Pharma Market Perspectives 2017 – 2023

Key Insights

Strategic Implications for Pharma Companies

Position Paper

November 2018

Smart Pharma Consulting

1, rue Houdart de Lamotte – 75015 Paris – France
Tel.: +33 6 11 96 33 78 – Fax: +33 1 45 57 46 59
E-mail: jmpeny@smart-pharma.com – Website: www.smart-pharma.com

The purpose of this report is to analyze the current situation and the key trends of the pharmaceutical market by the end of 2023 at both global and French level

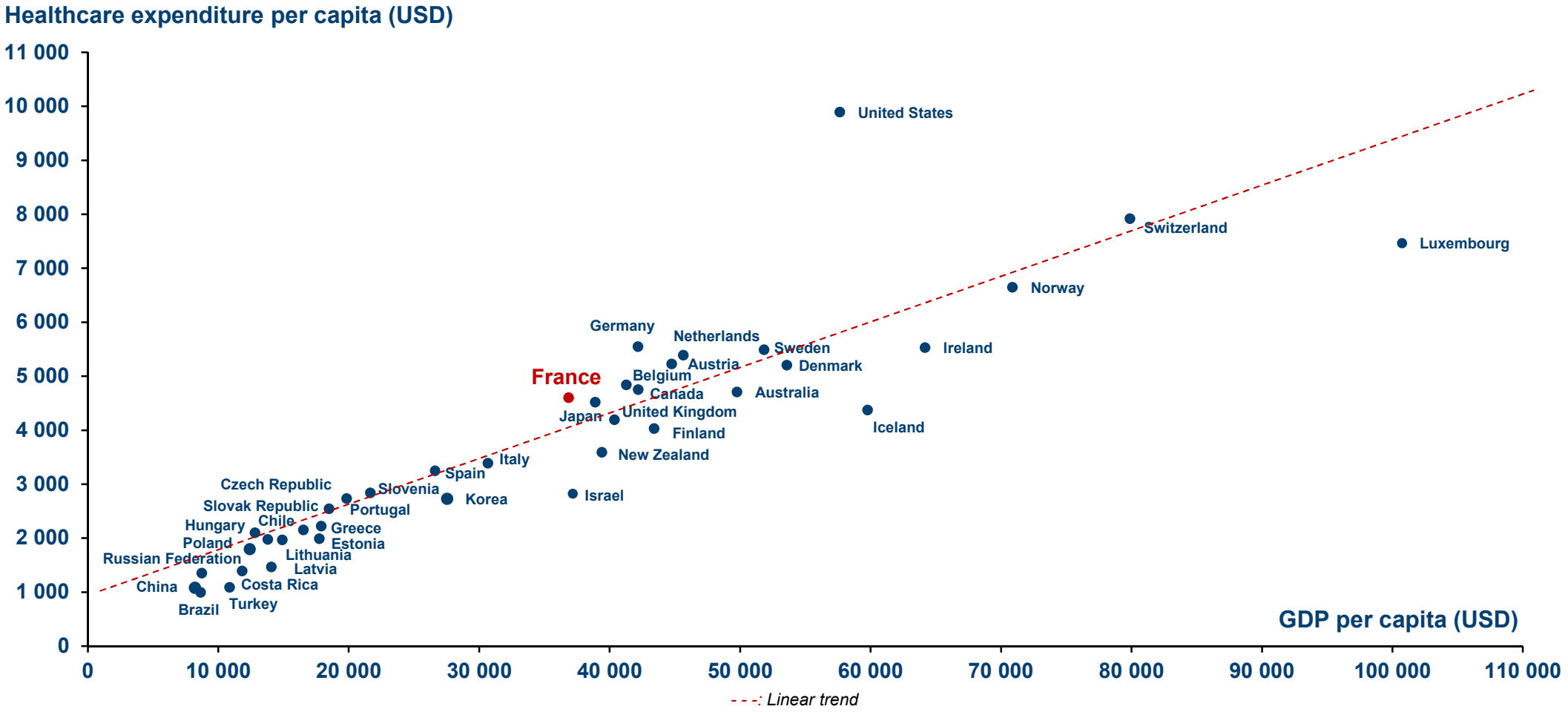
Pharma Market Perspectives 2017 – 2023

- Smart Pharma Consulting proposes to address the following key issues related to the pharma market evolution by the end of 2023, to better grasp its strategic impacts

- What should the global pharma market look like in 2023?
- What is the R&D cost to bring a new drug to market?
- What have been the recent performance and strategies of the top 30 pharma companies worldwide?
- How does France stand in comparison with other countries?
- What are the French pharma market forecasts by strategic segment by 2023?
- What could be the strategic implications for pharma companies by 2023?

Healthcare expenditure and GDP per capita are highly related and the ranking[1] of France (#14 and #20 respectively) shows that healthcare is a key national priority

Relation between GDP and healthcare expenditure per capita (2016)

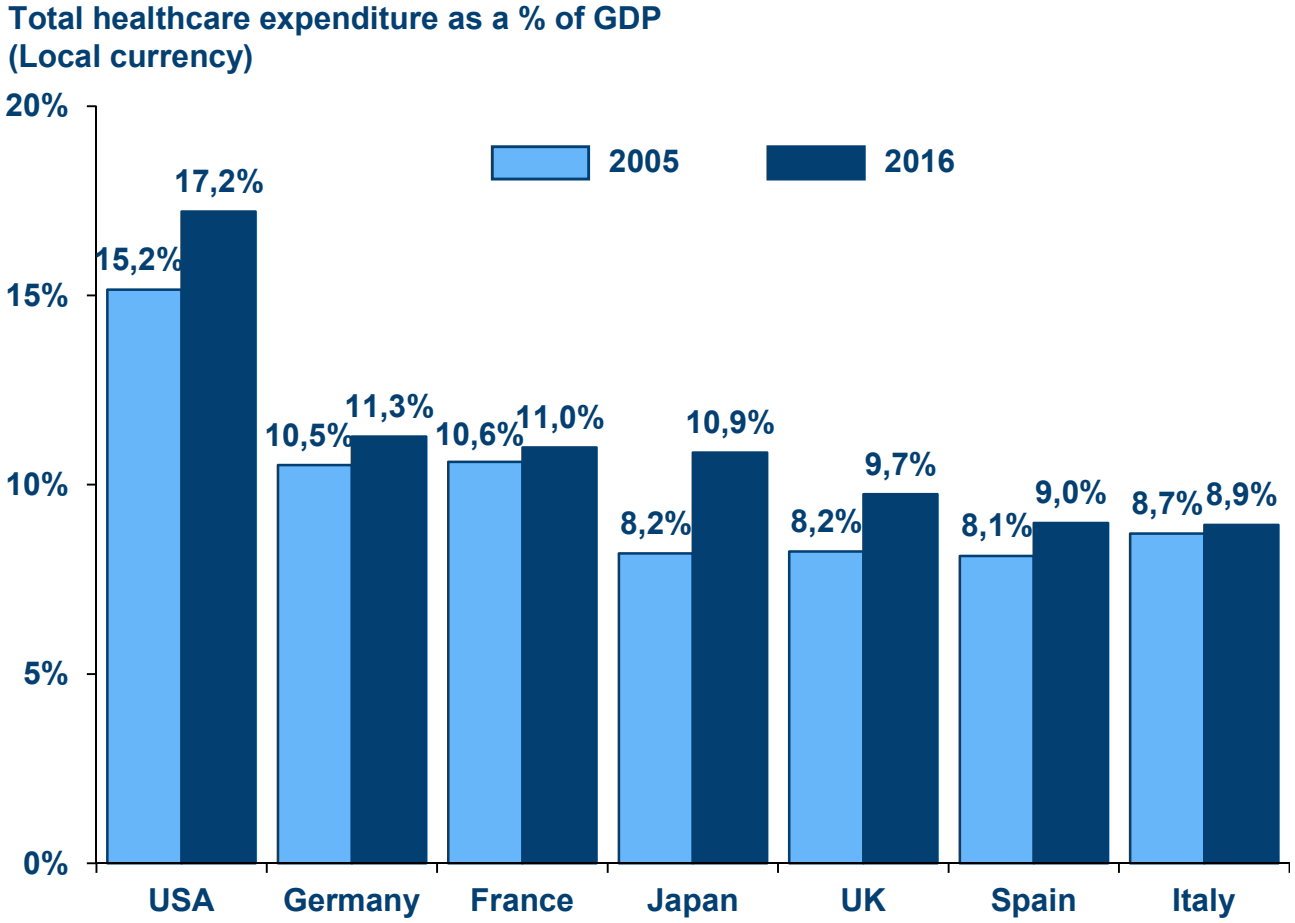


Sources: Health at a Glance, OECD (2017) – World Bank National Accounts Data (November 2018) – Smart Pharma Consulting analyses

[1] Amongst 44 countries in the world

Healthcare expenditure will keep on growing faster than national economies due to demographic factors and willingness of citizens to have better access to healthcare

Healthcare expenditure as a percentage of GDP



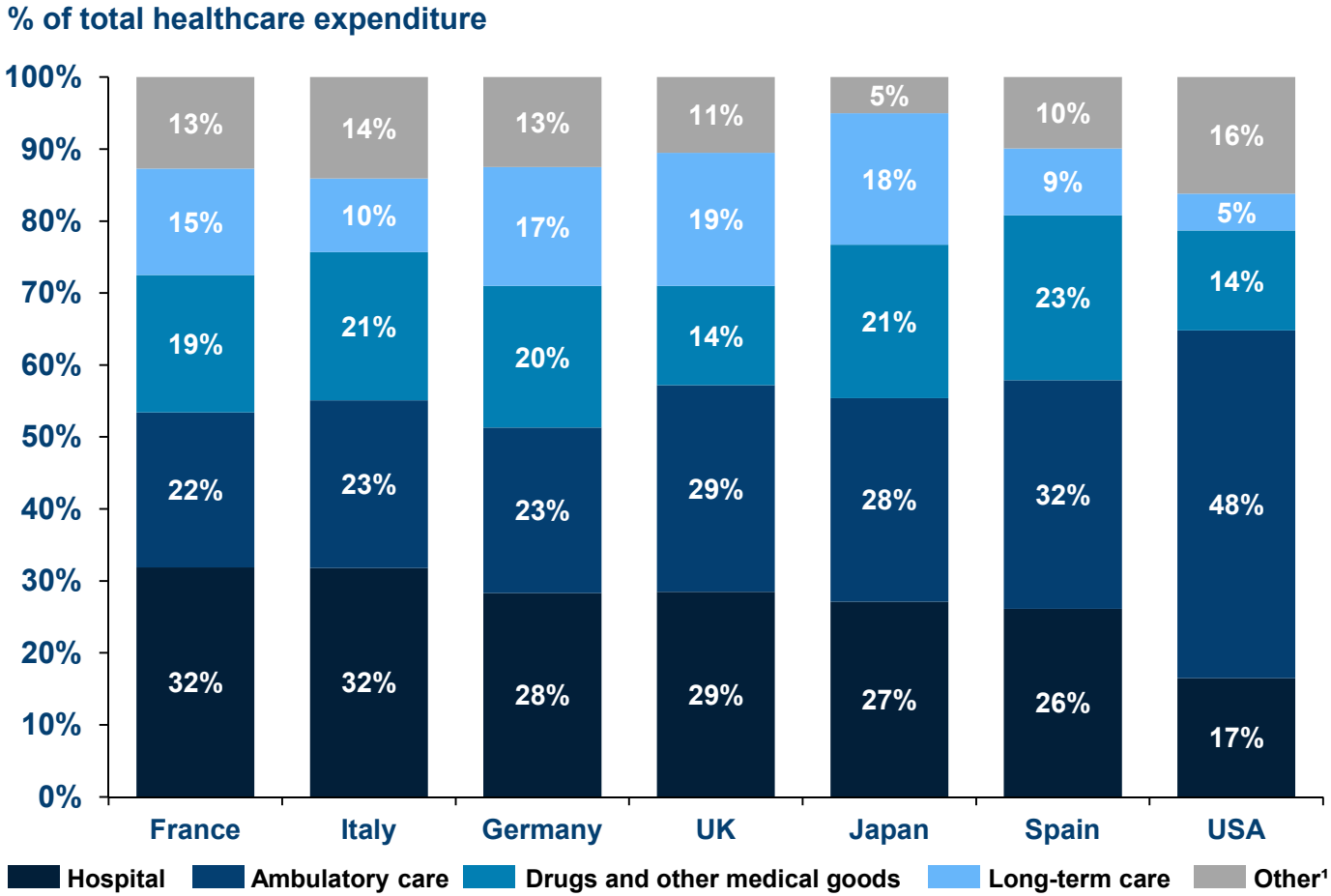
- Healthcare expenditure represent one of the largest public spending items in most developed economies: 1st (USA), 2nd (France, Germany, Japan, and UK)[1] and 3rd (Italy and Spain)[2]
- At best, governments and payers will manage to slow down the rise of healthcare expenditure as a percentage of GDP but would not be able to stop it
- There is no optimal ratio of healthcare expenditure over GDP, it primarily results from:
  - Public health conditions
  - Governments investment prioritization
  - Citizens willingness to seek for care
  - Healthcare cost

Sources: Health at a Glance, OECD (2017) – Government at a Glance (2017) – Smart Pharma Consulting analyses

[1] After social protection – [2] After social protection and general public services

The cost of drugs is far behind that of hospital and ambulatory care, yet this segment is targeted by governments because it is easier and quicker to reduce

Breakdown of healthcare expenditure per country (2017*)



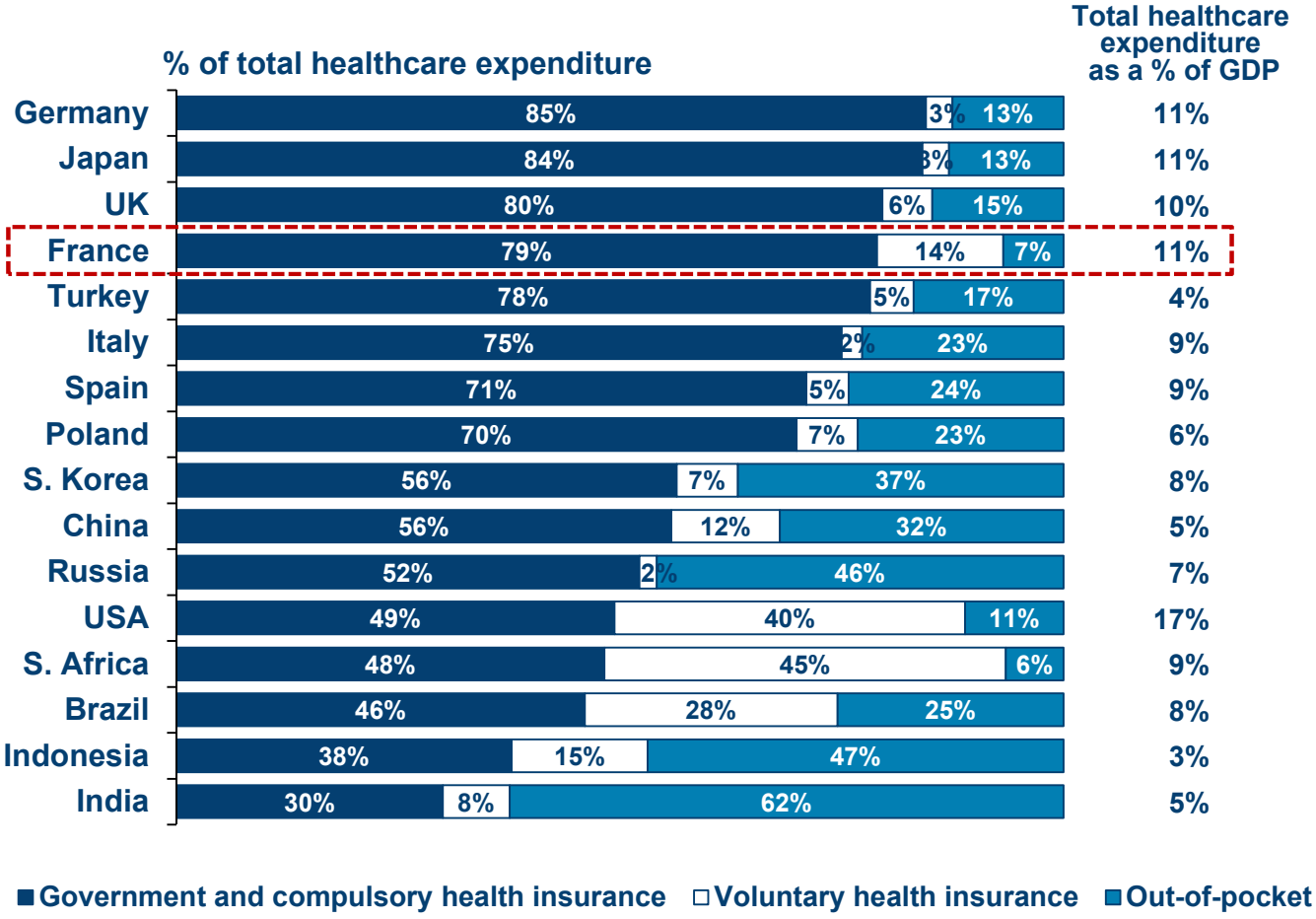
- Drugs represent the **3rd largest source** of healthcare expenditure in major developed countries
- Drugs are typically the **easiest segment** to apply cost-containment measures on, as decisions are:
  - Made by payers (either public and/or private), with a limited bargaining power of suppliers
  - Much better accepted by citizens than restriction measures on the other segments
- However, to significantly reduce total healthcare costs, governments will need to apply cost-optimization measures on all healthcare segments, irrespective of their relative importance

Sources: OECD Health Database (November 2018) – Smart Pharma Consulting analyses

[1] Other expenditure include ancillary services, preventive care & governance, health system and financing administration
** Data 2017 (Italy), 2016 (France, Germany, UK, Spain and USA) and 2015 (Japan)*

France is one of the countries where the percentage of "out-of-pocket" spending to cover the healthcare expenditure is the lowest

Share of public spending in total healthcare expenditure (2016*)



- With 11% of its GDP spent in healthcare, France belongs to the countries allocating the largest share of their resources
- Its level of public spending on healthcare is amongst the highest, just behind Germany, Japan and the UK, showing a highly protective healthcare system
- The great majority of the French citizens have a complementary private healthcare insurance (compulsory for all employees, irrespective of their employers company size, since the 1st of January 2016)
- As a result, "out-of-pocket" money is limited to 7% only

Sources: World Bank and OECD Health Databases (November 2018) – Smart Pharma Consulting analyses

** Note: Data 2016 (Italy and S. Korea), 2015 (Germany, UK, France, Turkey, Spain, Poland and USA) and 2014 (Japan, China, Russia, S. Africa, Brazil, Indonesia and India)*

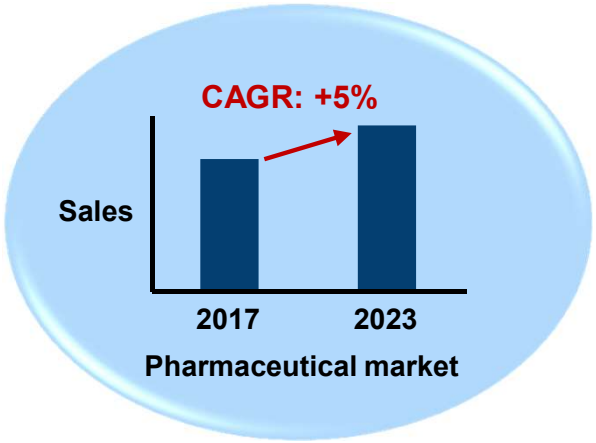
The key drivers and limiters of the global pharmaceutical market by the end of 2023, as well as their probable impact on sales trends, are well identified

Global pharmaceutical market drivers and limiters (2017 – 2023)

DRIVERS

1. Population increase and ageing
2. Better access to medicines in emerging markets (e.g. BRICS[1], Mexico, Turkey, etc.) as a result of an increasing GDP per capita
3. Strong development of generics market (access to a larger number of people, especially in low-income countries)
4. Strong demand from patients / PAGs[2] for new drugs more effective and better tolerated

Key forces



LIMITERS

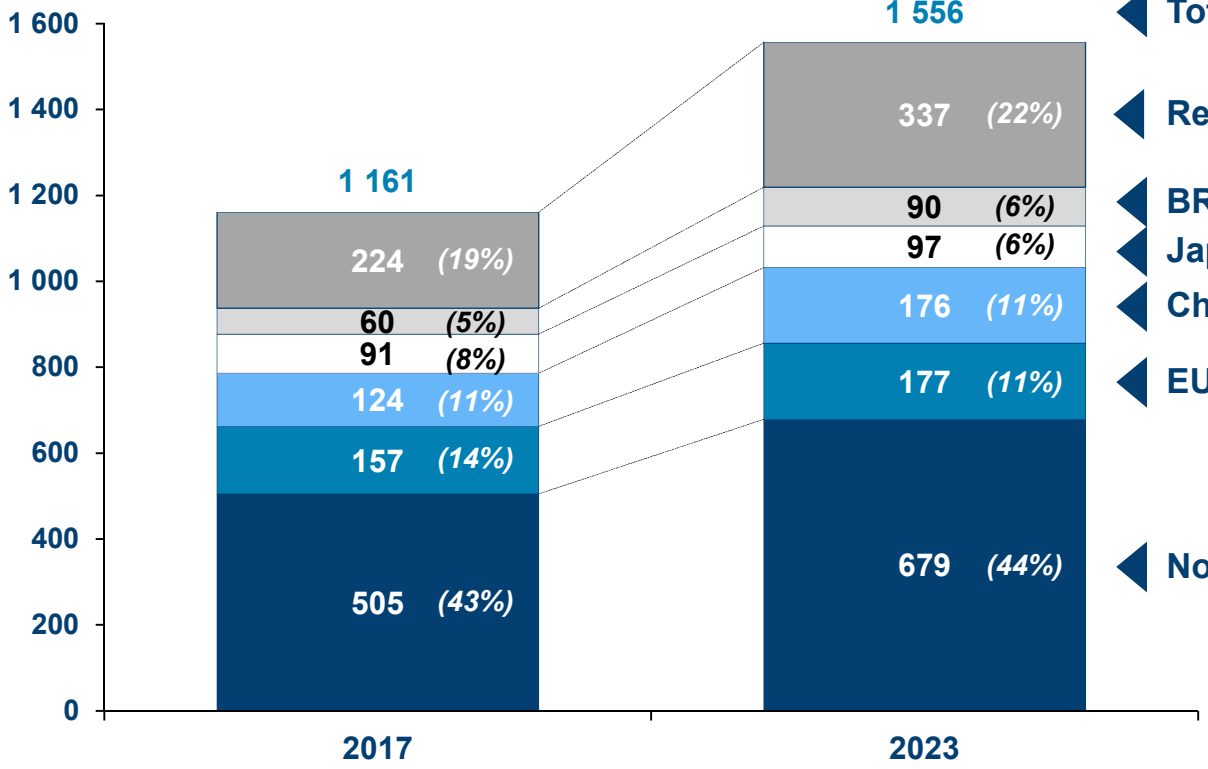
1. Decreasing R&D productivity of pharma companies re. breakthrough innovations
2. Increasing barriers to market access and price pressure from payers (governments, HMOs, patients, etc.), exacerbated by the economic environment
3. Increasing price sensitivity of customers for non-reimbursed drugs
4. Intensification of competition from generic and biosimilar drugs

Sources: Smart Pharma Consulting analyses

[1] Brazil, Russia, China, South Africa – [2] Patient advocacy groups

Sales of EU5[1] should grow slowly by 2023 due to stringent cost containment measures leading to a three-point decrease of their weight in the global pharmaceutical market

Global pharmaceutical market size and growth (2017 – 2023)



	CAGR 2017-2023	Growth in absolute value 2017-2023	Contribution to growth 2017-2023
Total	+5%	USD 395 B	
Rest of the word	+7%	USD 113 B	+29%
BRI[2]	+7%	USD 30 B	+8%
Japan	+1%	USD 6 B	+1%
China	+6%	USD 52 B	+13%
EU5	+2%	USD 20 B	+5%
North America[3]	+5%	USD 174 B	+44%

Sources: IQVIA Institute (March 2018) – Global OTC Drugs Market, Mordor Intelligence (May 2018) – Smart Pharma Consulting estimates

[1] France, Germany, Italy, Spain, UK – [2] Brazil, Russia, India – [3] USA and Canada

By 2023, the French Pharma market is expected to step back from the 5th to the 6th place at the global level and to keep its 2nd position after Germany in Europe

Global pharmaceutical market ranking in value[1] (2012 – 2017 – 2023)

Rank	2012	2017	2023	CAGR 2017-2023
1	USA	USA	USA	++
2	China	China	China	+++
3	Japan	Japan	Japan	+
4	Germany	Germany	Germany	++
5	France	France	Brazil	++++
6	Italy	Brazil	France	+
7	Brazil	Italy	Italy	+
8	UK	UK	UK	+
9	Spain	Spain	India	++++
10	Canada	Canada	Spain	+
11	India	India	Canada	++
12	South Korea	Russia	Russia	+++
13	Australia	South Korea	South Korea	++
14	Russia	Australia	Australia	+
15	Mexico	Mexico	Turkey	+++
16	Argentina	Turkey	Mexico	+++
17	Saudi Arabia	Poland	Argentina	+++
18	Poland	Saudi Arabia	Poland	+++
19	Switzerland	Argentina	Saudi Arabia	++
20	Belgium	Switzerland	Switzerland	++

CAGR 2017 – 2023

++++ → >8%

+++ → 6 – 8%

++ → 3 – 5%

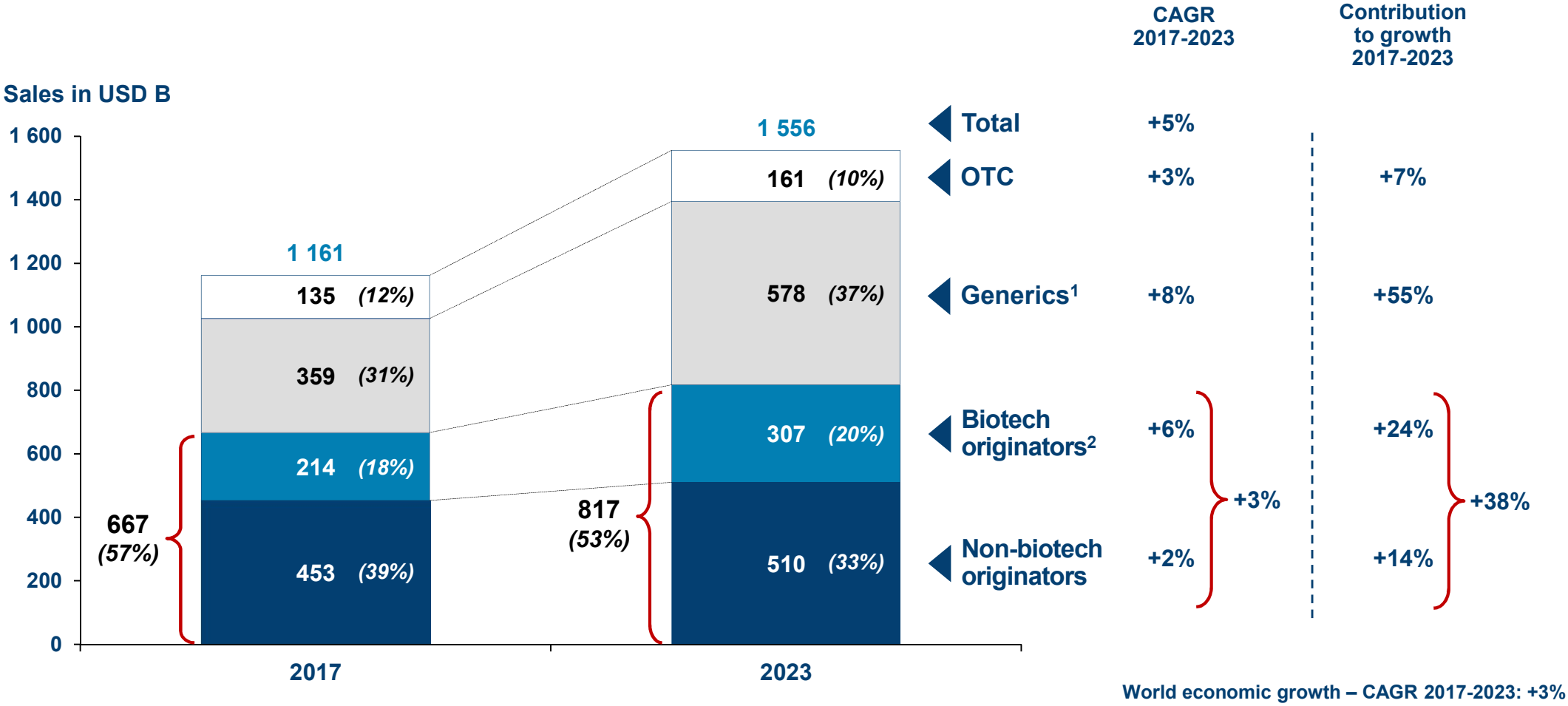
+ → 0 – 2%

Sources: IQVIA Institute (March 2018) – Smart Pharma Consulting estimates

[1] In 2017 USD, at constant exchange rate

The generics segment should become more important in value than non- biotech original drugs one in 2023 and contribute to 55% of the growth between 2017 and 2023

Global pharmaceutical market growth by strategic segment (2017 – 2023)

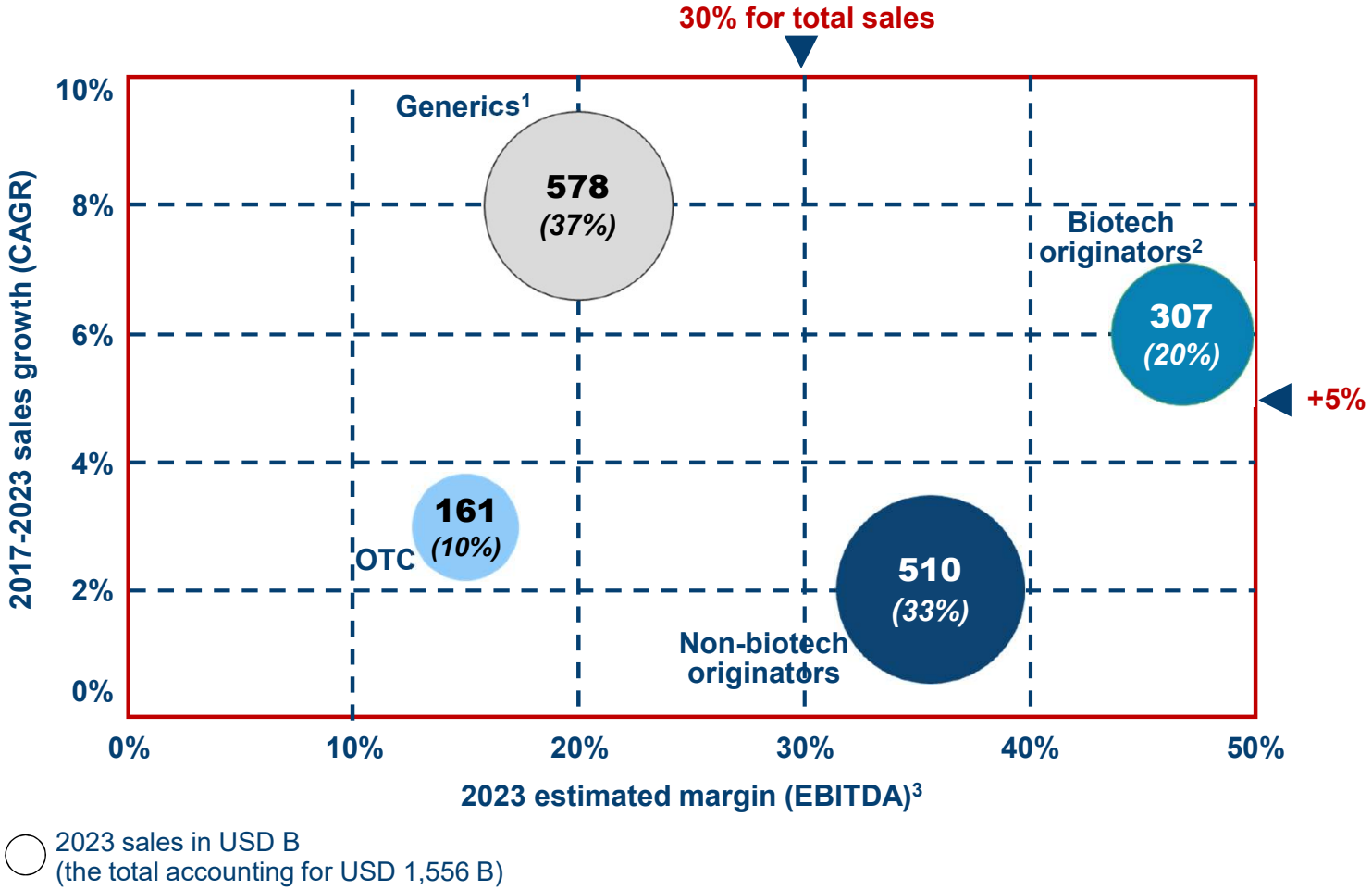


Sources: IQVIA Institute (March 2018) – Global OTC Drugs Market, Mordor Intelligence (May 2018) – Global economic growth projections, The Conference Board (November 2018) – Smart Pharma Consulting estimates

[1] Including branded and unbranded generics and biosimilars, excluding OTC –
[2] Excluding biosimilars, already included in the "Generics" segment

By 2023, the sales growth of the pharma market should be essentially driven by generics and biotech originators, but pharma companies should lose two points of profitability

Global pharmaceutical market growth by strategic segment (2017 – 2023)



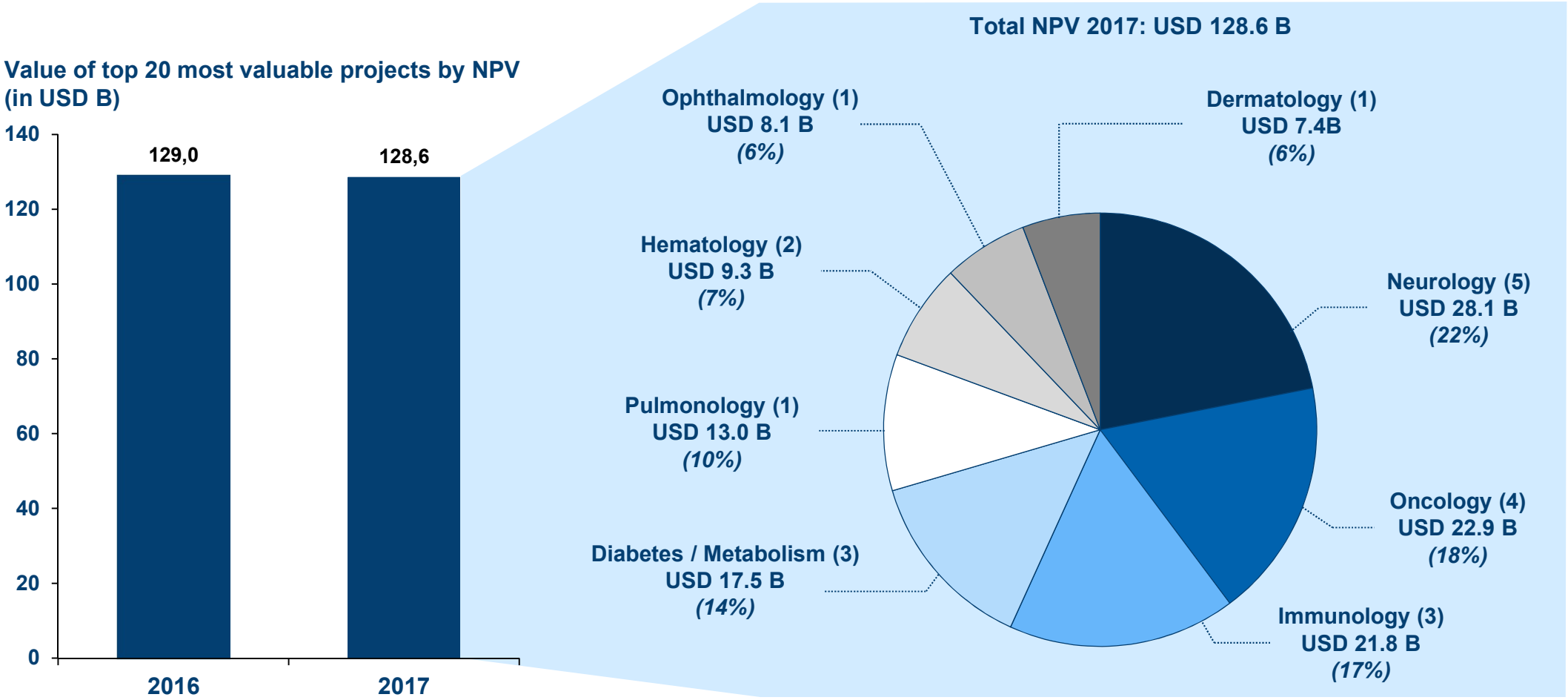
- By 2023, the sales (incl. human drugs only for the non-OTC segments; medical devices and food supplements for the OTC segment) should reach USD 1,556 B and grow at a pace of +5% p.a.
- The average EBITDA of the Pharma industry should decrease from ~32% in 2017 to ~30% in 2023, mainly as a result of increasing price pressure
- The OTC segment appears to be the least attractive
- The biotech segment will remain attractive but biosimilar competition will ramp up

Sources: IQVIA Institute (March 2018) – Global OTC Drugs Market, Mordor Intelligence (May 2018) – Smart Pharma Consulting estimates

[1] Including branded and unbranded generics and biosimilars, excluding OTC –
[2] Excluding biosimilars, already included in the "Generics" segment –
[3] Earnings before interest, taxes, amortization and depreciation

In 2017, the top 20 most valuable R&D projects by net present value reached USD 128.6 B (vs. 129 B in 2016), with 22% of the potential in neurology

Top 20 most valuable R&D projects by therapeutic area (2017)



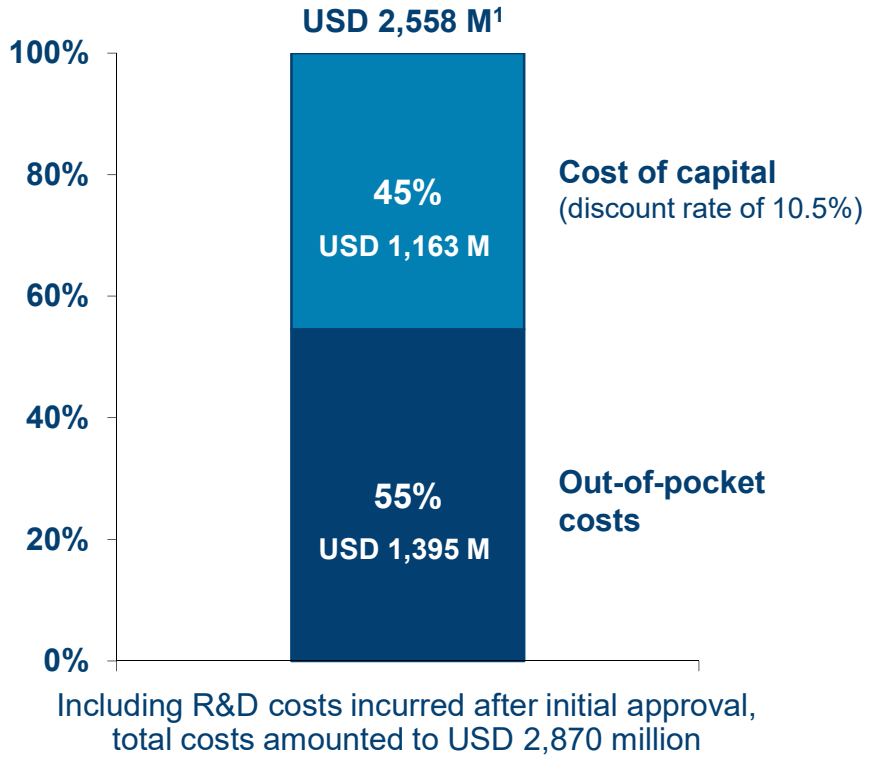
Sources: Evaluate Pharma "World Preview 2018, outlook to 2024" (June 2018) and previous version – Smart Pharma Consulting analyses

Note: (x): number of projects – USD B: total NPV by therapeutic area – (x%): Contribution in total NPV of Top 20 most valuable R&D projects

The latest estimates by DiMasi concluded in an important out-of-pocket spending growth while cost of capital discount rate was decreased by one point of percentage

R&D costs estimates for drugs (2016)

Estimated capitalized cost per approved new drug (pre-tax)



Including R&D costs incurred after initial approval, total costs amounted to USD 2,870 million

- DiMasi followed a similar methodology compared with its previous estimates on drugs costs (based on 106 new chemical and biologic drugs first tested in humans between 1995 and 2007)
- The database was also the same: Tufts Center for the Study of Drug Development proprietary database
- The cost of capital applied to out-of-pocket costs (10.5%) was decreased compared with previous analysis (11.5%)
- Out-of-pocket and capitalized preclinical costs were estimated at USD 430 M and USD 1,098 M, respectively
- Out-of-pocket and capitalized clinical costs were estimated at USD 965 M and USD 1,460 M, respectively
- Results showed an important increase of out-of-pocket costs compared with previous estimates. The CAGR of out-of-pocket R&D was estimated per period as follows:
  - 1970s to 1980s: +7.0%
  - 1980s to 1990s: +7.6%
  - 1990s to early 2010s: +9.3%

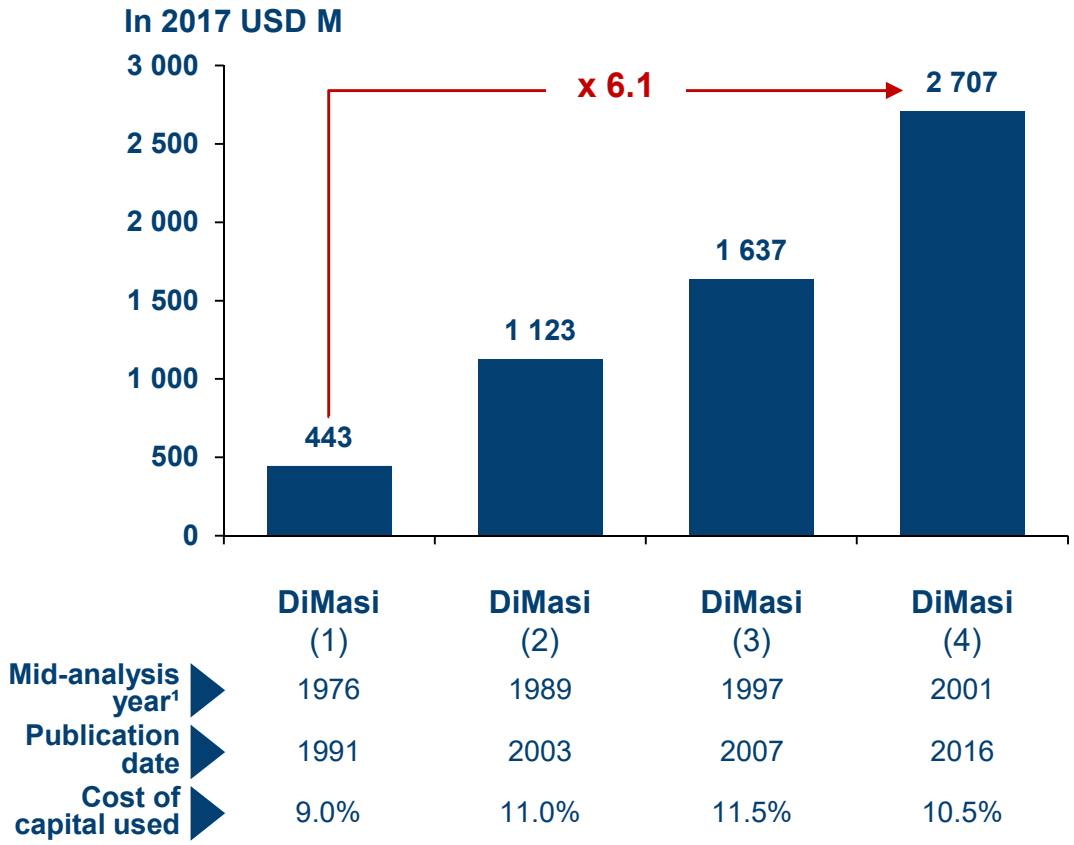
Source: DiMasi & Al. (February 2016) – Smart Pharma Consulting analyses

[1] Capitalized costs in 2014 USD

The analysis of four studies carried out with the same methodology shows that the development cost of new drugs has more than sextupled over the last three decades

Evolution of R&D costs

Estimated capitalized cost per approved new drug (pre-tax)



- The evolution of the capitalized R&D costs per approved new drug, after neutralization of the inflation, can be mainly explained by:
  - The growth of the out-of-pocket costs, especially the growth of clinical trials spending: x10.8 between the 1991 and the 2016 estimates (vs. preclinical spending which grew less: x3.9)
  - The decrease of the success rates to reach approval from phase I, ranging from 23% in the first 1991 estimates to 12% in the 2016 estimates
  - The overall increase of the used cost of capital, even if, in the 2016 estimates, a 10.5% cost of capital was used, in decrease of 1 point of percentage from the previous estimates. These assumptions of cost of capital seem overestimated compared with available data from NYU Stern School of Business for biotech products (9.2%, based on 411 firms) and for traditional pharma (7.7%, based on 157 firms)

Note: For the sake of comparability, all values are adjusted to USD 2017 prices using data of the US GDP implicit price deflator from the US. Bureau of Economic Analysis
The GDP implicit deflator shows the rate of price change in the economy as a whole, being the ratio of GDP in current local currency to GDP in constant local currency

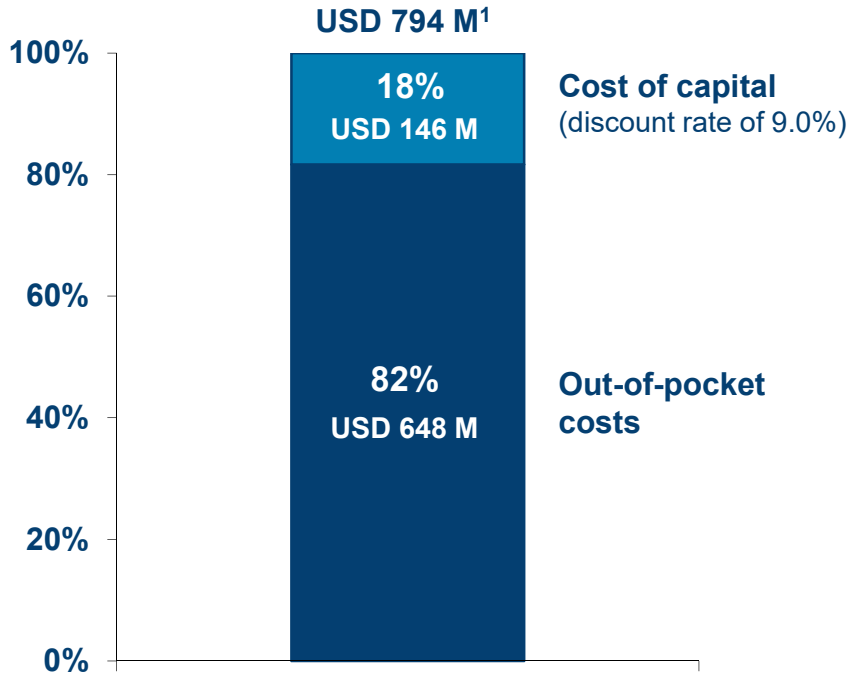
Sources: DiMasi (1991) – DiMasi et al. (2003) – DiMasi, Grabowski (2007) – DiMasi (2016) – Cost of Capital, NYU Stern School of Business (January 2016) – Implicit price deflators for GDP, Bureau of Economic Analysis – Smart Pharma Consulting analyses

[1] Products with first testing in humans over the analyzed period

In the JAMA Internal Medicine study, the median cost of developing a single cancer drug was estimated at USD 794 M, including a 9% per annum cost of capital

R&D costs estimates for oncology drugs (2017)

Estimated capitalized R&D cost per new cancer drug



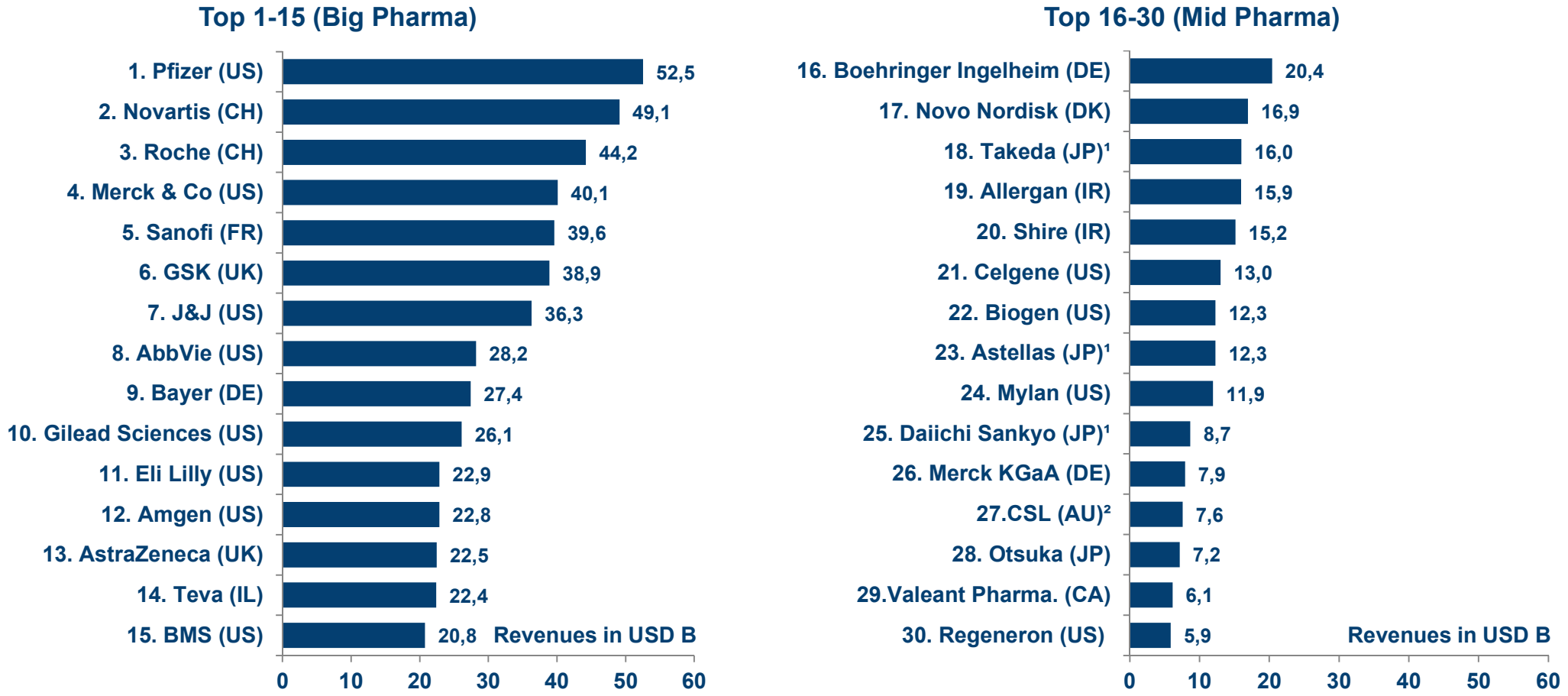
- The study was conducted from December 2016 to March 2017
- 10 companies having received approval by the US FDA[2] for a cancer drug from January 1, 2006 to December 31, 2015 were included in the analysis
- Cumulative R&D spending was estimated from initiation of drug development activity to date of approval
- The 10 companies had a medium time to develop a drug of 7.3 years (range, 5.8 to 15.2 years)
  - 5 drugs received accelerated approval from the US FDA
  - 5 drugs received regular approval
- The median cost of drug development was estimated at USD 648 M (range, USD 157 M to USD 1,951 M) representing:
  - For a 7% per annum cost of capital[3], USD 757 M (range, USD 204 M to USD 2,602 M)
  - For a 9% per annum cost of capital[3], USD 794 M (range, USD 219 M to USD 2,827 M)
- With a median of 4.0 years (range, 0.8 to 8.8 years) since approval, the total revenue from sales of these 10 drugs since approval was USD 67.0 B compared with total R&D spending of USD 7.2 B

Source: JAMA Internal Medicine (November 2017) – Smart Pharma Consulting analyses

[1] Capitalized costs in 2017 USD – [2] Food and Drug Administration – [3] Opportunity cost

The top 30 pharma companies based on prescription sales counts 12 companies from the USA and 11 from Europe

Top 30 prescription sales pharma companies (2017)



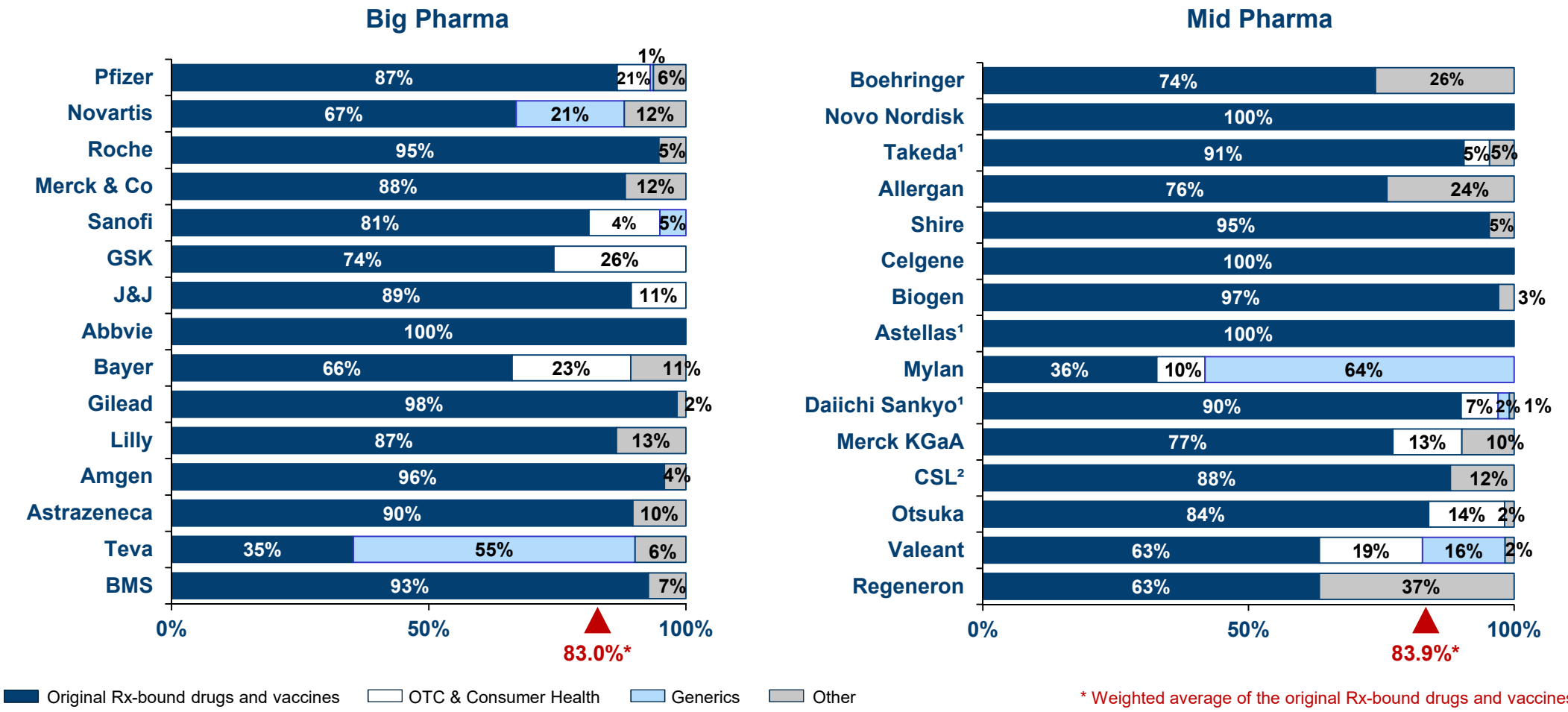
Note: panel of the 30 biggest pharma companies in terms of prescription sales in 2017 (excluding diagnostics, medical device and nutrition products)

Sources: Companies annual reports (2017) – Smart Pharma Consulting analyses

[1] Fiscal year ended March 31, 2018 – [2] Fiscal year ended June 30, 2018

In 2017, original Rx-bound drugs and vaccines was the main source of revenue for most Big and Mid Pharma companies

Strategic segments (2017)



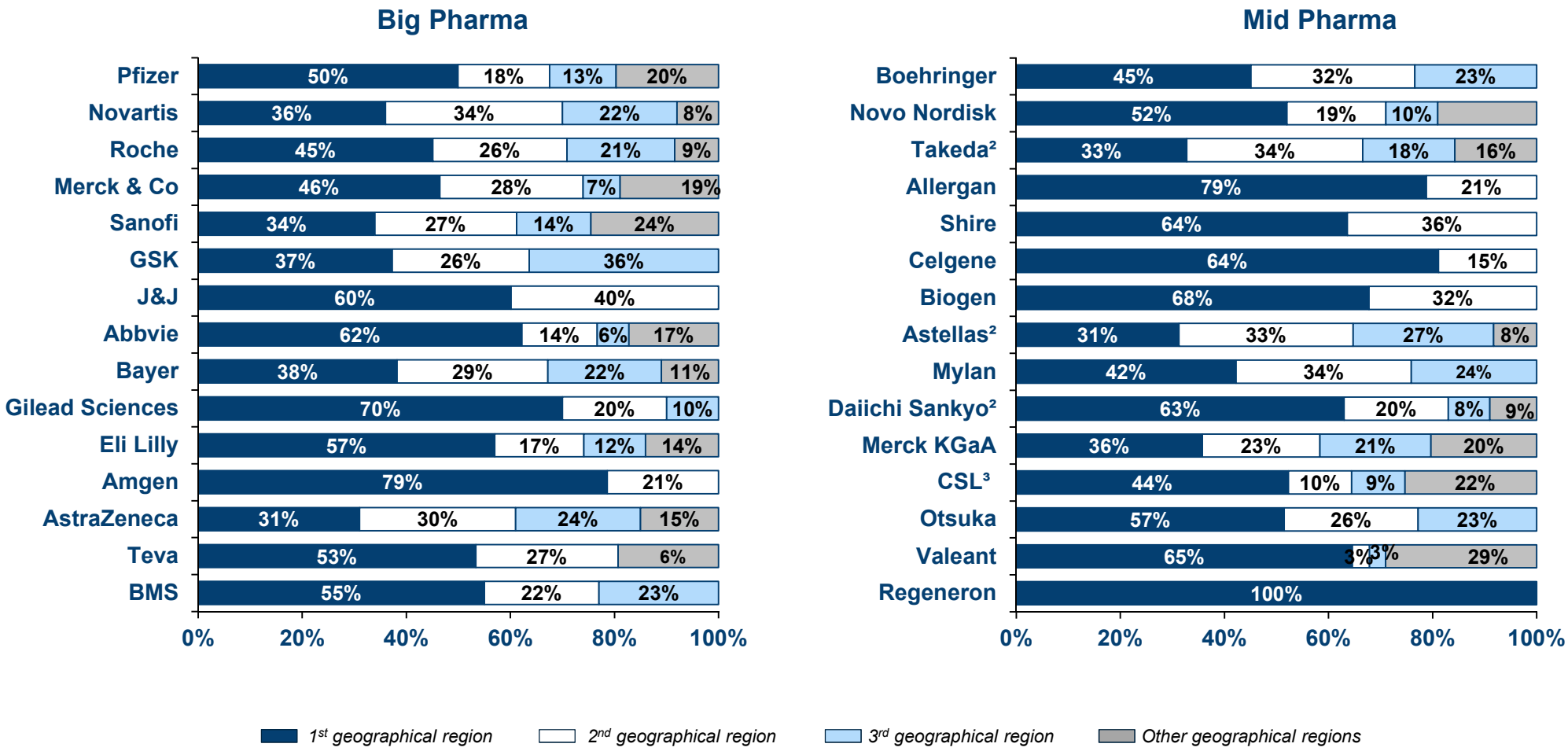
* Weighted average of the original Rx-bound drugs and vaccines

Sources: Companies annual reports (2017) – Smart Pharma Consulting analyses

[1] Fiscal year ended March 31, 2018 – [2] Fiscal year ended June 30, 2018

Mid Pharma companies tend to be less geographically diversified, with most of them generating more than half of their revenues in a single region

Geographical distribution[1] (2017)



Sources: Companies annual reports (2017) – Smart Pharma Consulting analyses

[1] 1st & 2nd geographical regions include North America (USA and Canada), Europe and Japan depending on companies – [2] Fiscal year ended March 31, 2018 – [3] Fiscal year ended June 30, 2018

Most of the recent M&A operations have been carried out to strengthen Big and Pharma companies positions on their core strategic segments

Major M&A operations (2015 – 2017)

Big Pharma

Acquirer	Acquired (> USD 2.0 B)	Strategic objectives		
		Diversification	Strengthening	Expansion
Pfizer	▪ **Hospira** *(Generics / Biosimilars)* ▪ **Medivation** *(Oncology)* ▪ **Anacor** *(Anti-inflammatory)*	✓ ✓	✓	
Novartis	▪ **Advanced Accelerator Applications** *(Oncology)*		✓	
Sanofi	▪ **Boehringer Ingelheim** *(Consumer healthcare business of the company)*		✓	
J&J	▪ **Actelion** *(Pulmonary arterial hypertension)*		✓	
AbbVie	▪ **Pharmacyclics** *(Oncology)* ▪ **Stemcentrx** *(Oncology)*		✓ ✓	
Gilead Sciences	▪ **Kite Pharma** *(Cancer immunotherapies)*		✓	
AstraZeneca	▪ **Acerta Pharma** *(Cancer and autoimmune diseases)* ▪ **ZS Pharma** *(Cardiovascular and metabolic diseases)*		✓ ✓	
Teva	▪ **Actavis Generics** *(Generics business of Allergan)* ▪ **Auspex Pharmaceuticals** *(CNS disorders)* ▪ **Rimsa** *(Latin America)*		✓ ✓	✓
BMS	▪ **Cardioxyl** *(Cardiovascular)* ▪ **IFM Therapeutics** *(Cancer immunotherapies)*		✓ ✓	

Mid Pharma

Acquirer	Acquired (> USD 2.0 B)	Strategic objectives		
		Diversification	Strengthening	Expansion
Boehringer Ingelheim	▪ **Merial** *(Animal health business of Sanofi)*		✓	
Takeda	▪ **Ariad Pharmaceuticals** *(Oncology)*		✓	
Allergan	▪ **Life Cell unit of Acelity** *(Aesthetics & Regenerative)* ▪ **Kythera Biopharmaceuticals** *(Aesthetics)*		✓ ✓	
Shire	▪ **Baxalta** *(Rare diseases)* ▪ **Dyax Corp** *(Rare diseases)* ▪ **NPS Pharmaceuticals** *(Rare diseases)*		✓ ✓ ✓	
Celgene	▪ **Receptos** *(Immune-inflammatory diseases)*		✓	
Mylan	▪ **Meda** *(OTC, Emerging markets such as China, Asia or MEA)*	✓		✓
Valeant Pharma	▪ **Salix Pharmaceuticals** *(Gastrointestinal)*	✓		

Note: Diversification means entering new strategic segments/balancing minor segments – Strengthening means reinforcing major strategic segments – Expansion means geographical coverage

Sources: ThePharmaLetter – Companies press releases – Smart Pharma Consulting analyses

Big and Mid Pharma companies are mainly focused on Rx branded segment, but Big Pharma companies are more geographically diversified

Pharma companies development strategy (2017)

Big Pharma

Strategic segments

Geographical coverage	Rx branded Focused	Diversified
Focused	BMS, Lilly, Gilead, Amgen, AbbVie, J&J	Teva
Diversified	Roche, AstraZeneca, Merck & Co, Pfizer, Sanofi	Bayer, Novartis, GSK

Mid Pharma

Strategic segments

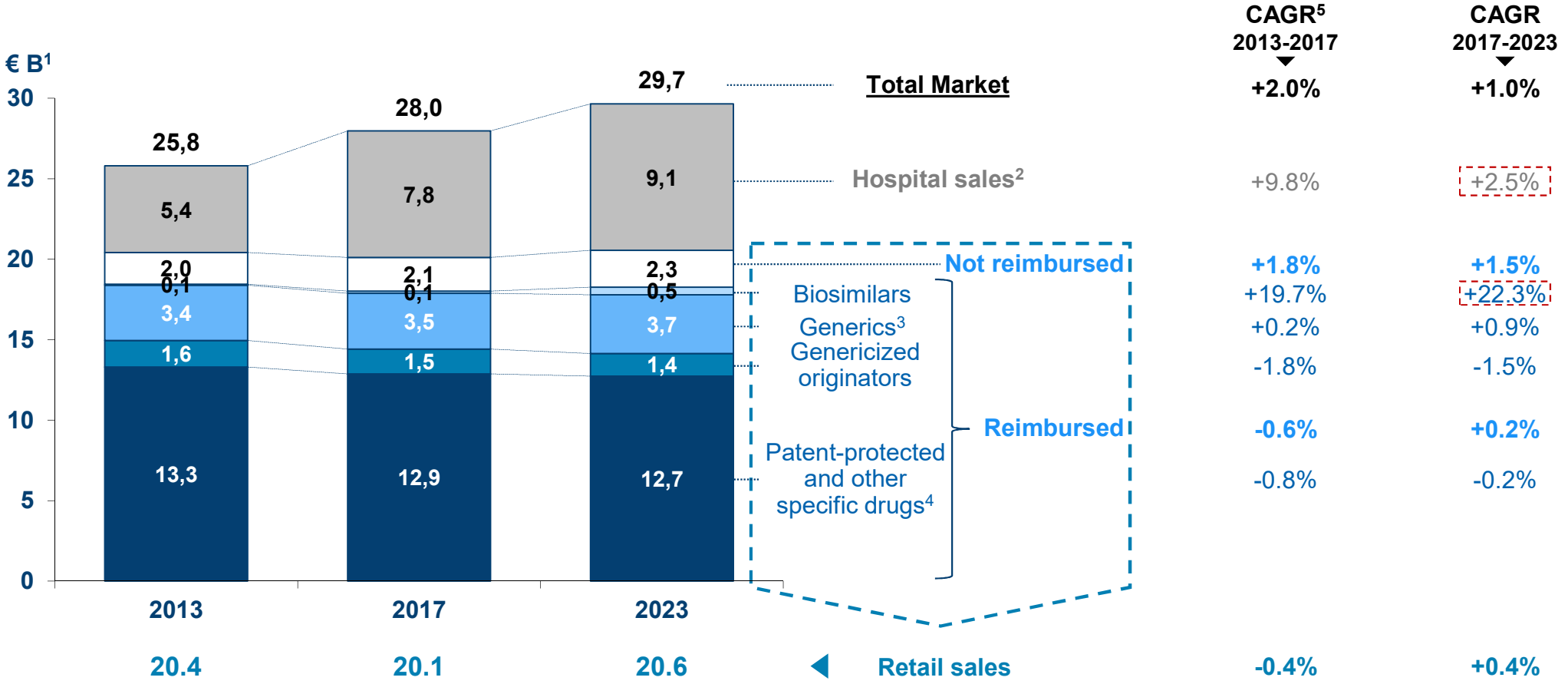
Geographical coverage	Rx branded Focused	Diversified
Focused	Allergan, Amgen, Shire, Celgene, Biogen, Novo Nordisk, CSL, Daiichi Sankyo, Otsuka	Valeant, Regeneron
Diversified	Boehringer, Astellas, Merck KGaA, Takeda	Mylan

Note: **Rx Branded focused**: Original Rx-bound drugs and vaccines ≥ 75% of total product sale – **Geographically focused**: >50% of sales in a single geographical region (e.g. USA, Europe, Japan, etc.)

Sources: Companies annual reports (2017) – Smart Pharma Consulting analyses

By 2023, the French pharmaceutical market should be mainly driven by innovative hospital products and biosimilars

Evolution of drug sales by segment (2013 – 2017 – 2023)



* *Hospital rebates are estimated to -30% of total hospital sales*

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

¹ Constant ex-factory prices – ² Estimated rebated sales including hospital sales of biosimilars, 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 medicines whose patents have not expired and of other specific products (calcium, sodium, potassium, paracetamol, etc.) – ⁵ Compound Annual Growth Rate

When compared to the other EU5 countries, a wider array of indicators are used by French health authorities to evaluate the economic value of drugs

Health economic evaluations: Submission requirements in Europe

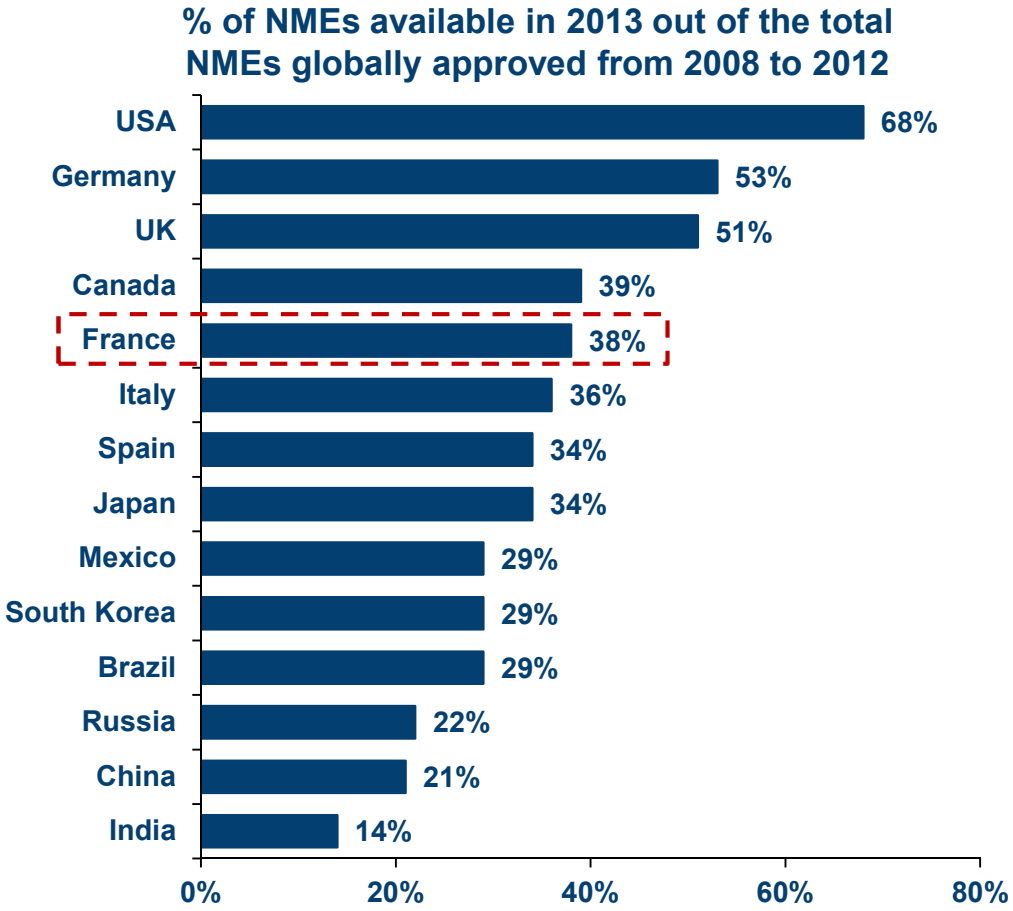
	Therapeutic benefit	Cost-effectiveness modeling	Budget impact modeling	HRQoL[1] data	Data vs. SoC[2]	Innovation	Comments
	✔	✔	✔	✔	✔	✔	Cost-effectiveness considered since 2013 with the creation of the CEESP (Economic committee for healthcare products)
	✔		✔	✔	✔		Free pricing during the first six months on the market: i.e. before the assessment by IQWG (Institute for Quality and Efficiency in Health Care)
	✔	✔	✔	✔	✔		One of the first countries to implement a form of value-based pricing including cost-effectiveness and QoL (Quality of Life) data
	✔	✔ (national or regional requirement)	✔ (national and regional requirement)		✔	✔	Requirements may vary from a region to another
	✔	✔ (national or regional requirement)	✔ (national and regional requirement)		✔		Requirements may vary from a region to another

Sources: "An Introduction to European Market Access", PRMA Consulting – Smart Pharma Consulting updates

[1] Heath-Related Quality of Life – [2] Standard of Care

A small proportion of globally approved drugs are launched in France mainly due to market access obstacles (non-reimbursed, low price, etc.)

Market access to new drugs – International comparisons

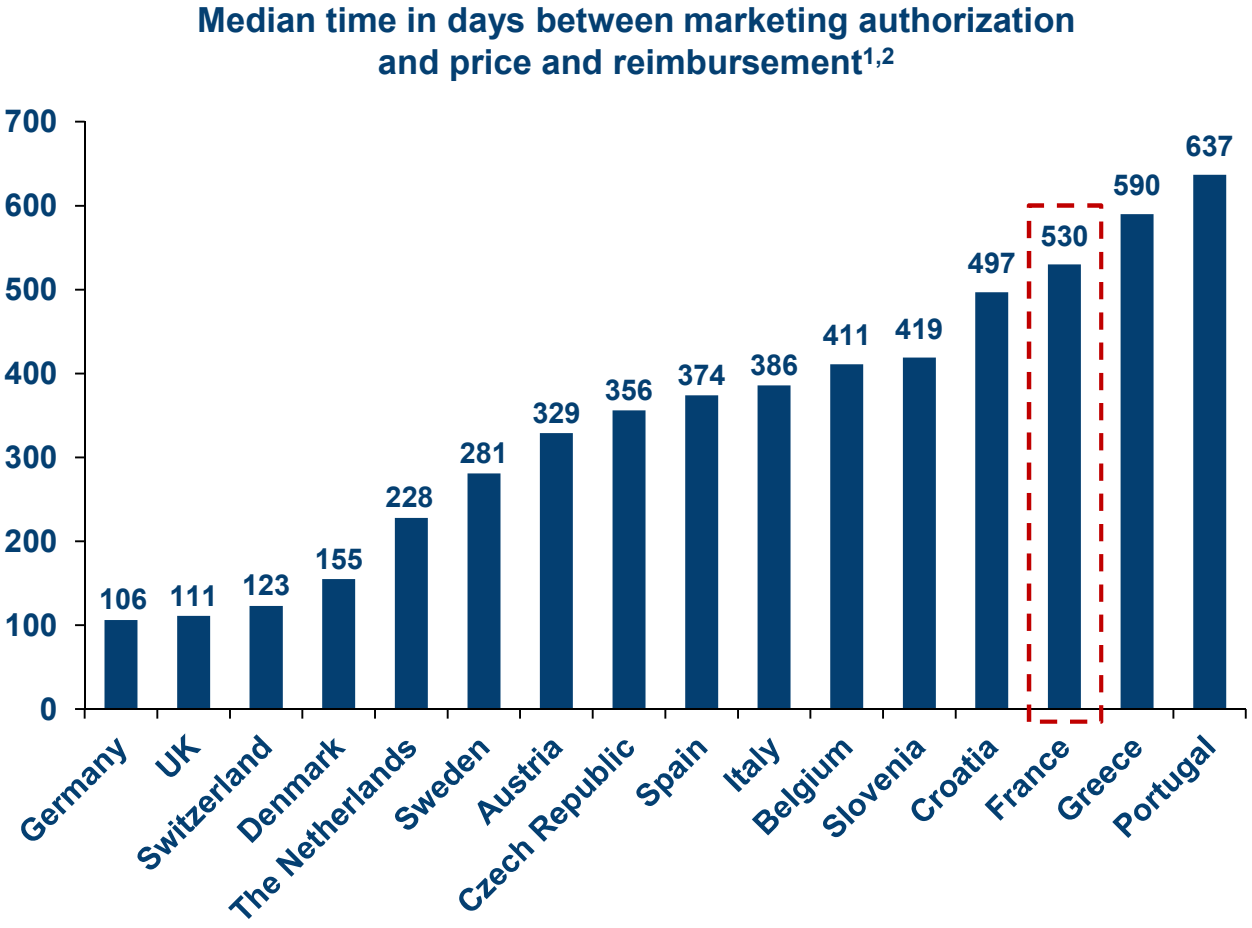


- The fact that all approved new molecular entities (NMEs) are not introduced everywhere depends on several factors:
  - **Different regulatory systems** and authorities (FDA, EMA, etc.) impose different market access requirements and procedures
  - Even when there is a centralized approval procedure like in the European Union, the approved drug is not necessarily introduced in all countries as **local pricing and reimbursement policies** can make the launch unattractive
  - Generally, market potential and attractiveness (epidemiology, pricing and reimbursement policies, etc.) are key factors in the decision of introducing a drug in a particular country by pharma companies
  - New drugs are usually more expensive, which makes their introduction more difficult in lower income countries, where the public budget for pharmaceuticals is lower
- In the future, the availability of new medicines might be reduced in developed countries (with the exception of the USA) due to **stricter cost containment measures**, but increased in emerging countries where spending on pharmaceuticals is growing strongly

Sources: "Global Outlook for Medicines Through 2018", IMS Health – Smart Pharma Consulting analyses

In eight European countries, including France, pharma companies and patients must wait more than a year after marketing authorization to get a new drug reimbursed[1]

Average time to market in European countries



- In Europe, the delay between marketing authorization of a drug and its availability on the market may vary widely, due to the time required to obtain its inclusion on reimbursement list and a price agreement
- In countries such as France, Italy or Spain, this delay exceeds the 180 days recommended by the European Commission
- An important delay may be harmful both for patients who do not have full access to innovative therapies and for companies which face a loss of revenues[1]
- The UK and Germany have no delay since the price and reimbursement negotiations occur once the product has reached the market

Sources: Patients W.A.I.T. Indicator – IFIP (June 2018)

[1] Excluding early access programs for breakthrough innovations (e.g. ATU / post-ATU in France) –
[2] For drugs receiving their first marketing authorization between 2013 and 2015

The implementation of managed entry agreements are most often time-consuming and costly for payers and/or pharma companies, outweighing their benefits

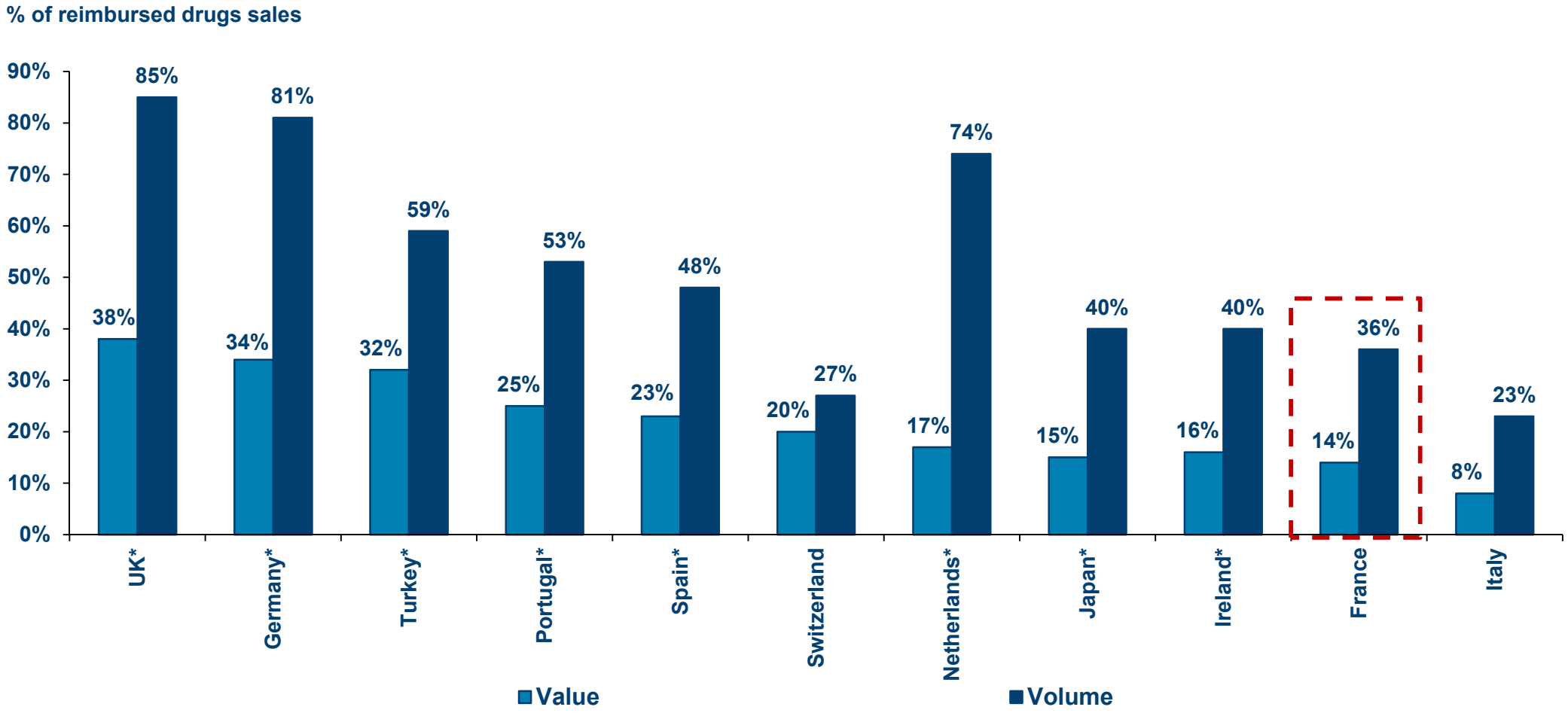
Pros & Cons of managed entry agreements

	Pros	Cons
CEPS	▪ Potential to **re-evaluate** the effectiveness of drugs at a later stage and **re-negotiate** the price based on **real-world evidence** ▪ Help **address post-licensing uncertainty** by offering flexibility in dealing with new and often expensive treatments ▪ Improve the **cost-effectiveness** through a **discount** or a **payback** agreement for non-responders ▪ Enable **different types of schemes** addressing **different needs**, both **financial** and **non-financial**	▪ **Additional efforts** required to make a new drug available to patients, such as **negotiation time, monitoring of patient response**, **data gathering**, development of **registries**, etc. ▪ Threat that manufacturers could start proposing **higher entry prices** in the expectancy of having to engage managed entry agreements ▪ **Limited capacity** to **implement** and **assess evidence**, notably if implementation takes place at regional/hospital level
Pharma companies	▪ Speed up **pricing** negotiations and **reimbursement** ▪ Potential to benefit from a better **corporate reputation** as a result of the willingness to take responsibility for the use of the drug in real-life ▪ Potential to **reinforce** the **long-term collaboration** between **payers**, **health authorities** and **pharmaceutical companies** ▪ Enable **discounts** without impacting list prices	▪ **Costs** related to the implementation of the managed entry agreement can, in some cases, totally **outweigh benefits** ▪ **Concessions** required such as refunds for non-respondent patients, discounts, gathering of additional data ▪ Voluntary versus no voluntary nature of such contracts leading to a **variability in stakeholders perception**

Sources: "Managed entry agreements for pharmaceuticals: the European experience", Alessandra Ferrario and Panos Kanavos, April 2013 – Smart Pharma Consulting analyses

France is below most OECD countries in terms of generics penetration in the pharmaceutical market mainly due to a more restrictive definition of generics

Share of generics in the reimbursed pharmaceutical market (2017)

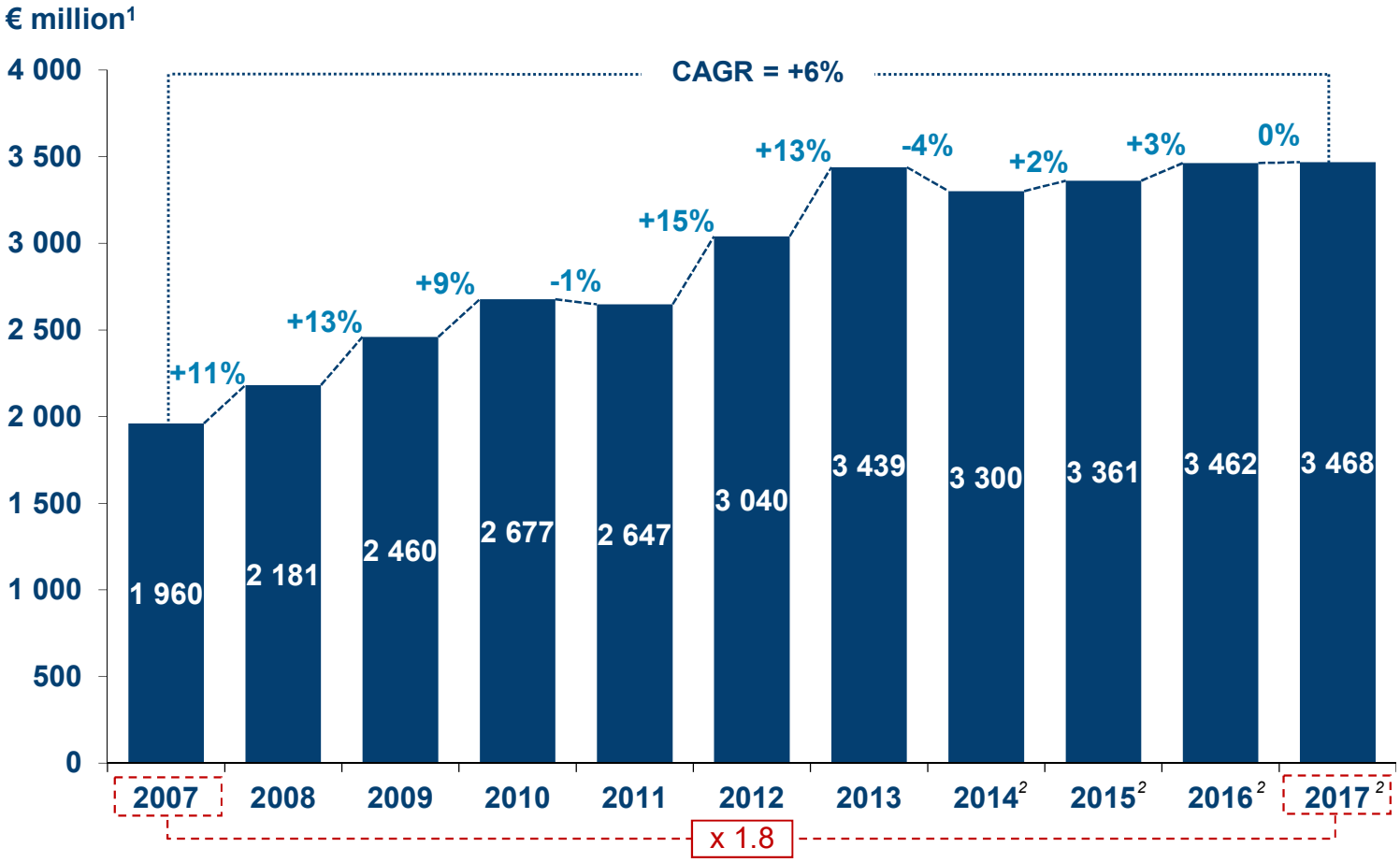


Sources: OECD Health Statistics for 2017 – GERS data for France – Smart Pharma Consulting analyses

** Data for 2016*

The retail generics market size has remained stable, in value terms, since 2013 due to strong price pressure applied by the French government

Evolution of reimbursable generics in the retail market



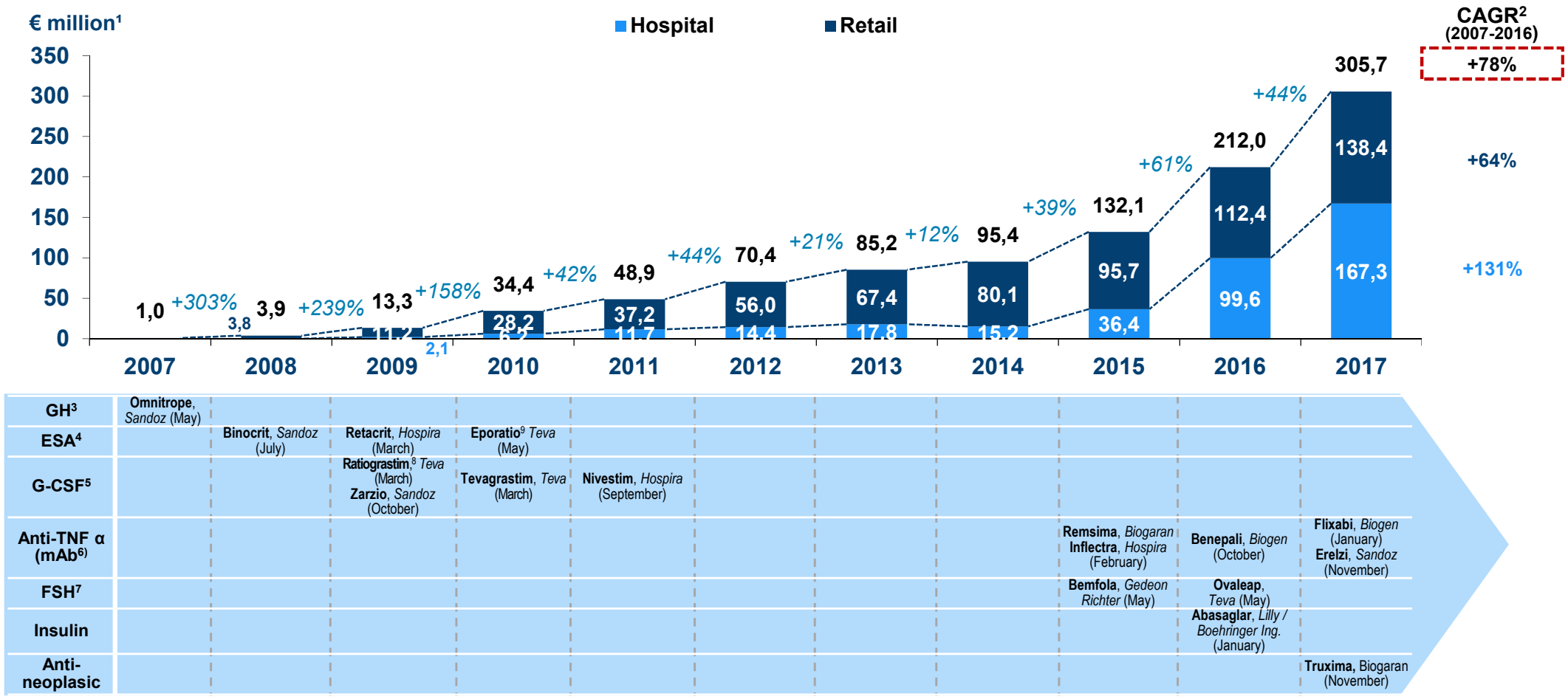
- After a decrease in 2011, the sales of the generics market have been re-boosted by governmental measures[3] introduced since 2012
- Since 2001, there **have been four successive waves of drugs de-reimbursement**. Thus, in 2011, 85% of the medicines were reimbursed. Since then, these waves have led to regular re-evaluations of the SMR (clinical benefit)
- Regarding the sales of non-reimbursable generics, they were estimated at:
  - € 233 M in 2014
  - € 241 M in 2015
  - € 252 M in 2016
  - € 284 M in 2017
- At the end of 2016, the Ministry of Health launched a campaign to promote the use of generics

Sources: GERS dashboard (December 2017) – Senate report – Smart Pharma Consulting analyses

[1] Constant ex-factory price – [2] Excluding sales of non-reimbursable generics from 2014 to 2017 – [3] Increase of the national objective of average generics penetration, introduction of individual incentives for pharmacists achieving substitution objectives on a selection of generic groups, generalization of the "Tiers Payant" system, which exempts from upfront payment patients accepting the generic substitution

Sales of biosimilars, which were launched since 2007 and belonged to seven types of products in 2017, reached a total ~ € 306 million on the total market in 2017

Evolution of the biosimilars market (2007 – 2017)

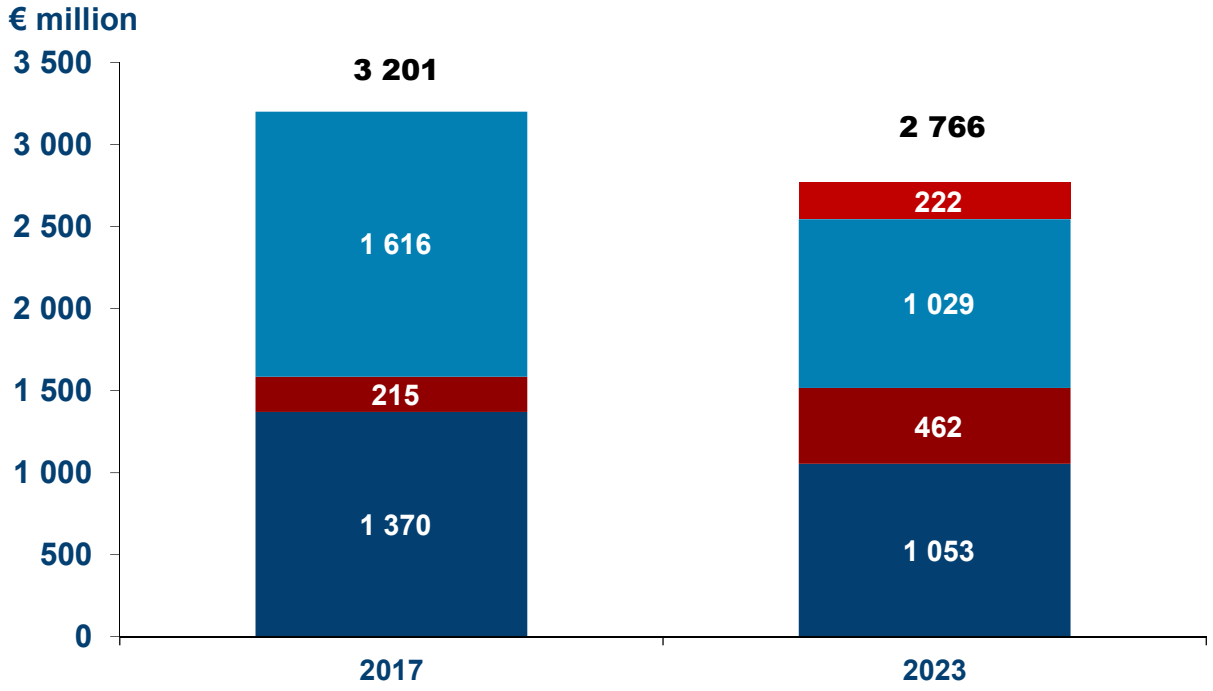


Sources: GERS – Smart Pharma Consulting analyses

[1] Ex-factory prices excluding rebates – [2] CAGR: 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] Ratiogastrim 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

Sales of biosimilars could increase significantly and reach € 684 million in 2023, thanks to new classes contribution

Originators and biosimilars sales forecasts – Retail and hospital markets (2017 – 2023)



	2017	2023	CAGR⁴ (2017-2023)
Original brands¹ sales (€ M)	2,986	2082	-6%
Biosimilars sales (€ M)	215	684	+21%
Biosimilars penetration rate¹	14%²	25%	

	CAGR⁴ (2017-2023)
Biosimilars (new classes of biosimilars² by 2023)	
Originators (new classes of biosimilars² by 2023)	-7%
Biosimilars (classes including biosimilars³ in 2017)	+14%
Originators (classes including biosimilars³ in 2017)	-4%

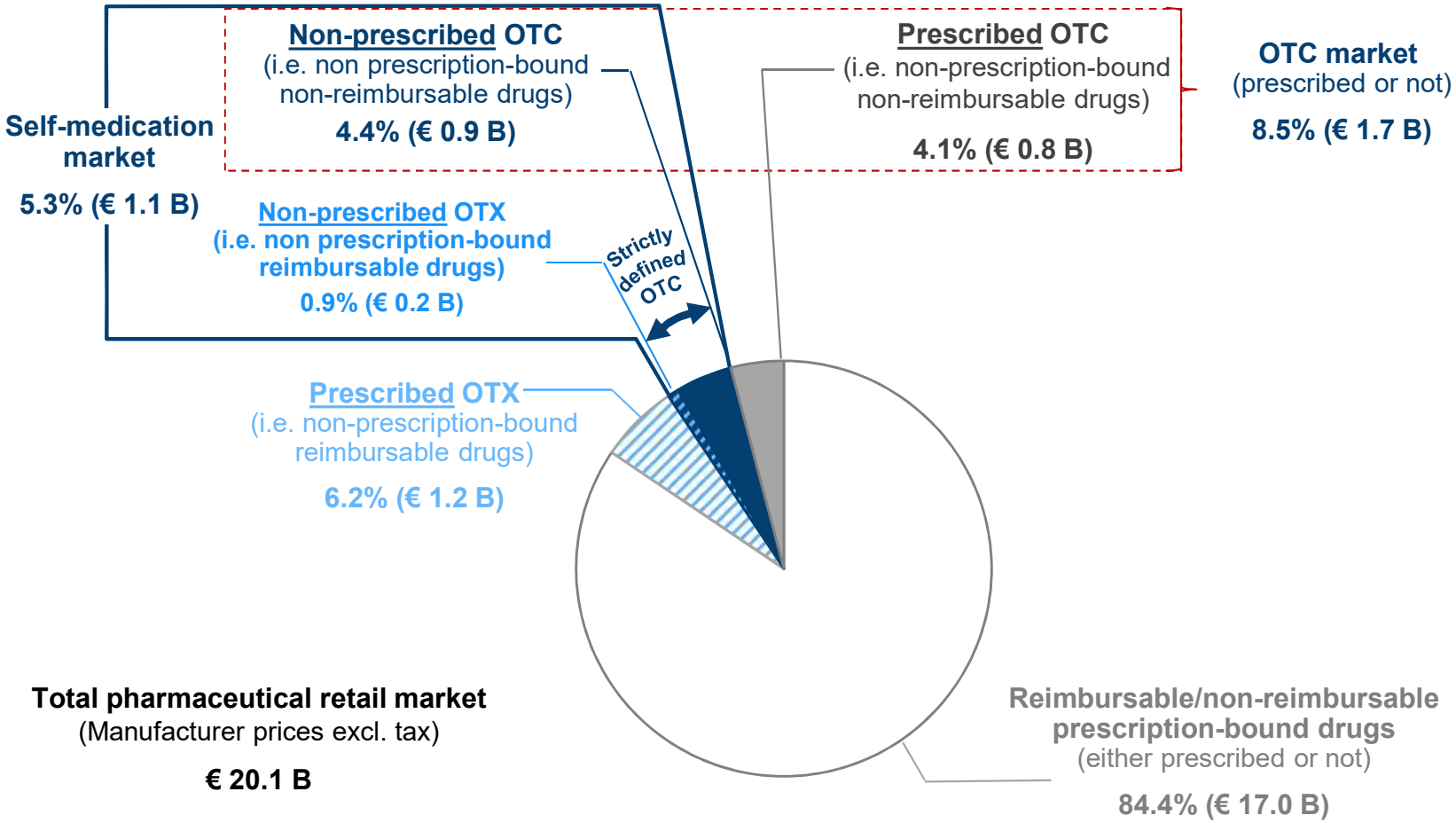
Note: Sales to hospitals including rebates

Sources: GERS – Smart Pharma Consulting analyses

¹ Include originators and other brands of the class without biosimilars – ² Only takes into account the classes for which biosimilar products are already marketed – ³ Pegfilgrastim (Neulasta), trastuzumab (Herceptin), cetuximab (Erbitux), palivizumab (Synagis), natalizumab (Tysabri), adalimumab (Humira), teriparatide (Forsteo), omalizumab (Xolair), tocilizumab (roActemra), panitumumab (Vectibix), ipilimumab (Yervoy), bevacizumab (Avastin) – ⁴ CAGR: Compound annual growth rate

In 2017, the self-medication market accounted for 5.3% of the retail pharmaceutical market and included both reimbursable and non-reimbursable non-prescribed drugs

OTC market size and structure (2017)

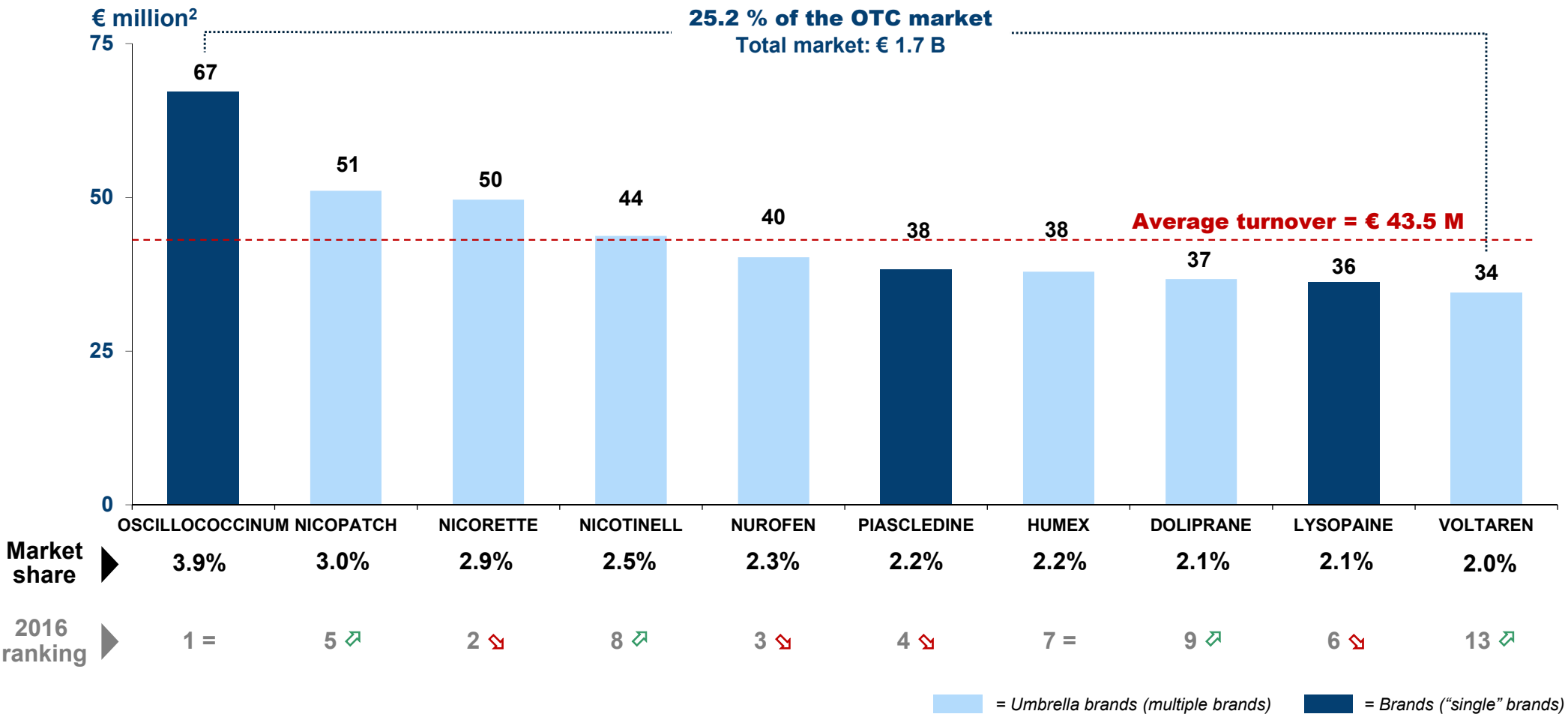


- The strictly defined OTC market accounts **for 84% of the self medication market**
- OTX or semi-ethical drugs (non-prescription-bound, reimbursed only if prescribed) are massively prescribed by physicians (sometimes on patient request), which limits the growth of the reconstituted self-medication sales

Sources: Smart Pharma Consulting estimates based on data from GERS and Pharmastat-IQVIA

The top 10 brands – including seven umbrella brands – of the OTC market generated 25% of the total sales in 2017

Top 10 brands and umbrella brands – OTC[1] market (2017)



Sources: GERS – Smart Pharma Consulting analyses

⇗: Rise - ⇘: Drop - = No change in 2017 vs. 2016 ranking

[1] Non-listed, non-reimbursable products – [2] Ex-factory prices

The French pharma market will remain a priority for global pharma players because, despite a slower growth, it will still belong to the top 10 markets worldwide in 2023

Competitive environment on the French pharma market

Opportunities

- Access to high quality healthcare will remain one of the top priorities of the current government and of French citizens
- Thus, the French pharma market should remain amongst the top ones in the world
- Shift from hospital to ambulatory care will be accelerated by the government
- Government wish to foster innovation

Threats

- Stricter control of reimbursed drug expenditure
- More transparency required from pharma companies by stakeholders, leading to a certain number of constraints:
  - Systematic control of partnerships between pharma companies and HCPs
  - Stringent control of medical calls content (basically limited to SmPCs) making them less interesting for HCPs

Sources: Smart Pharma Consulting analyses

The pharmaceutical market sales should keep on growing at a pace of +5% p.a. but pharma companies profitability will be significantly impacted by price cuts

Global Pharma Market SWOT analysis

Market Opportunities

- **Access** to high **quality healthcare** will remain one of the **top priorities** of governments and citizens
- Thus, the **pharma market** should keep on **growing at 5%** per annum, on average, over the 2017-2023 period
- Market **consolidation through M&As** will contain competitive intensity amongst pharma companies
- Increasing **collaborations with academics** contributing to discover more effective and better tolerated drugs

Market Threats

- **Increasing price pressure** on all categories of drugs (innovative or not, reimbursed or not) from public and private health insurers; and from patients for OTCs
- **Higher risks** and **stricter regulation** re. R&D and registration leading to higher costs to launch innovations
- Increasing **difficulties** to **interact with healthcare professionals** to inform them or create partnerships due to lack of interest and time; and regulatory constraints

Pharma Companies Strengths

- **Improving portfolio management** with a more focused strategy on the most attractive strategic segments
- **Breakthrough innovative** drugs to come by the end of 2023, especially in neurology, oncology and immunology
- Improved **clinical studies quality** and development of **real word data** contributing to optimize drugs benefits
- **Reduction** or **removal** of **marketing** and **sales** investments which have **no** or **limited business impact**

Pharma Companies Weaknesses

- **Poor reputation** of the global pharma industry
- **Weak negotiating power** of pharma companies vs. public payers or private payers (e.g. HMOs in the USA)
- **Lack of robust strategy** as shown by frequent changes of priorities amongst numerous pharma companies[1]
- **Rigidity** and **complexity** of internal **processes** preventing pharma companies from optimally seizing opportunities and addressing threats[1]

Sources: Smart Pharma Consulting analyses

[1] See the position paper "Best-in-class Pharma Strategy Crafting" released in March 2018 and freely available on our website: www.smart-pharma.com

Each pharma company should reinforce stakeholders preference to grow its market share by offering better drugs, highly valued services and building a good reputation

One-page Strategic implications

Strategic priority: Get Preferred to Gain Market Share

Innovative Product Portfolio

- Develop drugs to address **public health priorities** as set by **governments** (e.g. cancers, neuro-degenerative, infectious and cardio-metabolic diseases) at an **affordable** and **acceptable price** for the payers
- **Avoid** to launch (too many) **me-too** products with a minimum added value compared to existing drugs
- Carry out **clinical studies** which are **robust** enough to **raise** early **confidence** of **key stakeholders**, especially:
  - **Health authorities** and **payers** to ease market access
  - **HCPs** for earlier adoption

Highly Valued Services

- Offer services that are **highly valued** by **key stakeholders** (e.g. policy makers, payers, HCPs, patients and/or PAGS[1])…
- … and **related to** the company **products** (services around the pills) to enhance their perceived value
- Thus, these services **should be** perceived as **useful**, **interesting**, **convenient** and **properly executed**
- **Better communicate** about high added-value **services** to enhance stakeholders preference for pharma company drugs

Good Corporate Reputation

- Build a corporate reputation[2], better than competition, by:
  - Offering **highly valued drugs** at an acceptable price
  - Offering **highly valued services** to key stakeholders
  - **Communicating** on **R&D** activities and **product pipeline**
  - **Investing** in **R&D projects**[3] in strategic markets
  - **Strengthening** the **skills** and ethical **behavior** of **collaborators**
  - Developing a **good working** atmosphere …
  - … and possibly **going beyond CSR** legal obligations

Sources: Smart Pharma Consulting analyses

[1] Patient advocacy groups – [2] See the position paper "How to create a superior Pharma Corporate Reputation?" released in August 2016 and freely available on our Website: www.smart-pharma.com – [3] And to a lesser extent in distribution or manufacturing facilities

Smart Pharma Consulting

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

The Smart Pharma Business Reports

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

Pharma Market Perspectives 2017 – 2023

- Strategic Implications for Pharma Companies -

- In this short report, Smart Pharma Consulting:
  - Reviews international healthcare expenditure
  - Estimates the global pharma market (2017 – 2023)
  - Highlights latest publications re. R&D cost of drugs
  - Analyzes the top 30 pharma companies performance and strategy (portfolio, geographical coverage, M&A)
  - Presents the French pharma market 2017 – 2023 perspectives (incl. market access and strategic segments such as generics, biosimilars, OTCs)
  - Proposes a SWOT analysis and a one-page strategic implications for pharma companies

Smart Pharma Consulting Editions

- Besides our consulting activities which take 85% of our time, we are strongly engaged in sharing our knowledge and thoughts through:
  - Our teaching and training activities
  - The publication of articles, booklets, books and expert reports
- As of today, more than 100 publications in free access can be downloaded from our website
- Since 2017, we have published:
  - 2 business reports (The French Pharma Market 2016 – 2022 – The French Generics Market, incl. Biosimilars)
  - 8 position papers in the “Best-in-Class Series” and 3 in the “Smart Manager Series”
- Our research activities in pharma business management and our consulting activities have shown to be highly synergistic
- We expect that this new publication will interest you and we remain at your disposal to carry out consulting projects or training seminars to help you improve your strategic thinking

Best regards

Jean-Michel Peny

1, rue Houdart de Lamotte – 75015 Paris – France • Tel.: +33 6 11 96 33 78 • E-mail: jmpeny@smart-pharma.com • Website: www.smart-pharma.com