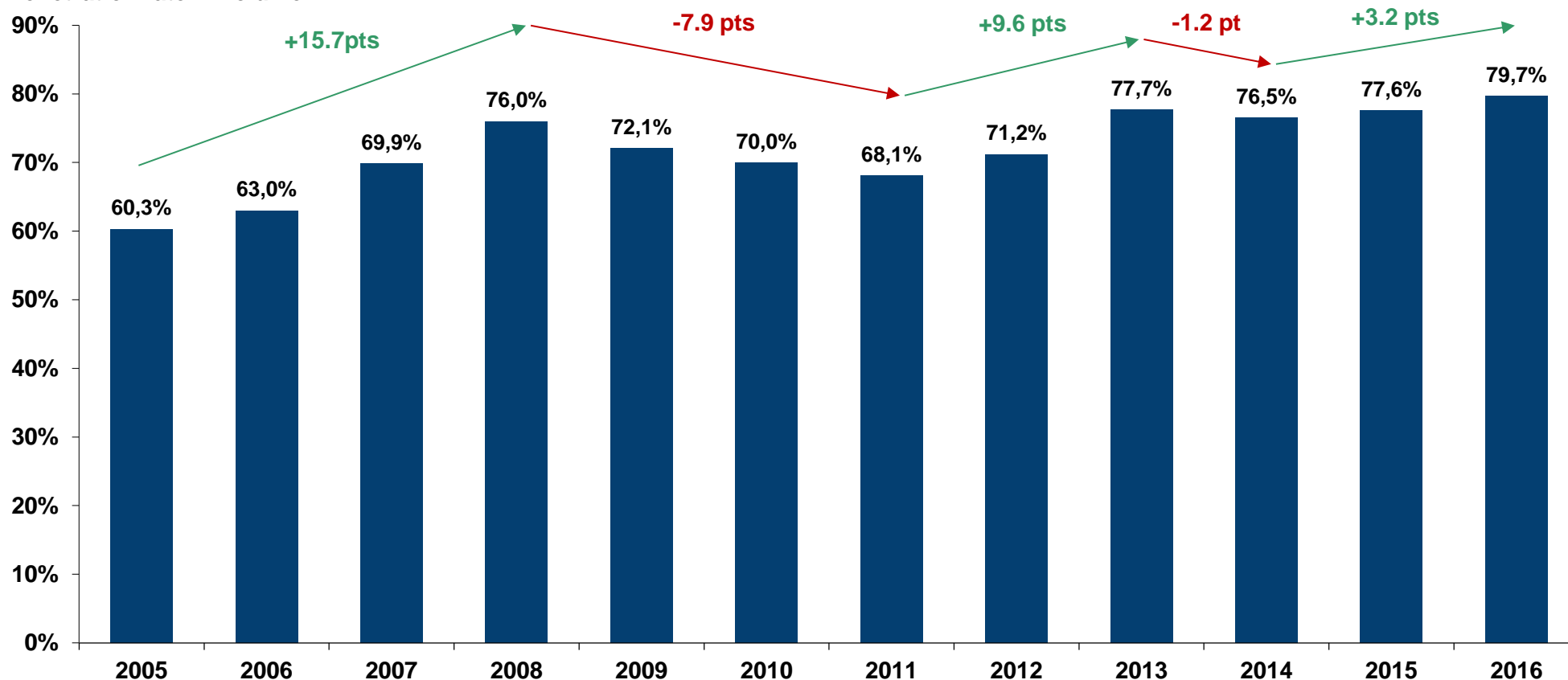
Sources: GERS – Smart Pharma Consulting analyses

¹ Compounded average of the different forms and dosages – ² Quasi-generics

The penetration rate, which had slightly declined in 2014 due to various political issues¹, has been increasing steadily during the last two years

Evolution of the generics penetration in the retail reimbursable market (2005 – 2016)

Penetration rate in volume

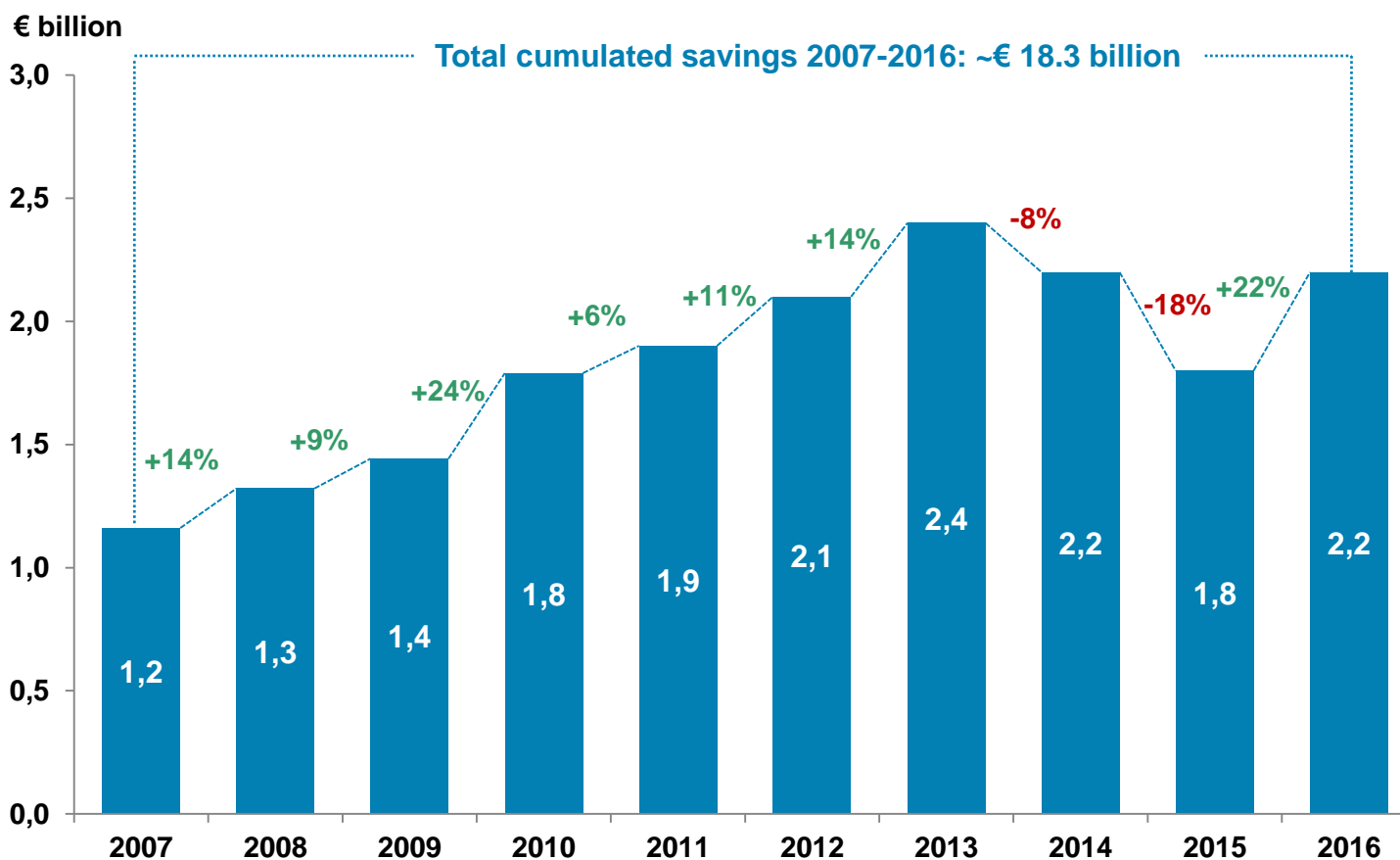


Sources: GERS data (December 2016) – Smart Pharma Consulting analyses

¹ Delayed signature of the amendments “remuneration” and “generics”, reconsideration of the monopoly of retail pharmacies, etc.

Savings generated by the use of generics reached ~€ 2.2 billion in 2016 and accounted for a cumulated ~€ 18.3 billion over the 2007-2016 period

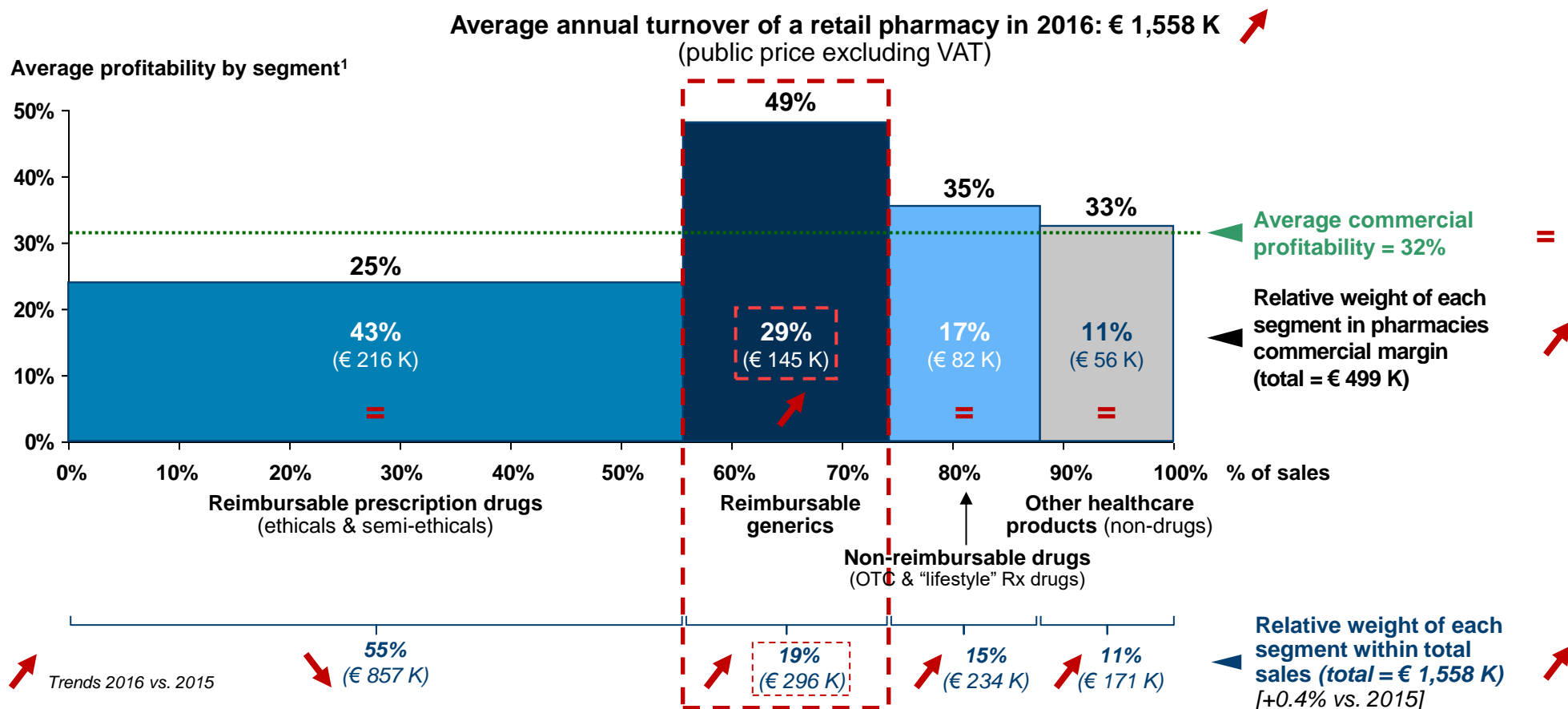
Savings generated by generics (2007 – 2016)



- In 2014, the launch of new generic medicines enabled the market to maintain an **upward dynamic in volume** (+ 2%) and a **fall in value** (-4%) due to price cuts on generics over the period (~ € 220 million)
- Nevertheless, price cuts have impacted even more reimbursable originators, reducing the price differential between originators and generics, and for the first time in 2014, the savings generated by generics decreased (-8%)
- The trend of price cuts in 2015 led to a further decline in savings (-18%) to € 1.8 billion, i.e. the level of 2010 but was reversed in 2016 to reach the level of 2014

In 2016, generics accounted for 19% of retail pharmacies sales on average, and for 29% of their margin, due to the high rebates offered by generics companies

Economic structure of retail pharmacies in France (2016)



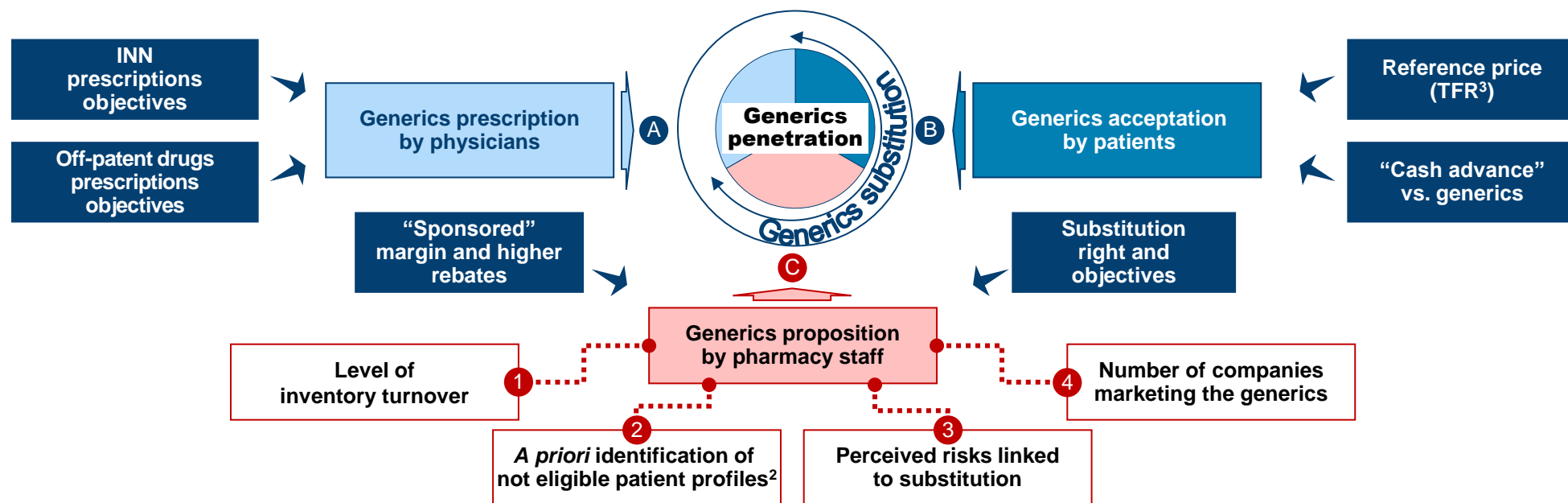
Sources: KPMG (2016) – Smart Pharma Consulting analyses

¹ Inclusive of legal margin, rebates, commercial agreements and remuneration for pharmaceutical services, notably those corresponding to the public health objectives (e.g. generics substitution objectives, pharmaceutical interviews with patients, etc.)

Generics penetration is facilitated by INN¹ prescription and substitution, both of which are enhanced by a favorable support from health authorities

Key drivers of generics penetration on the retail market

Health authorities measures supporting generics penetration

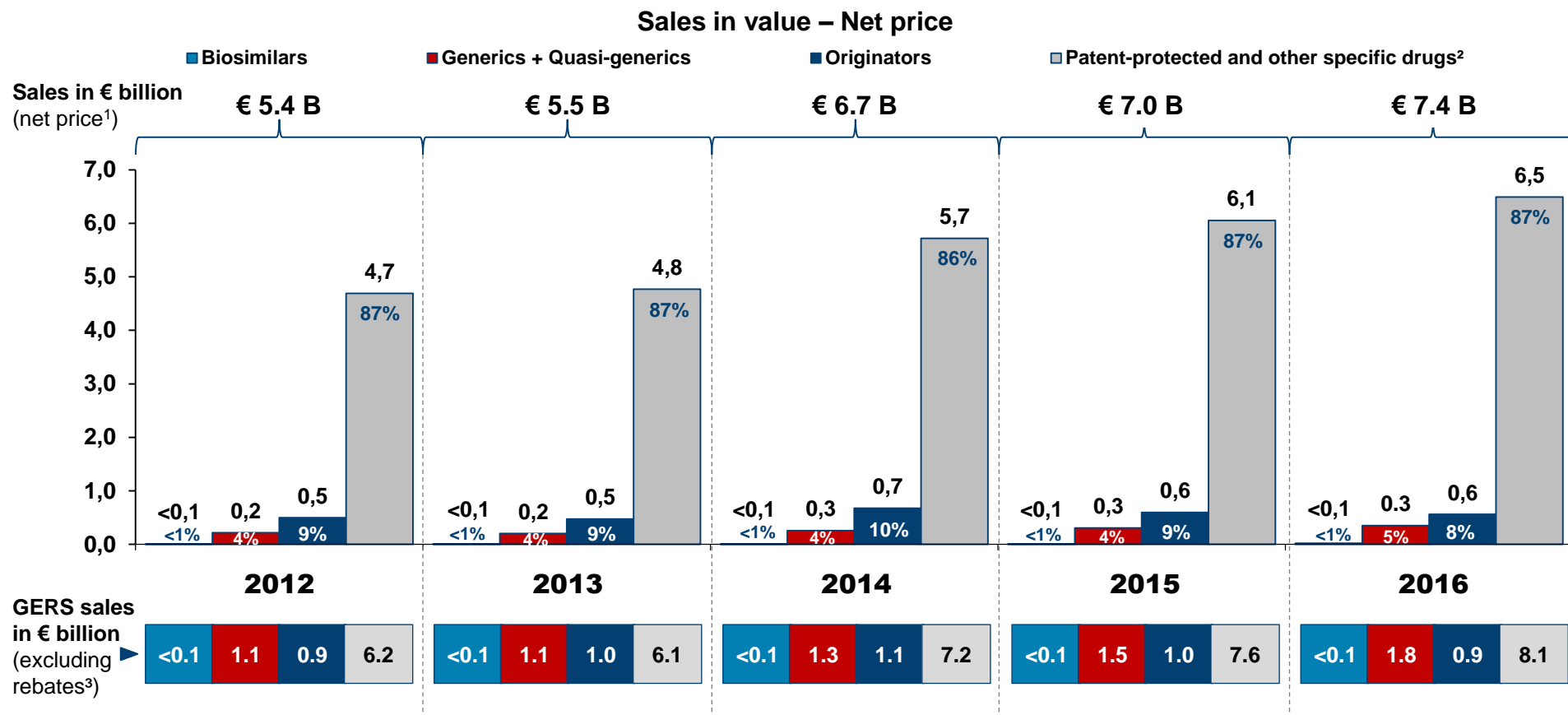


Sources: Smart Pharma Consulting analyses

¹ International non-proprietary name – ² To whom substitution will not be proposed (e.g. patients having refused substitution several times) – ³ “Tarif forfaitaire de responsabilité”: single reimbursement price for a generic group as a whole, based on the cheapest generic price

The share of generics in the hospital market in value weights for 4-5% and has been relatively stable since 2012

Hospital market dynamics



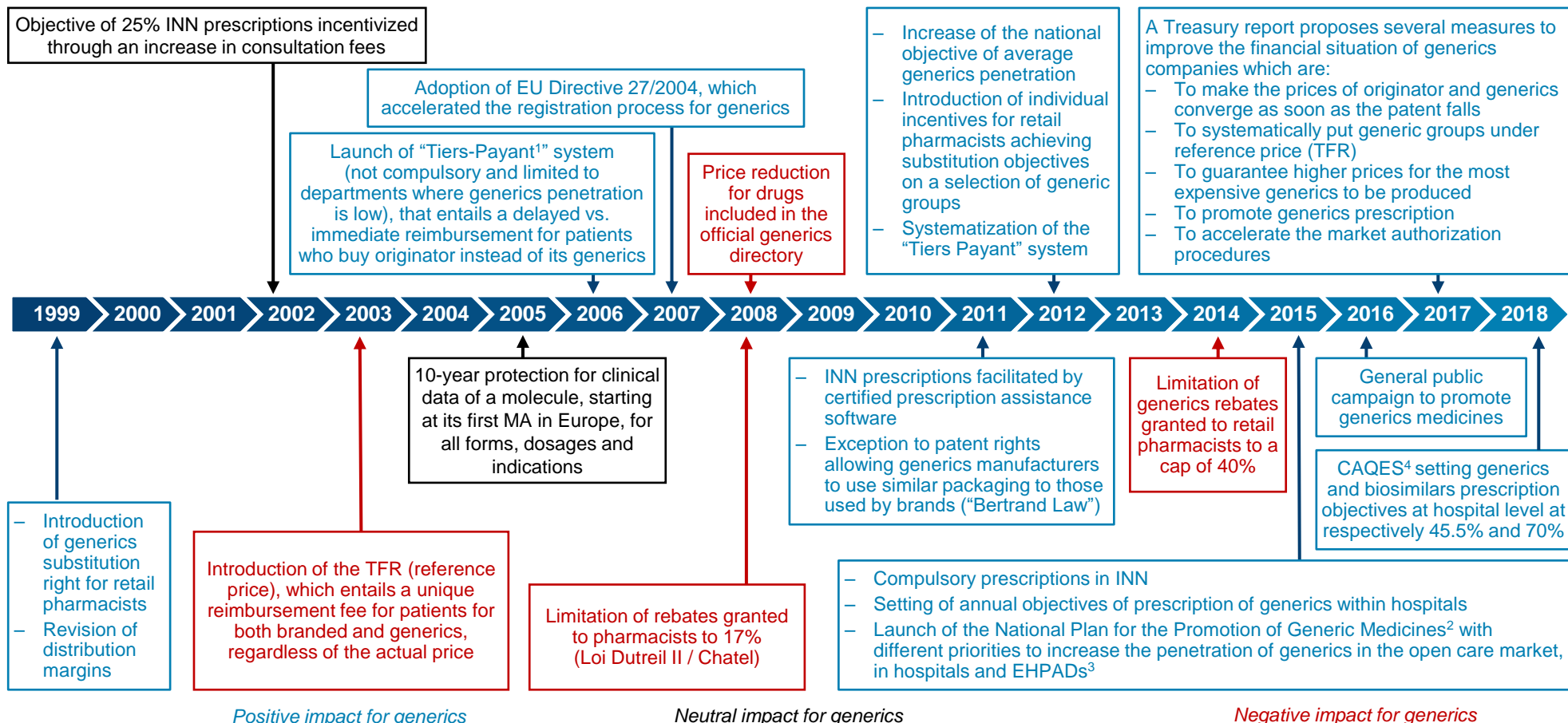
Sources: GERS – Smart Pharma Consulting analyses

¹ Net sales estimated based on GERS sales on which theoretical discounts have been applied: 20% for patent-protected and other specific drugs, 40% for originators and 80% for generics and biosimilars – ² Drugs not listed in the ANSM generics directory, including particular products (calcium, sodium, morphine, etc.) – ³ GERS price excluding taxes and rebates

Since the substitution right granted to retail pharmacists in 1999, the different governments have introduced several measures to favor the development of generics



Main governmental measures related to generics








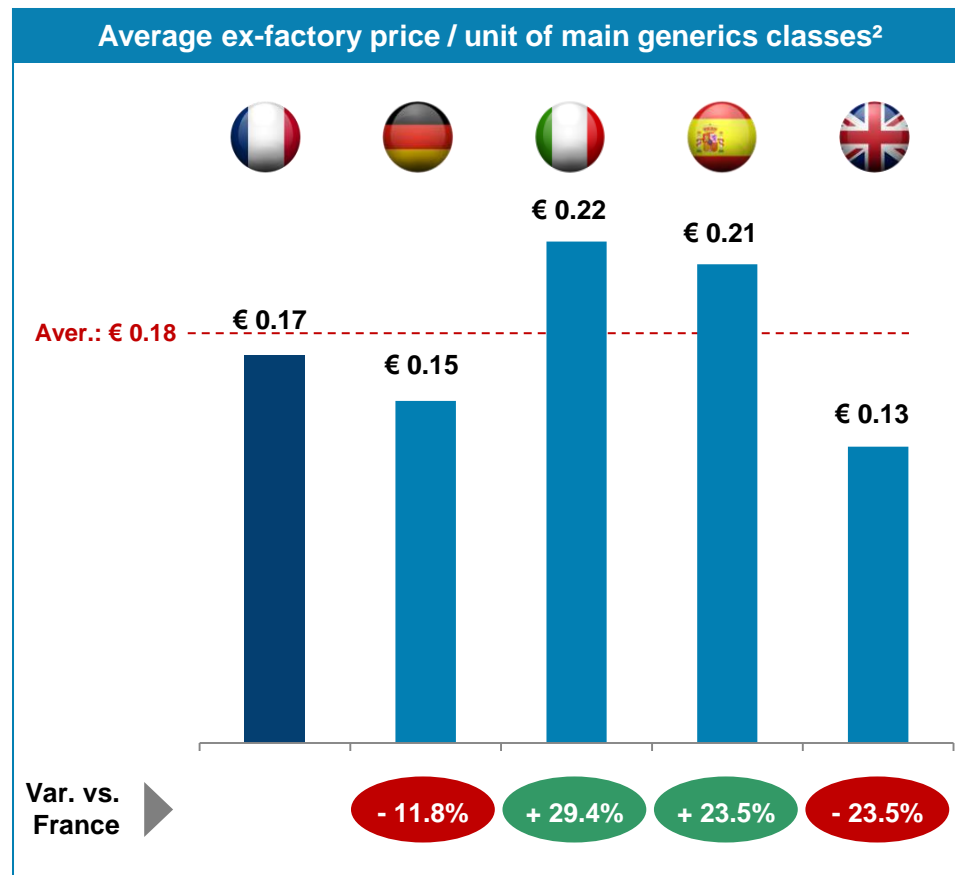
Sources: Smart Pharma Consulting analyses

With an average price of generics of € 0.17 per standard unit, France is now aligned with its European neighbors



Comparative study of generics prices – Overall result

Scope of the study	
Studied reference countries	<ul style="list-style-type: none"> Germany  Spain  France  Italy  United Kingdom 
Studied generics classes	<ul style="list-style-type: none"> 4 studied classes: statins, proton pump inhibitors (PPI), angiotensin-converting enzyme (ACE) inhibitors and sartans In 2014, these classes represented a turnover of € 735 M in France, i.e. ~22% of the generics market
Selected samples	<ul style="list-style-type: none"> Generics marketed in retail
Data sources used	<ul style="list-style-type: none"> For France, the data come from the GERS and the price base of the CEPS (taking into account the price cuts achieved in 2015) For the 4 other reference countries, the 2014 data come from the IMS MIDAS database (price data)
Unit of measure used	<ul style="list-style-type: none"> The unit of measure of the price is the average ex-factory price (in standard unit) charged in a country weighted by the French units in order to neutralize the structural effects

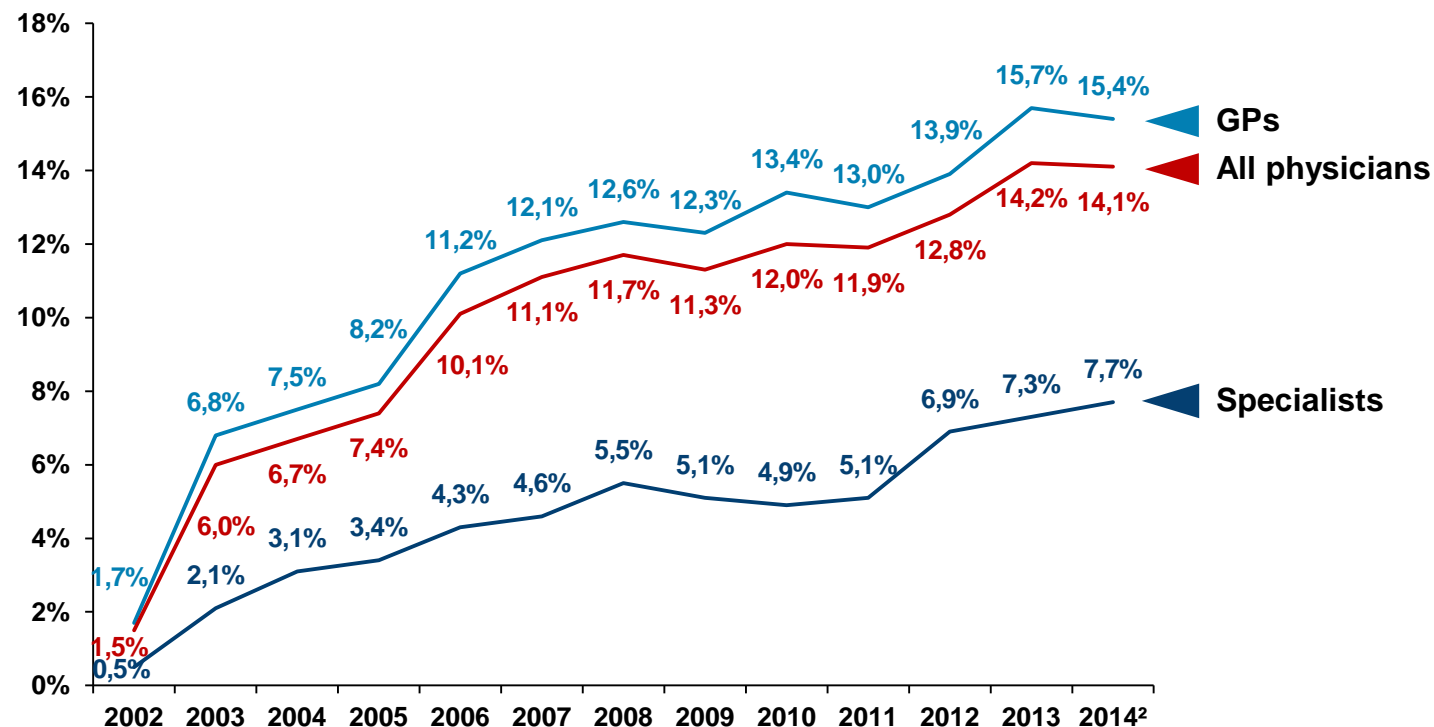


Since physicians' INN¹ prescription rates are relatively low, generics penetration is mainly due to substitution in retail pharmacies



Evolution of the INN¹ prescription rate (2002-2014)

As a % of prescriptions



Mesures affecting INN prescriptions

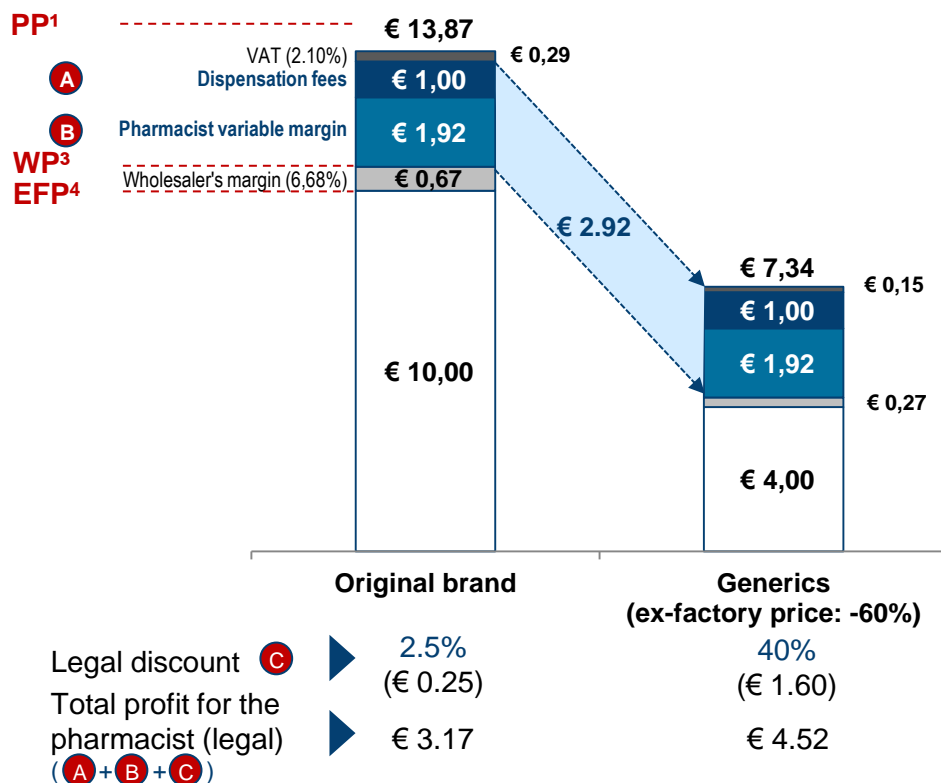
- **LFSS 2009:** imposes physicians to mention the INN for generic drugs prescriptions (measure not well respected)
- **Medical agreement signed with the National Health Insurance, July 2011:** provides a remuneration based on physicians' performance on, among other things, generics prescription objectives
- **"Bertrand law", December 2011:** stipulates that all the prescriptions must mention the INN from January 2015. However, the prescription can be supplemented by the brand name
- **2015:** Mandatory INN prescription

The levels of margins and rebates set by the CEPS for drugs sold on the retail market contribute to regulate the evolution of cost of reimbursed drugs

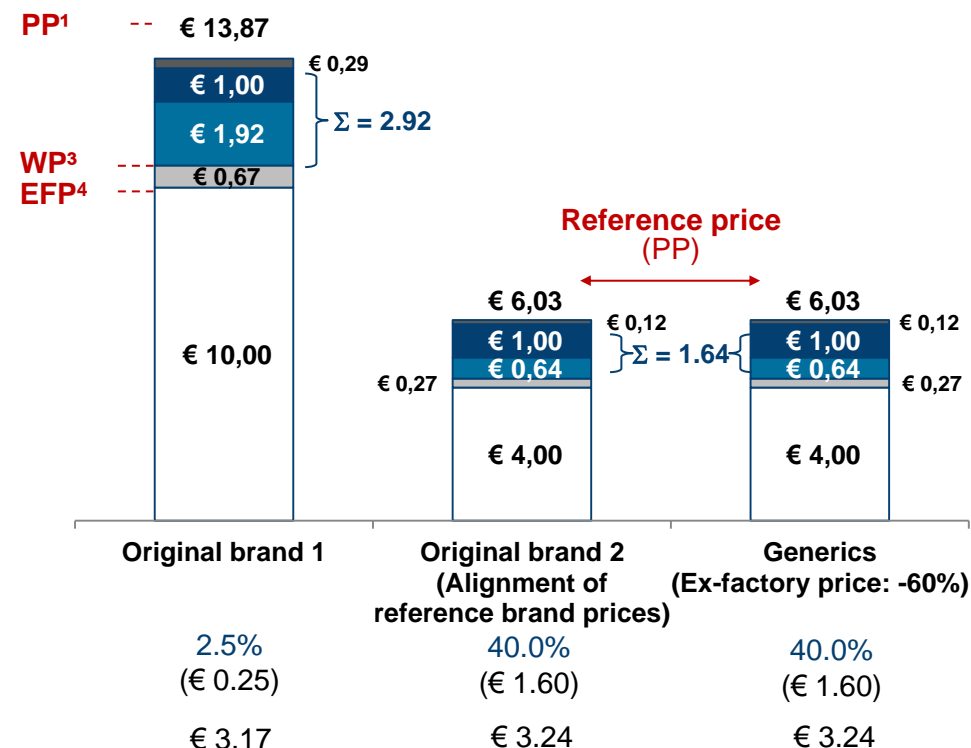


Legal margins and discounts for reimbursed generics (2018)

Without reference price (TFR)



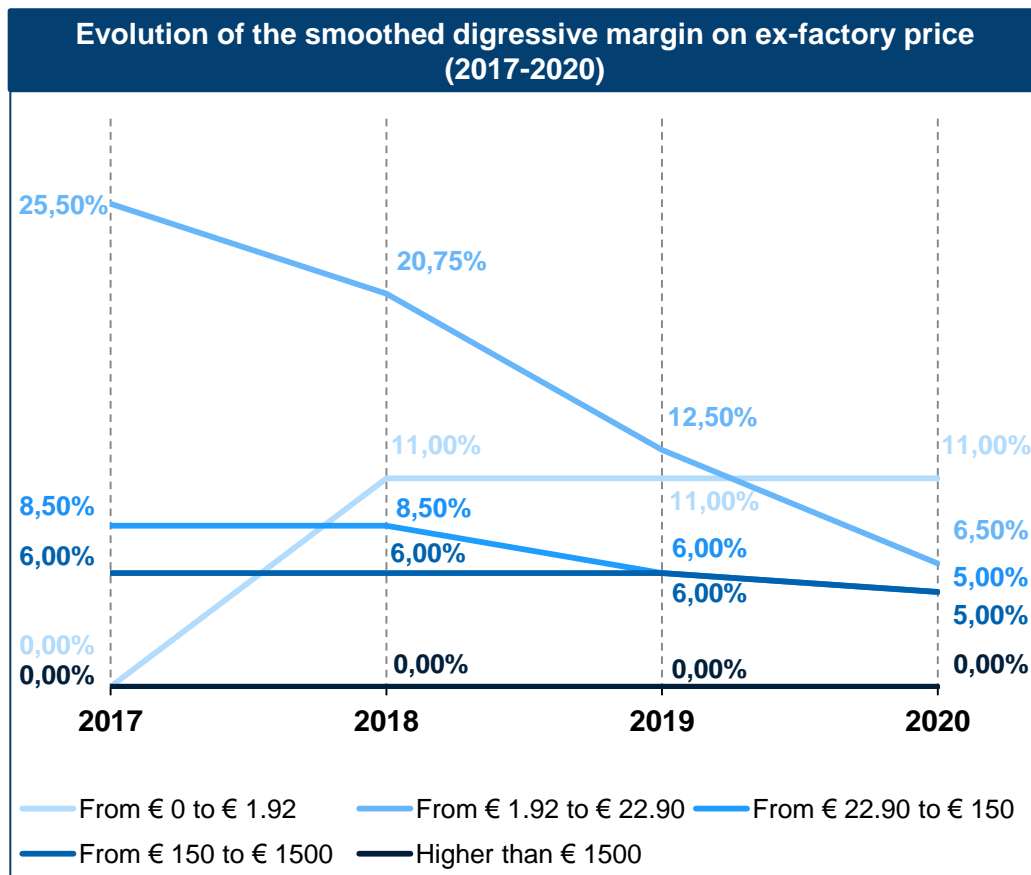
With reference price (TFR)



The 11th amendment to the National Pharmaceutical Agreement provides for reducing margin on ex-factory price of drugs over the 2018-2020 period for pharmacists



The 11th amendement to the National Pharmaceutical Agreement



- The main priority of the 11th amendment¹ to the National Pharmaceutical Agreement is to change the remuneration of pharmacies and make them **less dependent on the price and volume of reimbursable drugs**
- Thus, it proposes **progressive transfer** of a significant part of the regulated margin on the price of medicines to **new forms of remuneration** related to dispensing and to the improvement of patients' management
- Thus, three successive waves of **margins** on price **decreases** are expected in January of each year from 2018 to 2020
- The creation of **3 new dispensing fees** will only be settled from 2019 and only 2 of the 3 fees are expected to be re-evaluated in 2020:

New dispensing fee	2019 ²	2020 ²
Fees for the delivery of a prescription	€ 0.51	€ 0.51
Fees related to the age of the patient (youth children and elderly people)	€ 0.51	€ 1.58
Fees for the delivery of specific drugs (e.g. immunosuppressive drugs)	€ 2.04	€ 3.57

Sources: Le moniteur des pharmacies, August 26th, 2017 – 11th amendment to the National Pharmaceutical Agreement

¹ The 11th amendment was signed on July 20th, 2017 by only one of the three French pharmaceutical unions – ² All taxes included

The resistance of some drugs to generics substitution can be explained by several factors such as the complexity of the pathology and the narrow therapeutic margin



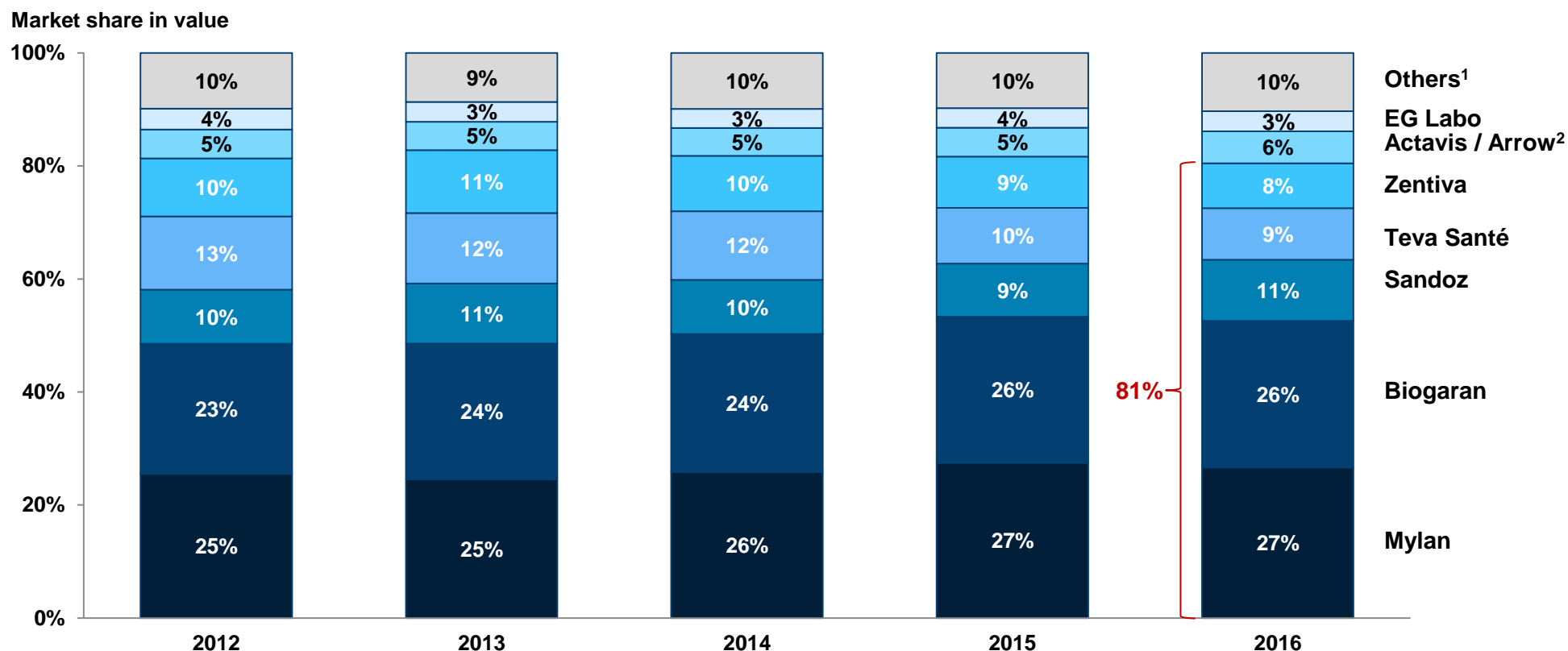
Main limiters of substitution for selected drugs

	Complexity / Severity of pathology	Narrow therapeutic margin	Low inventory rotations	Frequent "not substitutable" scripts	Difference of chemical forms in comparison with generics	Protection of an indication
Durogesic (fentanyl)	✓	✓	✓			
Levothyrox (levothyroxine)	✓	✓				
Epitomax (topiramate)	✓			✓		
Neurontin (gabapentin)	✓			✓		
Plavix (clopidogrel)				✓	✓	✓
Risperdal (risperidone)	✓			✓		

- For those drugs with specific conditions, in order to limit prosecutions engaging their responsibility, pharmacists tend to:
 - Follow the ANSM¹ recommendations regarding narrow therapeutic margins
 - Respect generic groups as defined in the ANSM directory
 - Respect substitution rules regarding protected indications (protection of intellectual property)

The French generics market is concentrated with 81% of the sales captured by the top 5 players, whose market shares have been relatively stable since 2012

Market share of generics companies in the retail market (2012 – 2016)

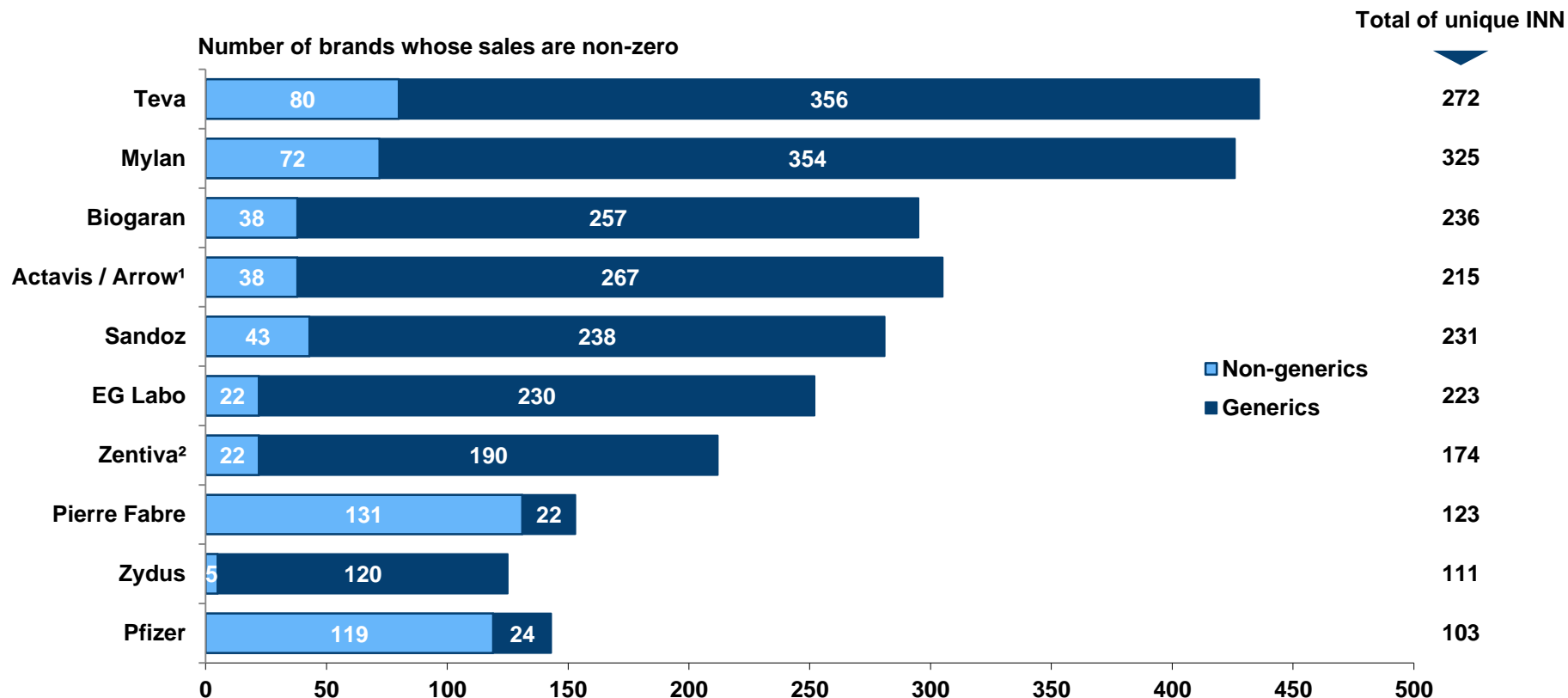


Sources: GERS – Smart Pharma Consulting analyses

¹ Mostly Pierre Fabre, Pfizer, Cristers and Zydus – ² Acquired by Teva on August 2nd, 2016

The scope of the portfolio proposed by the generics companies is a determining factor in their referencing by retail pharmacies

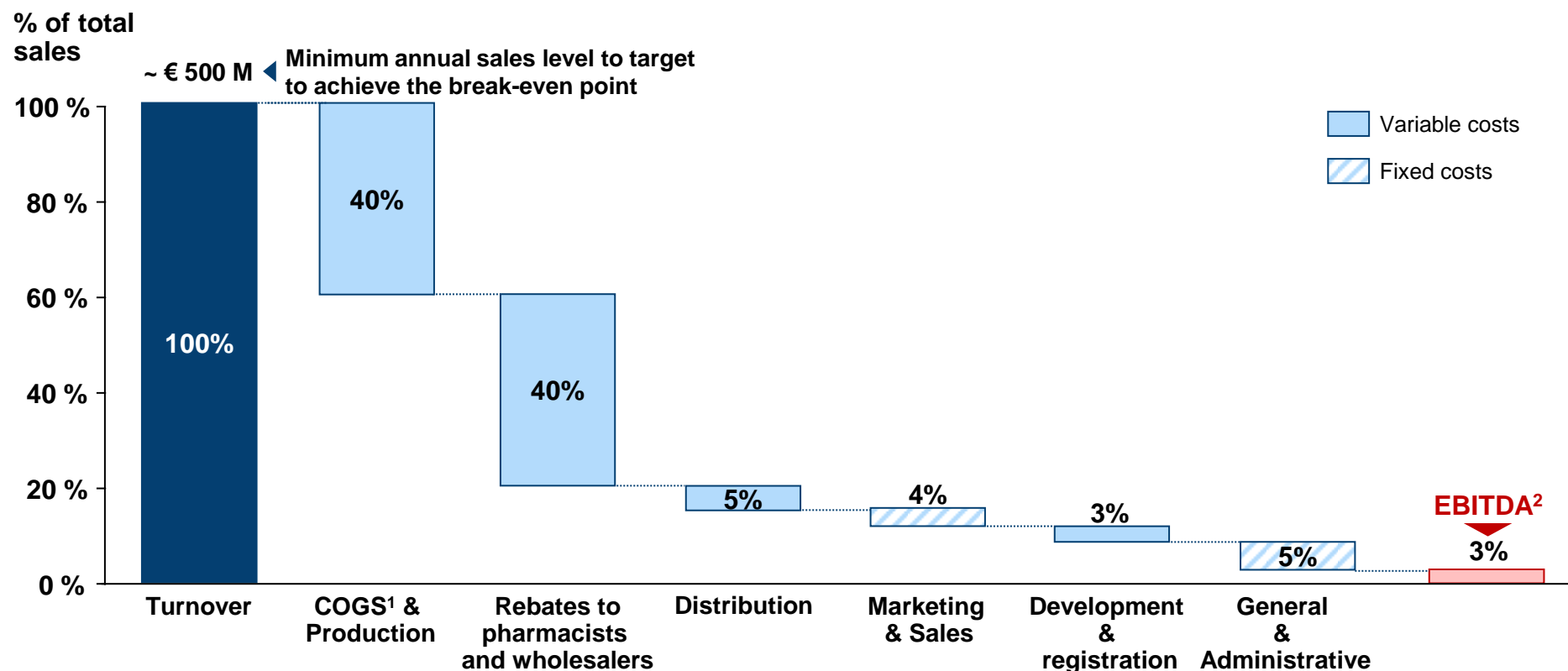
Product portfolio of generics companies in retail pharmacies (2016)



Notes: The ANSM directory contains 524 different INNs in September 2017
Some INNs may be registered as generic or non-generic depending on the presentation (dosage, packaging, form)

The average turnover to generate operating profitability (EBITDA¹) is estimated at ~ € 500 M for generics companies operating in the retail market

Estimated cost structure of generics companies in France



Sources: Smart Pharma Consulting analyses and estimates

¹ Cost of goods sold – ² Earnings before interests, taxes, depreciation and amortization



Key data for the French affiliate

Key financial data (2012-2016)¹

€ million	2016	2015	2014	2013	2012
Turnover	838	780	867	936	872
EBITDA/Turnover	10.5%	6.1%	9.1%	8.3%	5.5%
EBIT/Turnover	9.6%	5.6%	8.3%	7.1%	4.9%
Net result/Turnover	7.1%	4.6%	6.3%	5.8%	4.6%

Sales data (2016)^{2,3}

	Sales (€ million)	YoY change	Share of turnover
Generics	1,594	+4.9%	86.6%
Quasi-generics	30	+5.2%	1.6%
Biosimilars	0	N/A	N/A
Originators	218	+11.7%	11.8%
Total	1,842	+5.7%	100.0%

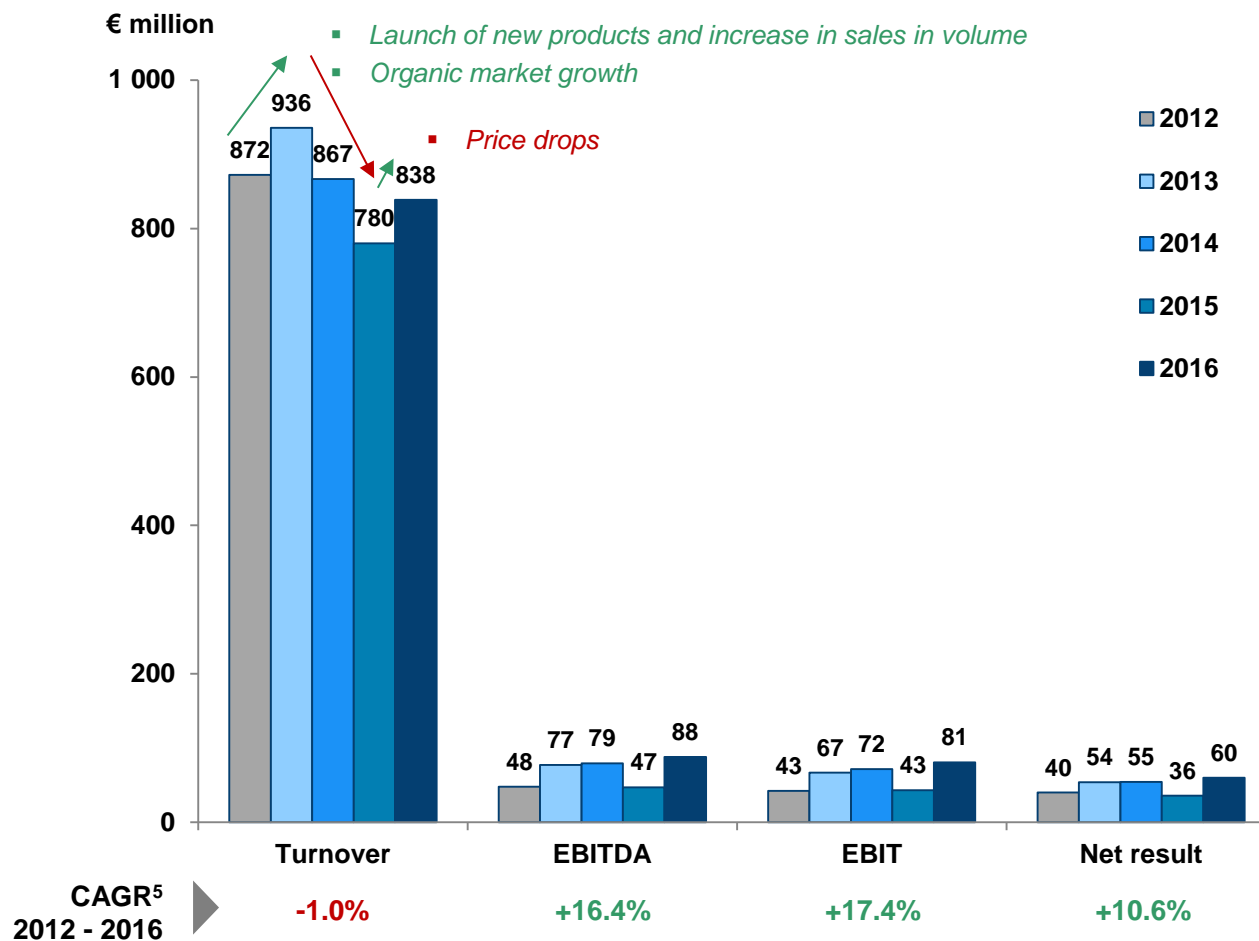
Top 3 generics therapeutic areas⁴

1. Injectable corticosteroids	88	+29.0%	4.8%
2. Proton pump inhibitors	71	+9.3%	3.9%
3. Non-narcotics & anti-pyretics	67	+0.4%	3.6%

Field team

~ 100 pharma reps

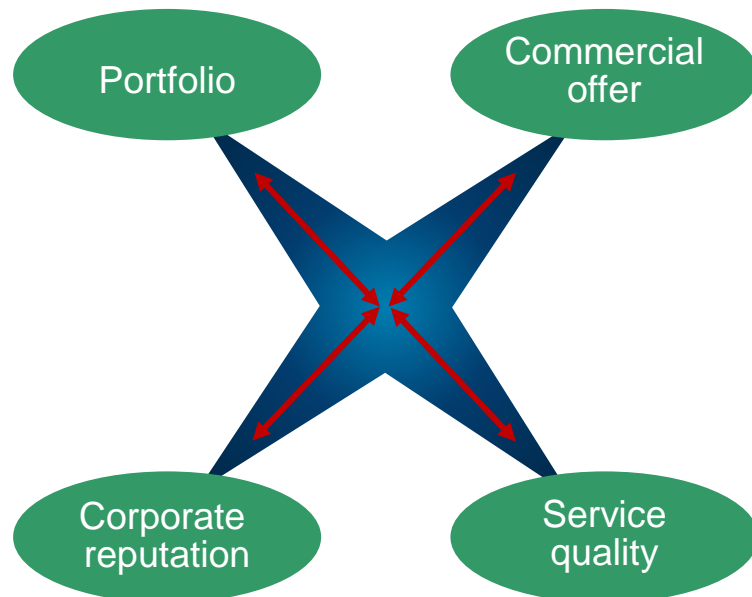
Profitability analysis (2012-2016)¹



The Generics Preference Mix allows generics companies to identify and evaluate the drivers of pharmacists' preference at the time of listing and handing out generics

Generic Preference Mix: Description

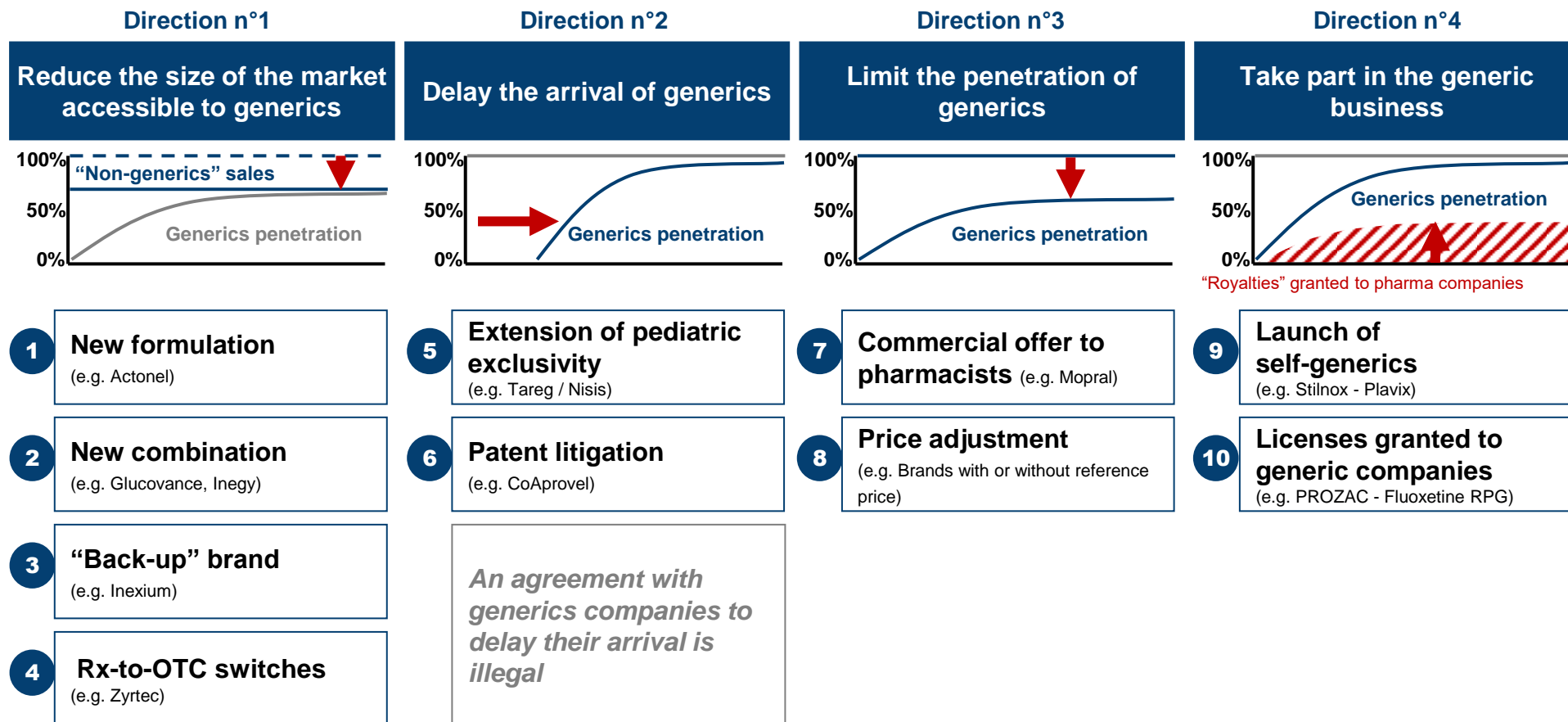
**The 4 components of the
*Generic Preference Mix***



- The *Generics Preference Mix* (GPM) has been developed by Smart Pharma Consulting
- To the extent that retail pharmacists generally focus the great majority of their generics orders on a single supplier and that they have an increasingly important role through counseling and the right of substitution ...
- ... it is essential for generics companies to increase the preference of pharmacists for their brands
- To develop and strengthen pharmacists' preference for their products, generics companies must seek to optimize their *Generics Preference Mix*, which relies on pharmacists' perception of:
 - The breadth and quality of their product portfolio
 - The attractiveness of their commercial offer
 - The quality and the interest of their offered services
 - Their reputation
- The links between the 4 components of *the Generic Preference Mix* should be well established in the minds of clients

Pharma companies can follow 4 directions and use 10 strategic levers to protect the value of their brand despite the arrival of generics...

Strategic options of the pharma companies

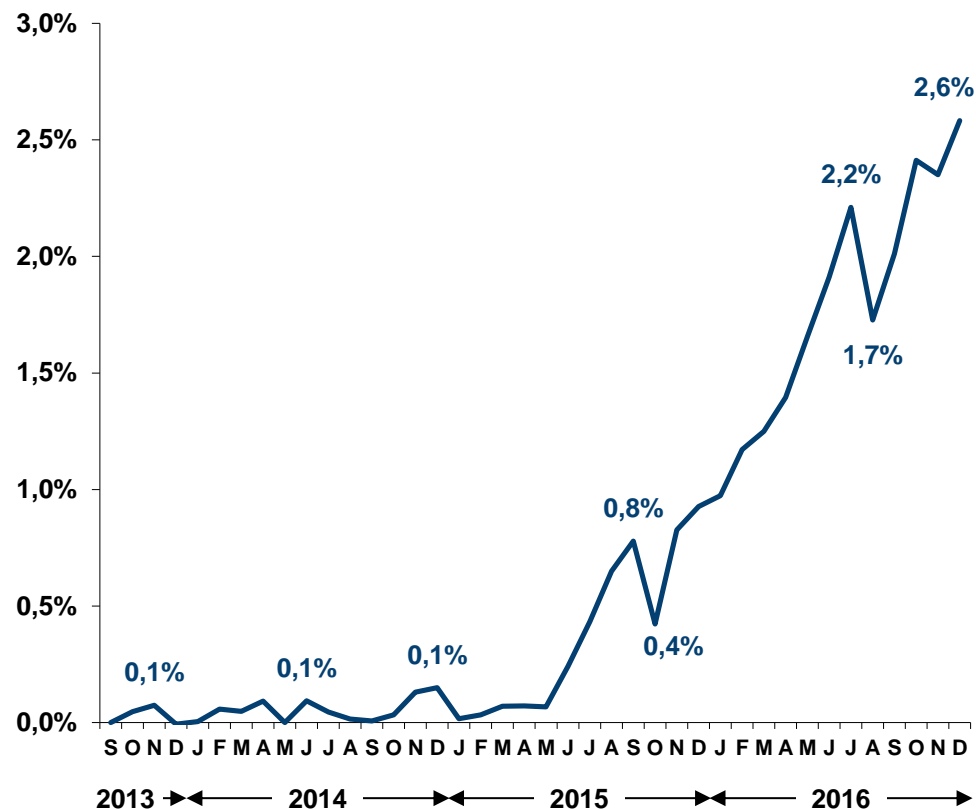


Sources: Smart Pharma Consulting analyses

The example of the immunosuppressive drug Adoport shows that it is very difficult for an essentially similar with narrow therapeutic index to penetrate

Adoport example – Penetration of generics companies

Penetration on Prograf in volume

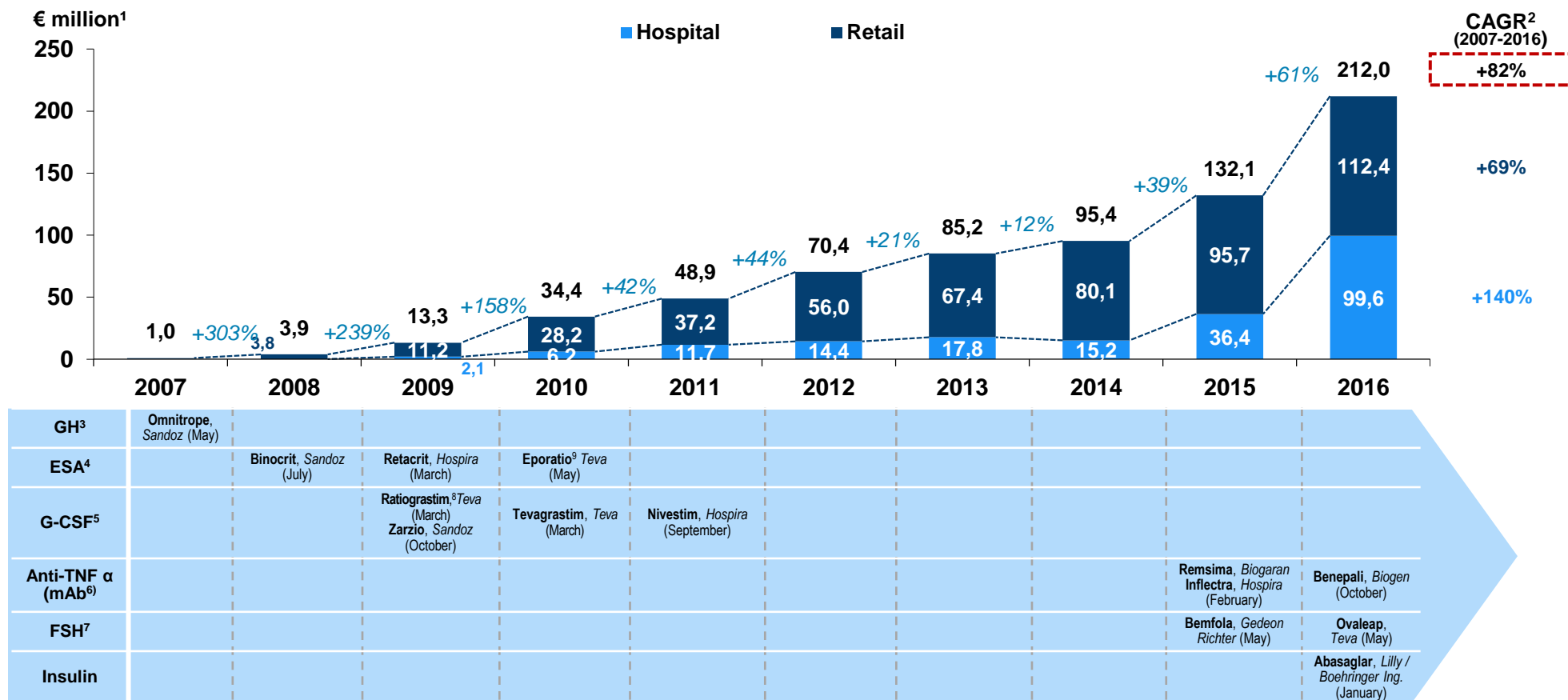


Comments

- **Adoport** is an **immunosuppressive agent** containing tacrolimus, indicated in the prevention or treatment of organ transplant rejection, marketed by **Sandoz** in August 2013 after the patent loss of exclusivity of tacrolimus Astellas, but whose first sales were referenced in October 2013 on the GERS database
- Astellas markets three tacrolimus drugs in capsules:
 - **Modigraf** (0.2 mg, indicated for children)
 - **Prograf** (0.5 mg, 1 mg and 5 mg)
 - **Advagraf, sustained-release form** (0.5 mg, 1 mg, 3 mg and 5 mg)
 ... while **Adoport** is available at 0.5 mg, 1 mg and 5 mg
- Tacrolimus is a drug with a **narrow therapeutic index**, its major adverse event is its nephrotoxicity and it has a high inter- and intra-pharmacokinetic variability
- Thus, no tacrolimus generics group was created in the directory of ANSM, so Adoport is considered as an “**essentially similar**” of Prograf
- At the end of December 2016, i.e. more than 3 years after launch, Adoport’s market share in volume in the 0.5 mg, 1 mg and 5 mg market (excluding prolonged-release form) reached **2.6%**
- A third player, **Chiesi**, entered the market in September 2015 with **Envarsus** and proposes 3 sustained-release doses: 0.75 mg, 1 mg and 4 mg

Sales of biosimilars, which were launched in 2007 and belonged to six types of products in 2016, reached a total of ~ € 212 million on the overall market in 2016

Evolution of the biosimilars market (2007 – 2016)

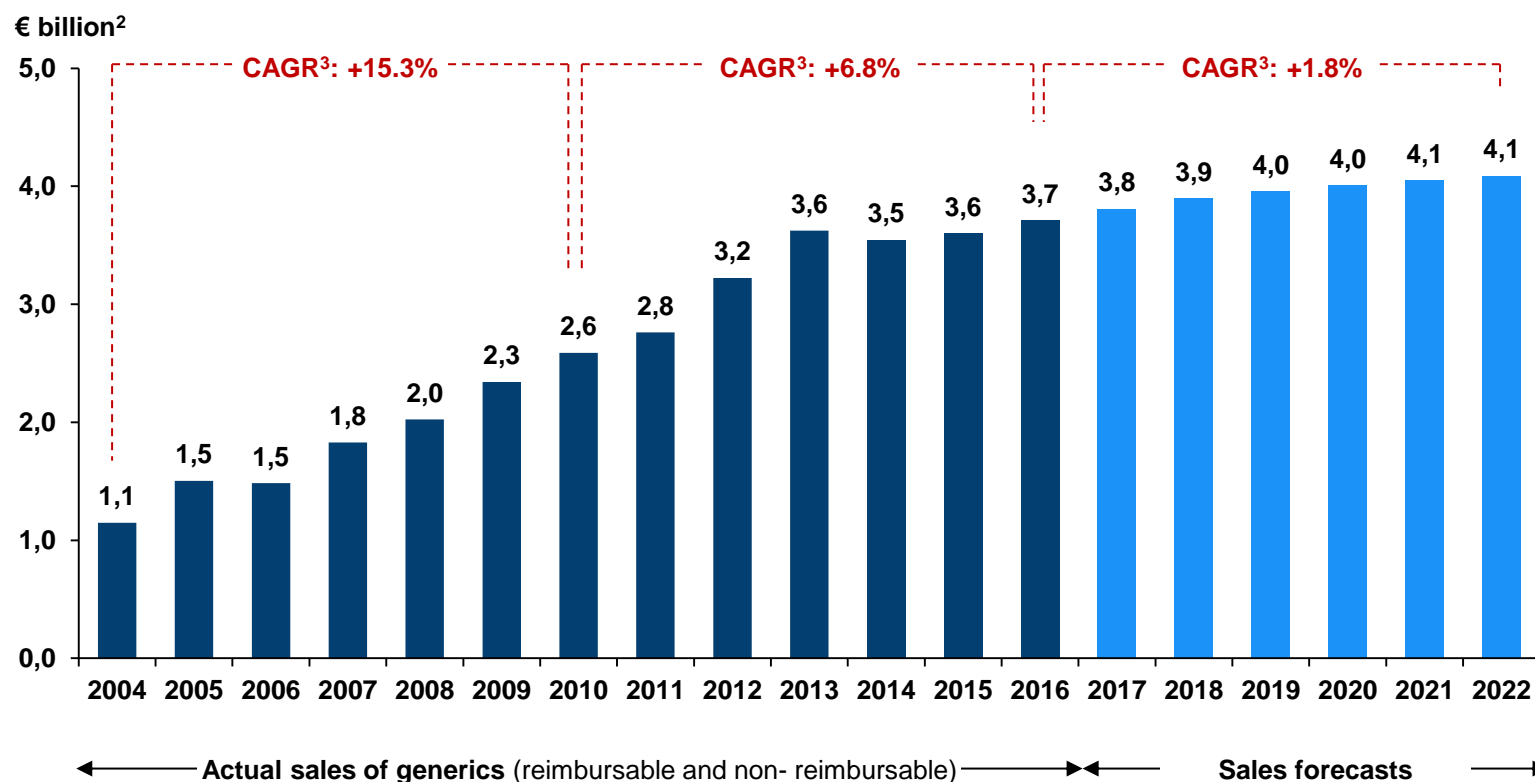


Sources: GERS – Smart Pharma Consulting analyses

¹ Ex-factory prices excluding rebates – ² Compound annual growth rate – ³ GH: Growth hormones – ⁴ ESA: Erythropoiesis stimulating agents – ⁵ G-CSF: Granulocyte colony stimulating factors – ⁶ mAb: Monoclonal antibodies – ⁷ FSH: Follicle Stimulating Hormone – ⁸ Ratiograstim was removed from market in 2016 – ⁹ 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 average annual growth in value of the generics retail market is expected to remain below 2% by 2020, in particular as a result of price cuts

Forecasts of generics sales¹ in the retail market – Value



Comments

- The low CAGR in value, estimated at 1.8% between 2016 and 2022 can be explained by two factors:
 1. The number of molecules with high potential for the generics market that will lose their patents during the period will be relatively limited
 2. The authorities will continue to regularly impose drastic price cuts

The market of biosimilars will benefit from the launch of new products in existing classes and in new classes by 2022

Evolution of the biosimilars market in France

- No new biosimilar class was commercialized between 2009 and February 2015, when **the first two biosimilars of infliximab**, whose originator brand is Remicade, were launched after an **EMA authorization** in September 2013:
 - **Inflectra**, developed by Hospira and marketed by Pfizer (Pfizer acquired Hospira in early 2015)
 - **Remsima**, developed and produced by Celltrion and marketed by Biogaran in France
- If these two products have the same indications as Remicade...
 - In **rheumatology**: rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis
 - In **gastroenterology**: hemorrhagic ulcerative colitis (HRC) in adults and children and Crohn's disease in adults and children
 - In **dermatology**: psoriasis... the **bioequivalence** of these biosimilars has been **demonstrated** in a pharmacokinetic study carried out **only in patients with ankylosing spondylitis** and its **clinical equivalence** has been **evaluated only in patients with rheumatoid arthritis**
- Inflectra and Remsima have the **same dosage**, the **same pharmaceutical form**, the **same route of administration** and **the same composition in excipients** as Remicade
- In May 2015, **Majorelle commercialized Bemfola¹**, the **first biosimilar of follitropin alfa** (Gonal-F), bringing to five the number of therapeutic classes on the French market
- In January 2016, the launch of **Abasaglar**, a biosimilar of **Lantus (insulin glargine)** by **Eli Lilly / Boehringer Ingelheim** implies the arrival of a sixth class
- The last one to enter the market was **Benepali (etanercept)**, marketed by **Biogen** (Samsung Bioepis), biosimilar of **Enbrel**, in October 2016
- By 2022, new biosimilars classes are expected. The total biosimilar market will notably be developed thanks to the **launch of hospital biosimilars** (bevacizumab, trastuzumab, rituximab) but also through penetration of classes **already commercialized** (e.g. ESA, G-CSF) and/or recently launched on the retail market (etanercept and insulin glargine)

Authorities and payers will continue to lower the prices of reimbursed drugs, generics or non-generics, and promote the use of generics and biosimilars

1 Position of health authorities and payers

2017 – 2022 Trends

Optimization

- Recent initiatives to stimulate generics growth
 - Substitution of inhaled drugs^{1,3} and biosimilars^{2,3}
 - Extension of the generic directory to inhaled respiratory drugs as well as for drugs of plant or mineral origin
 - Prescription objectives within the generics directory at hospital level (45.5%, conforming to the CAQES objective for 2018)
 - Prescription objectives within the biosimilars reference list at hospital (70.0%, conforming to the CAQES objective for 2018)
 - Simplification of generics instruction and notification processes
 - Prioritization of the generics dossier instruction
- Continuous price pressure on reimbursed drugs, originators and generics (price cut, reference prices (TFR⁴))
- Toughening of reimbursement and price attribution rules for originators (e.g. comparative studies, medico-economics data)

Quality control of drugs

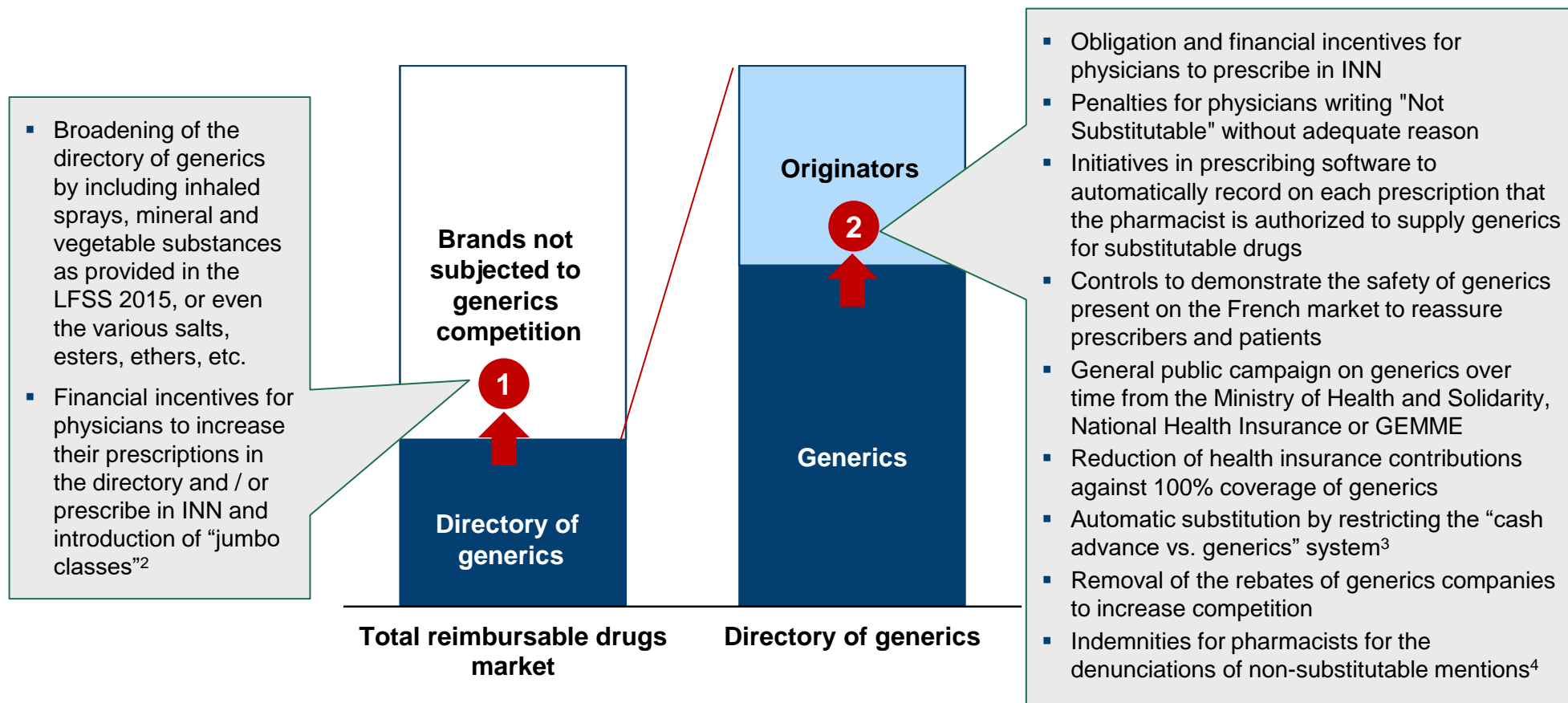
- Control of generics quality, particularly best-selling drugs, in comparison to originators

Rationale

- The “pact of responsibility”, launched in January 2014, foresees savings of € 3.5 billion over the period 2015 - 2017 due to lower drug prices and the development of generics. However, generics will also be subject to price cuts, tariff convergences with originators and new TFRs
 - The 2018 social security finance law includes measures to push further efficiencies. Over the € 4.2 billion potential savings, € 340 million should come from promotion and development of generics and € 40 million should come from biosimilars prescriptions
 - Healthcare expenditure objectives set by the government at an average of + 2.3% per year by 2022
 - Drugs accounted for only 17.4% of healthcare expenditure in 2016, but since price cuts have no negative political and social impact and are easy to implement, they are used as an adjustment variable
-
- The objective is to show the safety of generics present on the French market, these controls being part of the national action plan for the promotion of generics 2015-2017

... these measures follow two distinct axes: the expansion of the directory of generics and the gain of market shares of generics against originators

Possible government measures¹ to boost the generic market



Sources: Smart Pharma Consulting analyses

¹ Non-exhaustive list – ² Drugs are grouped into broad classes in which the products are presumed to have an equivalent benefit for patients and can thus claim the same rate of reimbursement – ³ Measure on the initiative of the CPAM of the Tarn but which meets the hostility of the three trade unions of pharmacists – ⁴ Proposal by the National Health Insurance Fund decrised by the National Union of Pharmacies of France

The Smart Pharma Business Reports

- Our business reports 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

The French Generics & Biosimilars Markets 2017 – 2022 Prospects

- This report has been conceived as a working tool to:
 - Strengthen and align the level of knowledge and understanding regarding the French generics and biosimilars markets and their key trends
 - Facilitate communication within companies
 - Support strategic decisions over the 5 upcoming years
- The purchase of this report includes:
 - A two-hour working session to address one or more specific points covered in this report
 - A free access to all employees of the buying company

Smart Pharma Consulting Editions



- Besides our consulting activities which take 85% of our time, we are engaged in sharing our knowledge and thoughts through our:
 - Teaching and training activities
 - Publication of articles, booklets, books and business reports
 - Since 2012, we have published **17 business reports** covering the following topics:
 - French healthcare system and pharma market (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)
 - We expect that this new publication will be helpful
- Best regards,
Jean-Michel Peny