20th Anniversary

Smart Pharma CONSULTING

Serving & Sharing with Passion

Market Insights

Concepts – Methods – Tools

COLLECTION 2021

Pharma Market Insight Studies

French Pharma Market 2020 – 2025

Global Pharma Market & Covid-19 Impact

French Retail Pharmacies

French Biosimilars Market

PART 1 October 2021

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This e-book is the Part 1 of the 20th anniversary collection of Smart Pharma Consulting's best position papers published, in line with its commitment to share knowledge and thoughts

Presentation of the 2016 – 2021 Publications

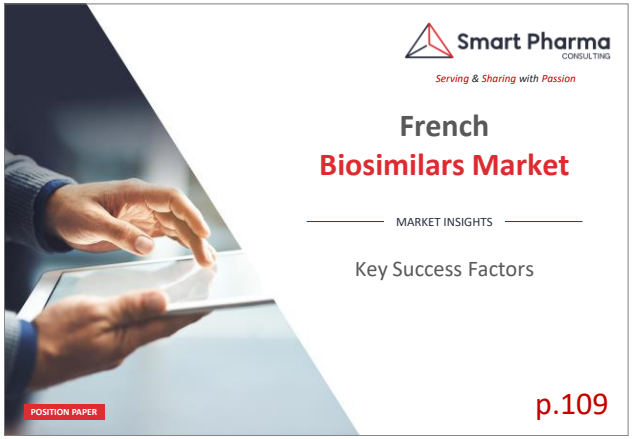
- On the 20th anniversary of Smart Pharma Consulting, we have compiled 34 position papers published since 2016
- These publications propose effective and practical solutions to help pharma companies improve their performance
- For so doing, we share openly:
  - Business insights
  - Concepts
  - Methods
  - Tools

  } The majority of which have been developed by Smart Pharma Consulting

- This "2021 Collection" will be released in six parts:
  1. Market Insights
  2. Strategy & Market Access
  3. Medical Affairs & Marketing
  4. Sales Force Effectiveness
  5. Management
  6. Training Programs
- We hope that this 20th anniversary "gift" will be of high value to you
- We will keep on sharing with you our thoughts and recommendations in the years to come

Jean-Michel Peny

Market Insights



Smart Pharma
CONSULTING

Serving & Sharing with Passion

Pharma Market
Insight Studies

MARKET INSIGHTS

Smart Pharma Expertise
- Methods & Tools -

POSITION PAPER October 2021

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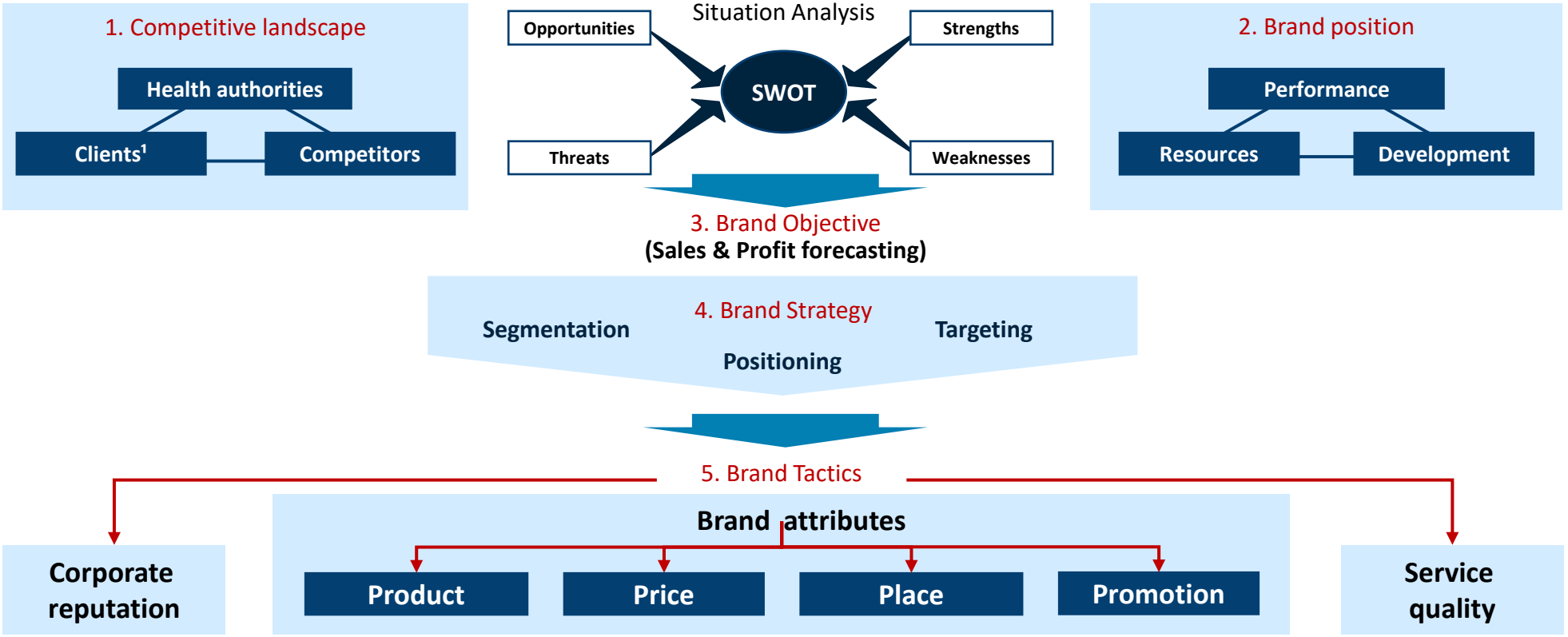
Smart Pharma Consulting carries out Market Insight Studies, at the 5 steps of the marketing thinking process, to help pharma companies improve their performance

Introduction

Marketing thinking process



Sources: Smart Pharma Consulting

[1] *Including payers, physicians, pharmacists, patients, patient advocacy groups, hospitals, distributors, etc.*

Our ability to collect insights from all market stakeholders and our robust analytical skills allow us to deliver high value-added recommendations

1. Competitive landscape

Methodological approach

Health authorities

- EMA
- ANSM
- HAS
- CEPS
- …

- **Marketing authorization**
- **Market access** (price and reimbursement)
- **Therapeutic guidelines**
- **Advertising and promotion regulations**

Clients

- Physicians
- Pharmacists
- Patients
- Hospitals
- Distributors
- Payers
- Learned societies
- Unions
- …

- **Therapeutic needs**
- **Prescription patterns**
- **Preference drivers**
- **Delivery standards**
- **Purchasing habits**

Competitors

- Innovators
- Generics Cos
- Biotech Cos
- OTC Cos
- …

- **Benchmarking**
- **Differentiating factors**
- **Growth drivers / orientations**

Sources: Smart Pharma Consulting

Smart Pharma Consulting is used to carrying out studies to better know and understand healthcare systems through in-depth desk researches and individual interviews

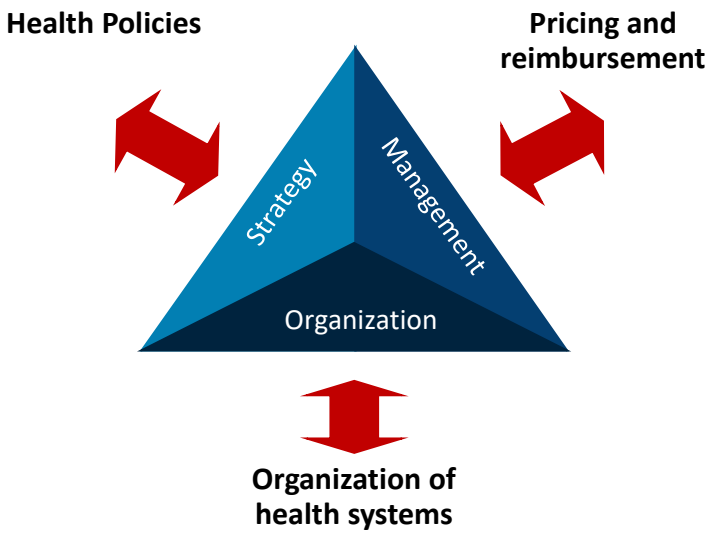
1. Competitive landscape

Health authorities

Market studies targeted at health authorities

Illustration

Health authorities & Payers



Types of studies recently undertaken

- **Organization of health systems**
  - Research on health systems across the world
  - Market access systems by country
  - Study of the organization, the composition and the strategic priorities of regional health bodies
- **Health Policies**
  - Analysis of healthcare reforms across Europe
  - Study of healthcare expenditure containment policies
  - Comparison of health policies regarding Rx-to OTC switches in Europe
- **Pricing and reimbursement**
  - Analysis of decision-making processes and key decision criteria re. pricing and reimbursement
  - Study of the copayment policies of supplementary health insurance funds re. drugs according to the reimbursed level by the Social Insurance

Sources: Smart Pharma Consulting

Smart Pharma Consulting has interviewed hospitals and regional health authorities's collaborators to evaluate the impact of a new measure on drug performance

1. Competitive landscape

Health authorities

Example: Measure to enhance drug prescription quality and efficiency

The French health authorities have recently introduced contracts between hospitals, regional health agencies and regional health insurance through which physicians are encouraged to prescribe more generics and biosimilars

Objective	Action plan	KPIs
▪ Development of **generics** and **biosimilars** prescription at **hospital** level to enhance drugs cost containment	▪ Promotion of **generics** prescription in the reference list	▪ % of generics in the reference list prescribed at hospital level and delivered in retail pharmacies ▪ **National target: 45.5%**
	▪ Promotion of **biosimilars** prescription in the reference list	▪ % of hospital biosimilars prescriptions in the reference list ▪ **National target: 70%**
	▪ **Increase** in the **share** of **generics** and **biosimilars** in hospital purchases	▪ **% of hospital generics and biosimilars purchased in units**

Sources: Smart Pharma Consulting

[1] Regional Health Agency (Agence Régionale de Santé) – [2] Hospital medical commission (Commission médicale d'établissement) – [3] Contract for healthcare quality and efficiency enhancement (Contrat d'amélioration de la qualité des soins)

Smart Pharma Consulting is used to collecting and analyzing information about all pharma companies' clients involved on the retail and the hospital markets

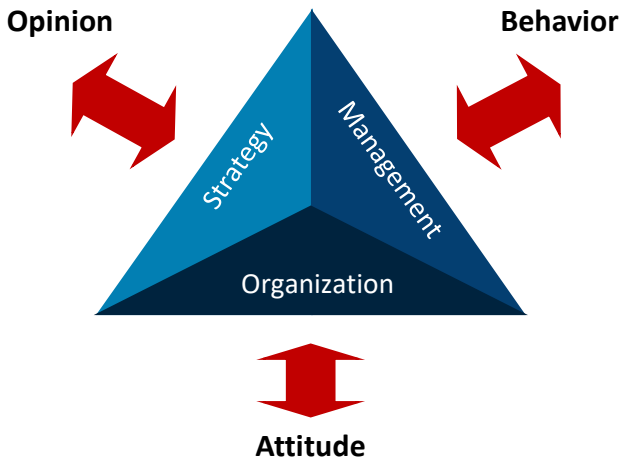
1. Competitive landscape

Clients

Market studies targeted at clients

Illustration

Clients
(payers, physicians, pharmacists, patients, PAGs[1], hospitals, distributors, etc.)



Types of studies recently undertaken

- **New launches**
  - Impact assessment of new product launches
  - Brand positioning studies and market segmentation
- **Generics / Biosimilars**
  - Attitudes and behavior of key stakeholders regarding generics and biosimilars
- **Reimbursement rate changes / Rx-to-OTC switches**
  - Impact assessment of changes in reimbursement rate or Rx-to-OTC switches on clients' attitude
- **Commercial policy**
  - Discounts and associated services offered to pharmacists
  - Analysis of pharmacists' expectations regarding direct sales offers
  - Price sensitivity studies
- **Decision-making process in hospitals**
  - Listing / purchasing in hospitals
  - Conditions of introduction and deployment of new care practices in hospitals
  - Physicians prescribing trends in oncology

Sources: Smart Pharma Consulting

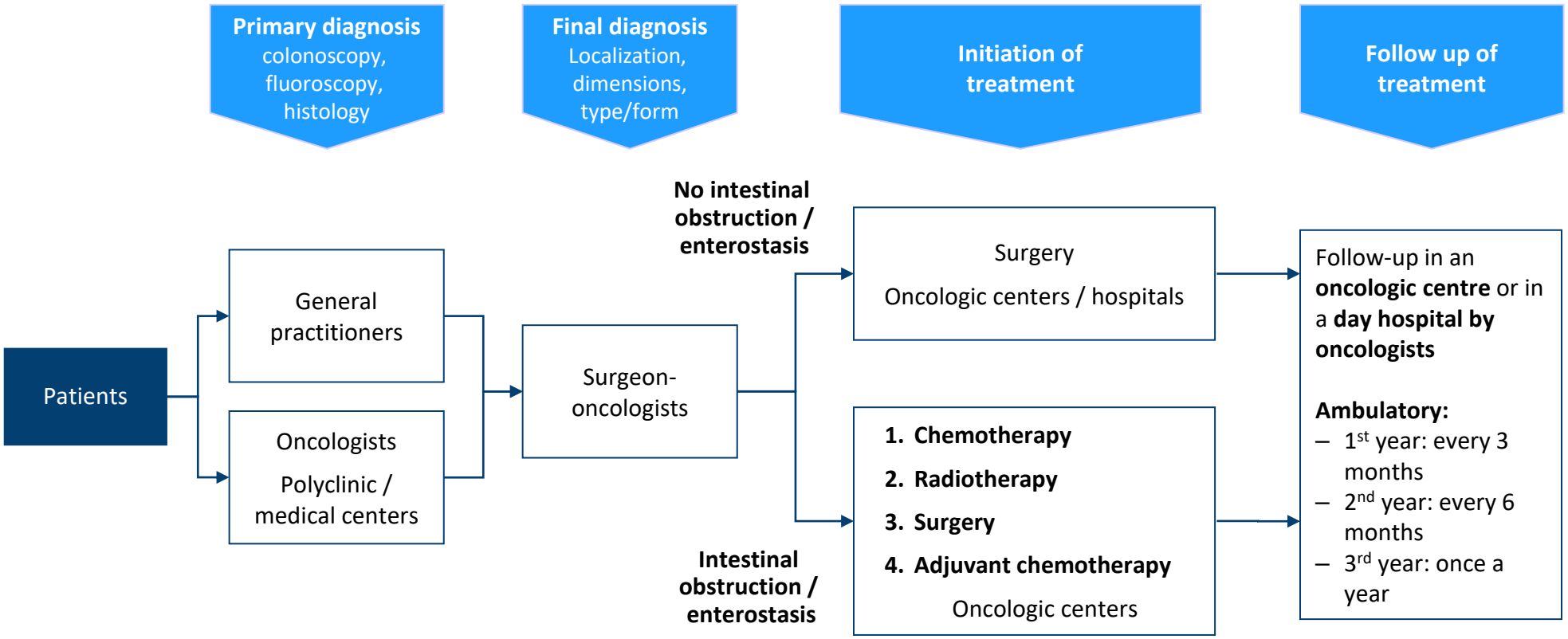
Smart Pharma Consulting is able to figure out protocols and disease management in countries where there is little data published, by interviewing stakeholders

1. Competitive landscape

Clients

Example: Colorectal cancer (CRC) management in Kazakhstan

Physicians



Sources: Smart Pharma Consulting

Smart Pharma Consulting assesses regularly the degree of physicians' preference for competing brands with the help of the " Brand Preference Mix" concept[1]

1. Competitive landscape

Clients

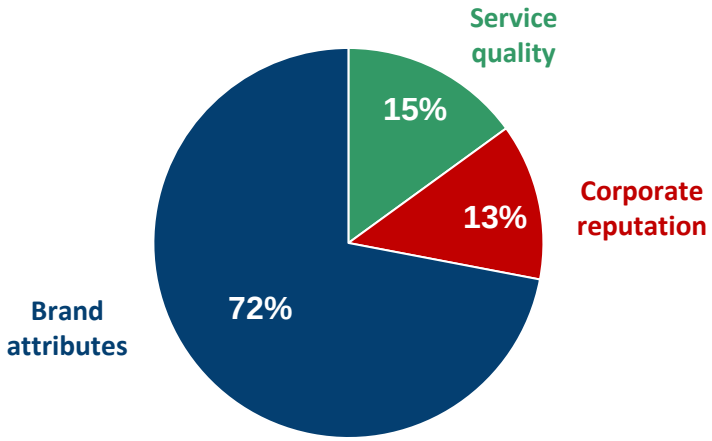
Example: Assessment of brand preference in the respiratory market

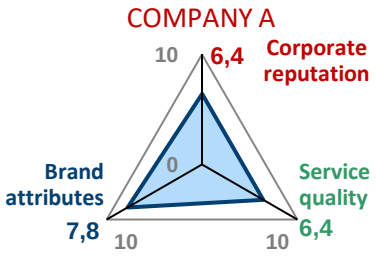
Physicians

The Brand Preference Mix (BPM) helps determine the key prescribing drivers that can be activated to enhance prescribers' preference for a brand, and thus increase its market share

General Practitioners

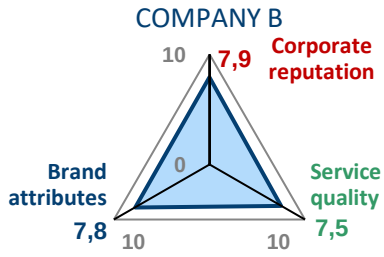
"When you decide to prescribe a maintenance treatment in COPD over another one, what is the relative weight in your decision of the three following components?"





BPM Index calculation:

(72% x 7.8) + (15% x 6.4) + (13% x 6.4) = 7.4



BPM Index calculation:

(72% x 7.8) + (15% x 7.5) + (13% x 7.9) = 7.8

Sources: Smart Pharma Consulting

[1] Developed by Smart Pharma Consulting (see position paper "How to get physicians prefer your brand?" on: www.smart-pharma.com)

The in-depth knowledge and understanding of the market, through regular studies, enables Smart Pharma Consulting to produce complex and insightful analyses

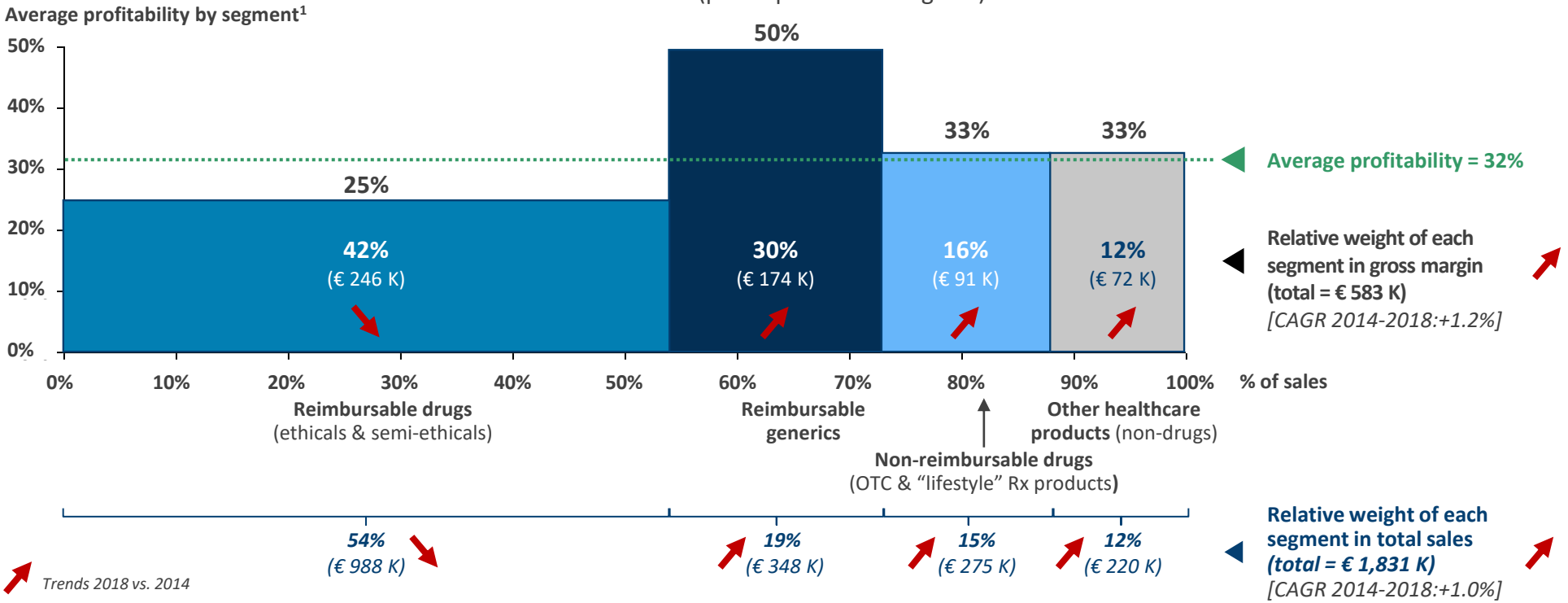
1. Competitive landscape

Clients

Marketing thinking process

Pharmacists

Average annual turnover of a retail pharmacy in 2018: € 1,831 K
(public price excluding VAT)



Sources: CGP Experts Comptables – KPMG – Smart Pharma Consulting estimates

[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.)

Smart Pharma Consulting is used to carrying out patient surveys to understand patients' behaviors and motivations

1. Competitive landscape

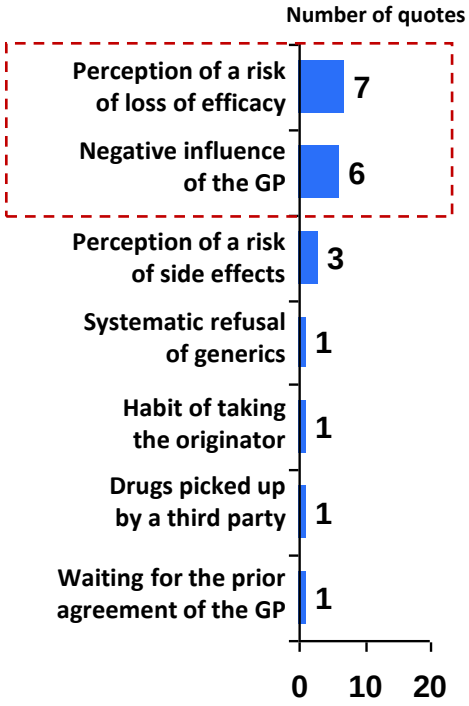
Clients

Example: Generics substitution refusal by patients

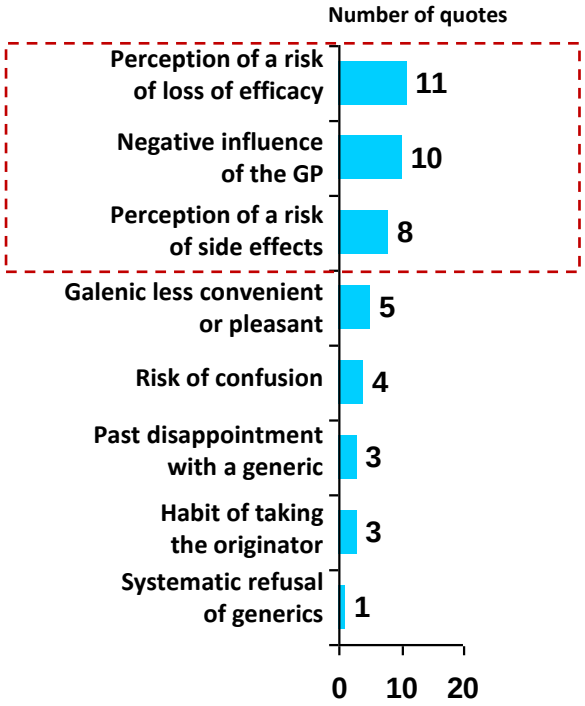
Patients

"Why do you refuse generics substitution?"

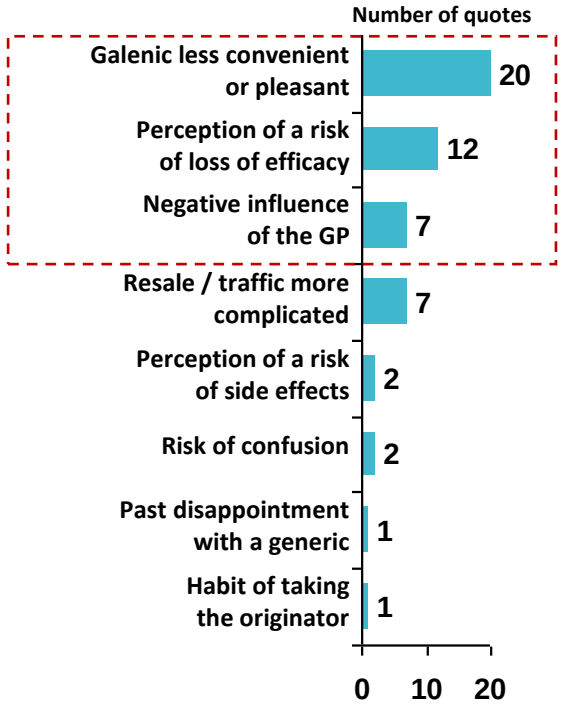
DUROGESIC



RISPERDAL



SUBUTEX



Sources: Smart Pharma Consulting

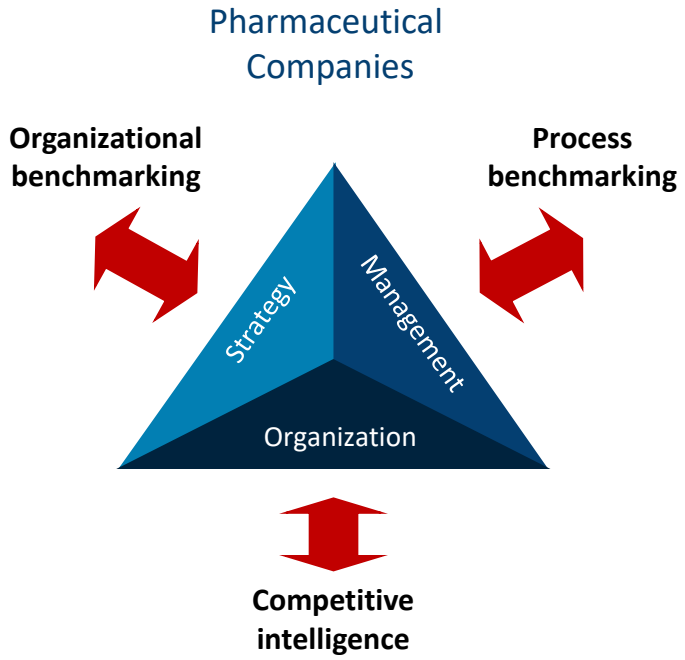
Smart Pharma Consulting carries out various types of benchmarking and competitive intelligence studies in the pharmaceutical sector, following a strict code of ethics

1. Competitive landscape

Competitors

Market studies on competitors

Illustration



Types of studies recently undertaken

- **Organizational benchmarking**
  - Surveys on organizational models
  - Surveys on different jobs in the pharmaceutical industry
  - Investigation of headcounts and the resources allocation
- **Process benchmarking**
  - Best practices identification
  - Surveys on adoption of new sales and marketing tools (CRM, trigger marketing, digital media, etc.)
- **Competitive intelligence**
  - Identification of future entrants and impact assessment
  - Investigation of product launches (dates and conditions)
  - Promotional investments assessment
  - Pricing policy at hospital

Sources: Smart Pharma Consulting

As shown in this example, Smart Pharma Consulting can realize organizational benchmarking such as detailed headcount surveys

1. Competitive landscape

Competitors

Example: Headcount survey in small to mid-sized pharma companies

Organizational benchmarking

	Pharma company A	Pharma company B	Pharma company C	Pharma company D	Pharma company E	Pharma company F	Pharma company G	Average
Sales	50 to 79 €M	20 to 49 €M	20 to 49 €M	50 to 79 €M	50 to 79 €M	80 to 120 €M	20 to 49 €M	
General management	2	2	1.5	1.5	1.5	2	2	2
Marketing	6	7	3	5	6	10	5	6
Sales management	5	1	4	3	2	7	9	4
Medical	3	0	2.5	2.5	3.5	8	5	4
Finance	8	5	3	3	2.5	13	4	6
Regulatory affairs	2	12	2	0.5	8	12	4	6
Legal	0	0	0	0	0	2	2	1
Human Resources	2.5	2	1	3	1	6	4.5	3
Public affairs / Communication	0	0	0	0	0	0	0	0
Commercial excellence	0	0	0	0	0	8	0	1
Training department	0	0	0	1	0	0.5	0	0
Business Development	0	1	0	0	0	1	0	0
Market access	0	0	0	1	0	2	0	0
General services	1	1	0	0	0	3	0.5	1
Logistic / IT	0	0	2	0	0	7	0	1
R&D / Clinical studies	0	0	0	0	4	12	0	2
Total headquarters	29.5	31.0	19.0	20.5	28.5	93.5	36.0	37
Sales Reps – GPs	66	8	48	160	20	111	33	64
First line managers – GPs	6	1	0	16	3	13	4	6
Second line managers	0	0	4	2	0	2	0	1
Sales Reps – Specialists & hospital	11	10	0	10	0	6	0	5
First line managers – Specialists & hospital	0	0	0	1	0	1	0	0
KAM & others	0	0.5	0	0	0	0	3	1
Total field forces	83.0	19.5	52.0	189.0	23.0	133.0	40.0	77
Grand total	112.5	50.5	71.0	209.5	51.5	226.5	76.0	114
Number of therapeutic areas	8	5	5	7	1	9	4	6
Number of products	18	7	16	17	1	32	16	15

Sources: Smart Pharma Consulting

Smart Pharma Consulting interviewed service providers and pharma companies to survey the remote e-detailing adoption, identify best practices and assess the impact

1. Competitive landscape

Competitors

Example: Benchmarking of remote e-detailing practices

Process benchmarking

Context

- Specific needs to strengthen detailing:
  - Inform physicians about new indications and side effects of non-promoted products
  - Vacancies
  - Campaigns with temporary increase of targeted physicians
  - Geographic dispersion of physicians (Russia)
  - Limited access to physicians (Sweden, Turkey)

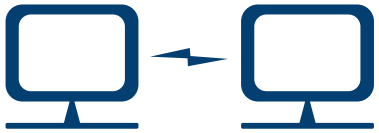
Objectives

- Increase the reach of the message by expanding the target
- Improve the efficacy of communication by increasing the call frequency
- Reduction of overall detailing costs

Implementation

- France: sales reps 100% dedicated to remote e-detailing, quantitative approach (20 contacts/day)
- Italy: sales reps 100% dedicated to remote e-detailing, qualitative approach (retention goal)
- Russia, Sweden: implementation of hybrid sales reps (face-to-face and remote e-detailing)

Results



- France: some physicians systematically refuse remote e-detailing
- Italy: 35%-40% of physicians regularly accept remote e-detailing
- Russia and Sweden: increase of call frequency

Key learning

- Remote e-detailing does not suit all physicians, hence, before implementing it, to identify those who:
  - Can have online access
  - Are likely to accept remote e-detailing
- The quality of calls is key to build a long-term relationship with physicians, thus it is important to:
  - Train the sales force properly
  - Propose interesting and useful contents, meeting customer expectations and needs
  - Fix appointment by telephone rather than by e-mail (risk of spamming)

Sources: Smart Pharma Consulting

Through desk research and interviews, Smart Pharma Consulting has been able to estimate the magnitude of generics price war overtime on the French hospital market

1. Competitive landscape

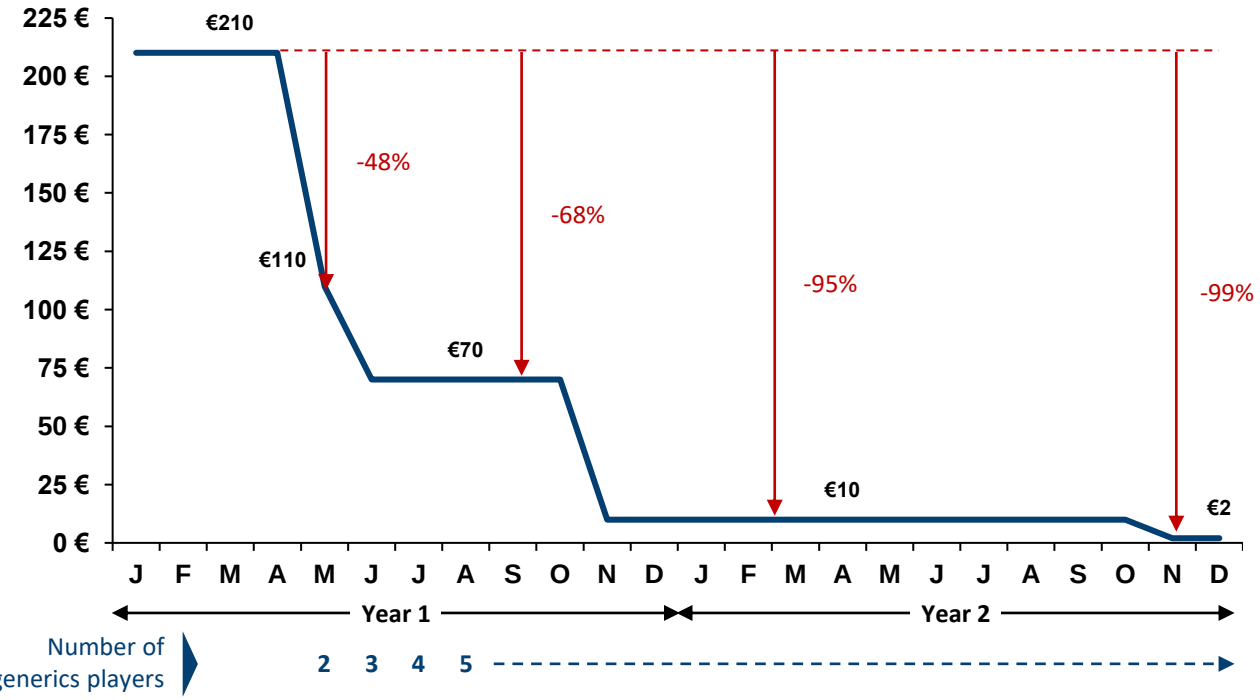
Competitors

Example: Hospital generics pricing

Competitive intelligence

Zometa case study in France

Estimated price on hospital market



Comments

- Zometa (zolendronic acid), marketed by Novartis, is a bisphosphonate used in:
  - The prevention of bone complications in adult patients with advanced malignant disease with bone involvement
  - The treatment of tumor-induced hypercalcemia in adult patients
- The first generic, marketed by Sandoz, entered the market mid-May 2013, a week before Mylan. Fresenius launched its 4 mg version in June, Pfizer (ex-Hospira) in May and Medac in October
- **Competition on price is usually even more aggressive in hospitals when there are more than one company marketing a generic version**
- According to a generics company: *"This behavior is illogical and is prejudicial for all generics companies as this price does not support the market and does not permit us to offer associated services"*

Sources: Smart Pharma Consulting

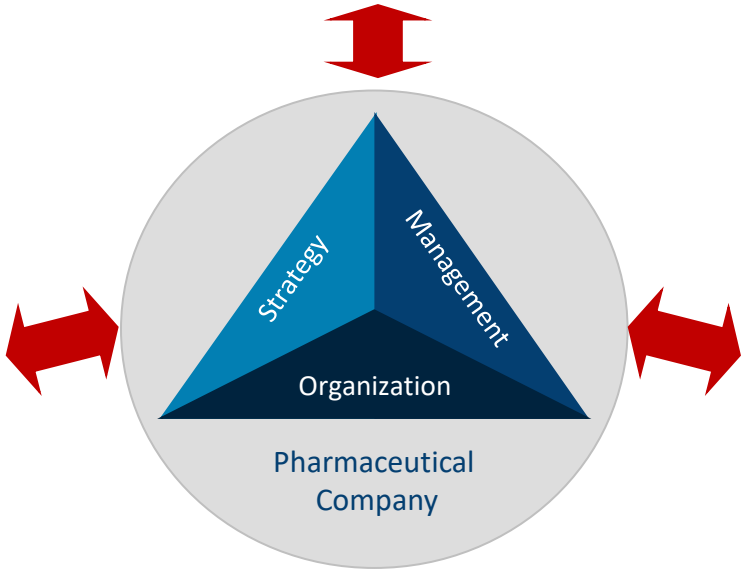
Smart Pharma Consulting rigorous and evidence-based analyses allow to transform information into actionable and added-value recommendations to pharma companies

2. Brand Position

Methodological approach

Performance

- In-depth historical sales analysis



Development

- Brand value assessment in a partnership perspective
- Potential partnership identification (e.g., in- and out-licensing)

Resources

- Sensitivity to promotion
- Sales force sizing
- Competencies requirement

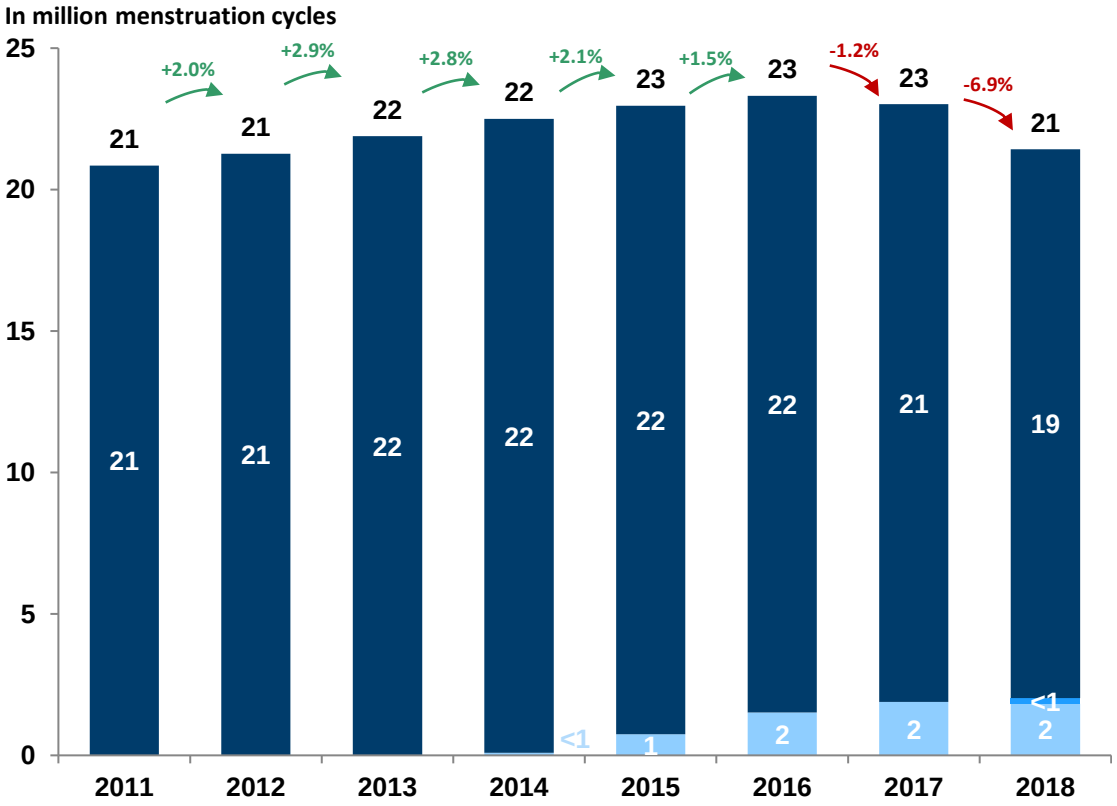
Sources: Smart Pharma Consulting

Smart Pharma Consulting regularly carries out in-depth brands analyses to get a comprehensive understanding of the dynamics of their performance

2. Brand Position

Performance

Example: Historical analysis of intra-uterine contraception systems



	CAGR[3] 2011-2018	CAGR 2014-2018	Market share 2011	Market share 2014	Market share 2018
IUS[1] market	+0.4%	-1.2%			
Mirena	-1.0%	-3.5%	100.0%	99.6%	90.6%
Kyleena[2]	N/A	N/A	0.0%	0.0%	1.0%
Jaydess	N/A	+113.0%	0.0%	0.4%	8.4%

Sources: Smart Pharma Consulting

[1] Intra-uterine system – [2] Product launched at the end of March 2018 – [3] Compound annual growth rate

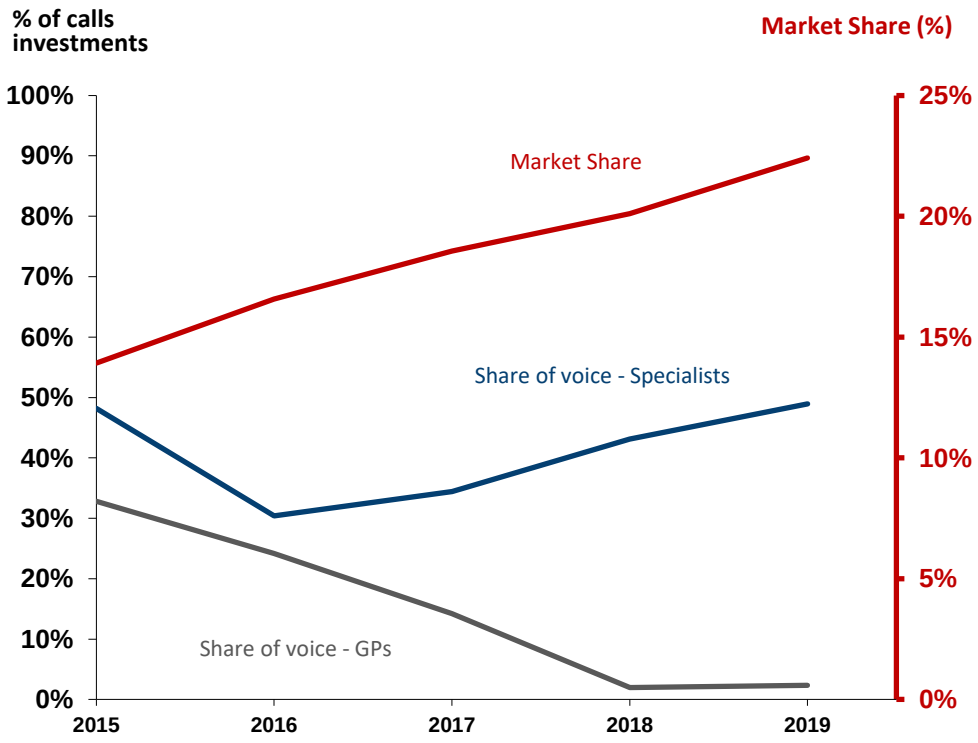
Smart Pharma Consulting can help pharma companies assess the sensitivity of their brands to promotional investments in quantitative and qualitative terms

2. Brand Position

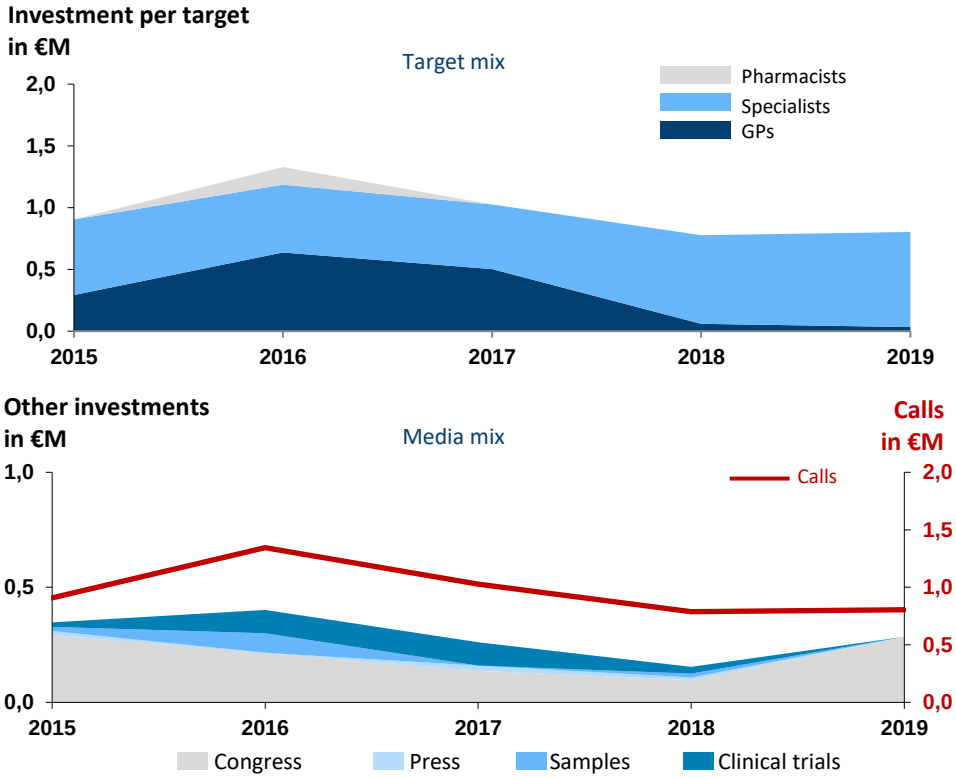
Resources

Example: Sensitivity to promotional investments

Performance & share of voice



Promotional mix



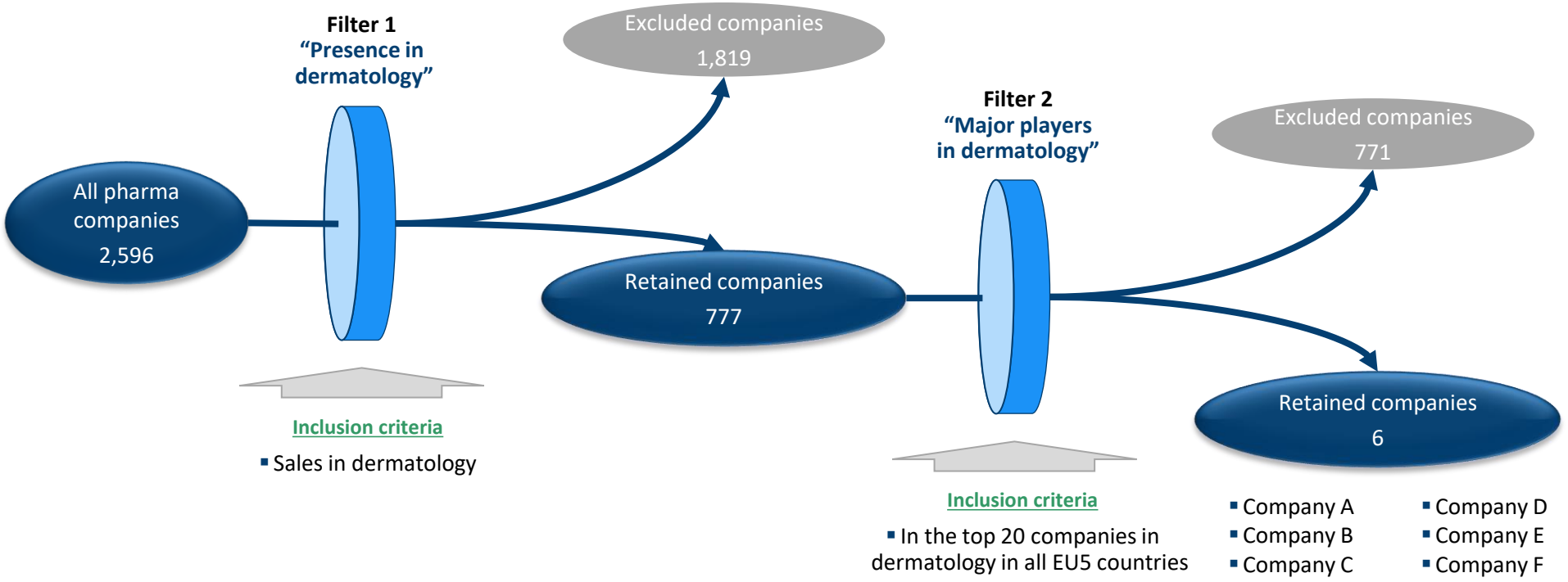
Sources: Smart Pharma Consulting

Based on rigorous market analyses and an effective methodology[1], Smart Pharma Consulting can help identify potential partners for in- or out-licensing deals

2. Brand Position

Development

Example: Identification of partners for an out-licensing deal



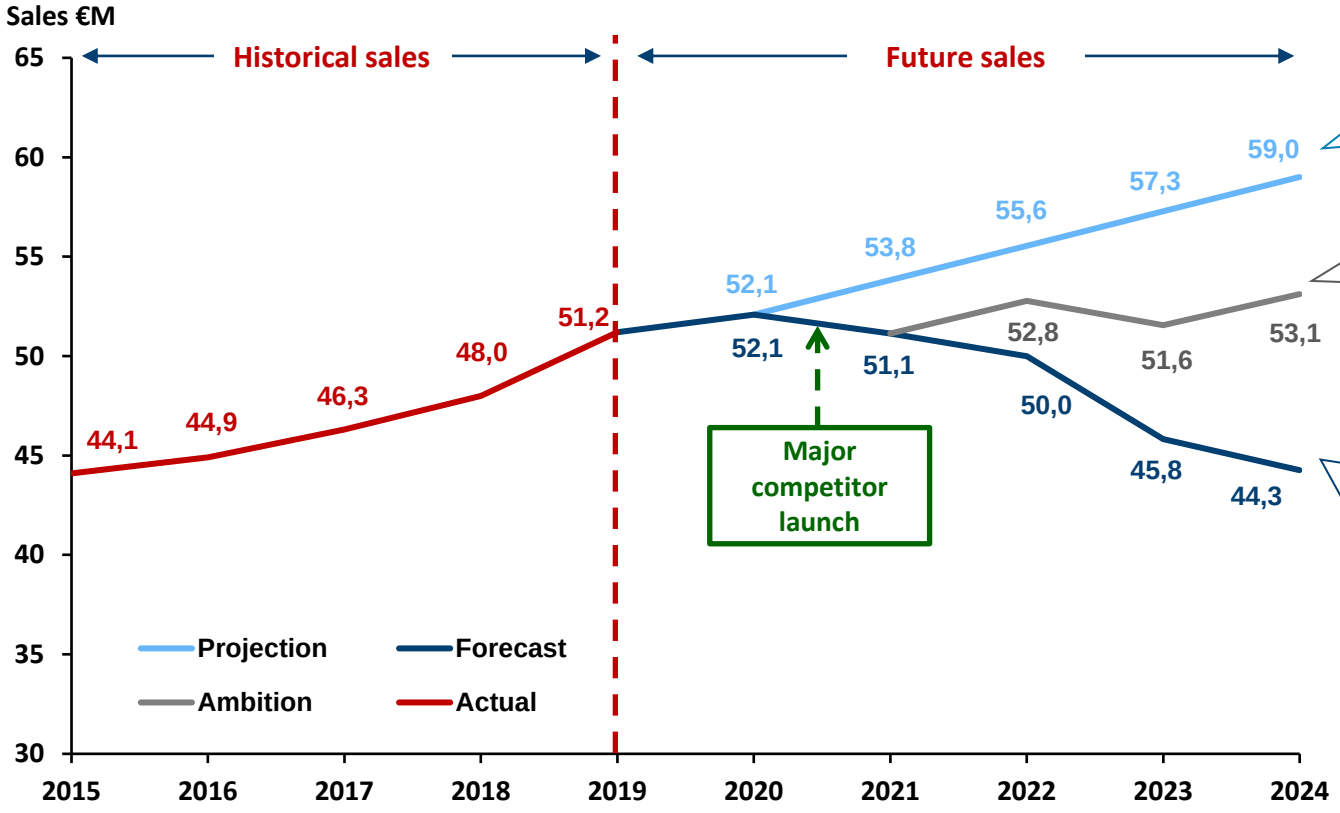
Sources: Smart Pharma Consulting

[1] Developed by Smart Pharma Consulting (see position paper "Best-in-Class Pharma BD&L" on: www.smart-pharma.com)

Smart Pharma Consulting is regularly asked by pharma companies to build scenarios to estimate sales and profits objectives according to the forecast method

3. Brand Objective

Methodological approach



Projection
Objectives based on historical trends, considering "other things being equal"

Ambition
Objectives based on top management commitment to shareholders (top – down approach)

Forecast
Objectives based on projections adjusted according to anticipated:

- Market events (new regulations, new market entrants, changes in customers behaviors, etc.)
- Company events (new marketing authorization, positive clinical study results, sales force cut, etc.)

Sources: Smart Pharma Consulting

A patient approach based on epidemiological data, diagnosis and treatment rates can be applied to estimate the evolution of a market size and of a brand market share

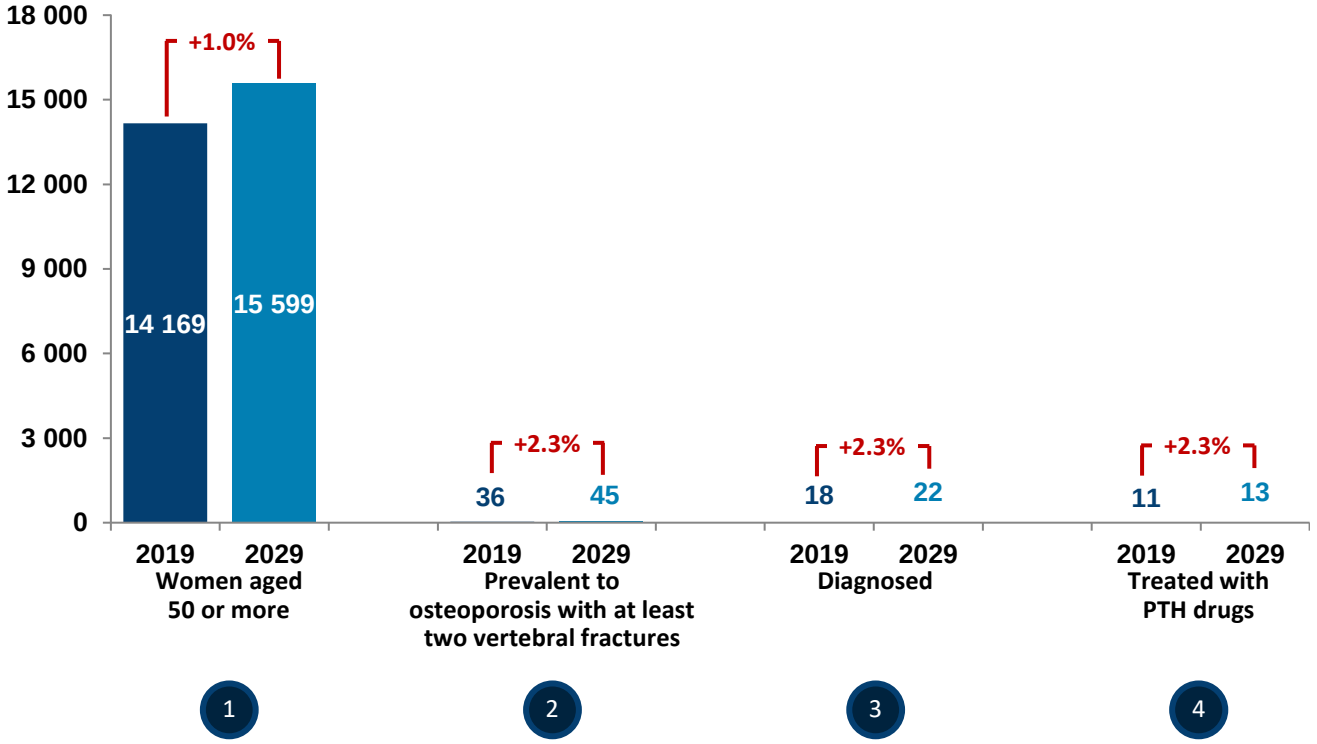
3. Brand Objective

Example: Sales forecasting in the osteoporosis market

Patient approach

Number of women, in thousands

In red: CAGR[1] 2019-2029



Comments

- **Prevalence** (+2.3% on average per year) **increases faster** than the total **population of women aged 50 or more** (+1.0% p.a.) because of a mixed effect :
  - **Ageing effect** (**baby boomers**): women aged **75 and more** will represent **~31%** of the women aged 50 and more in **2029**, vs. **~27%** in **2019**
  - In addition, the **prevalence** rate within women aged **75 and more** (**~0.85%**) is much higher than the prevalence of women **aged between 50 and 74 years** (**~0.04%**)
- **Diagnosis** and **treatment rates** have been maintained at a **stable rate** over the period, in accordance with interviewed KOLs feedback:
  - **Diagnosis** rate: **50%** of prevalent women
  - **Treatment** rate: **60%** of diagnosed women

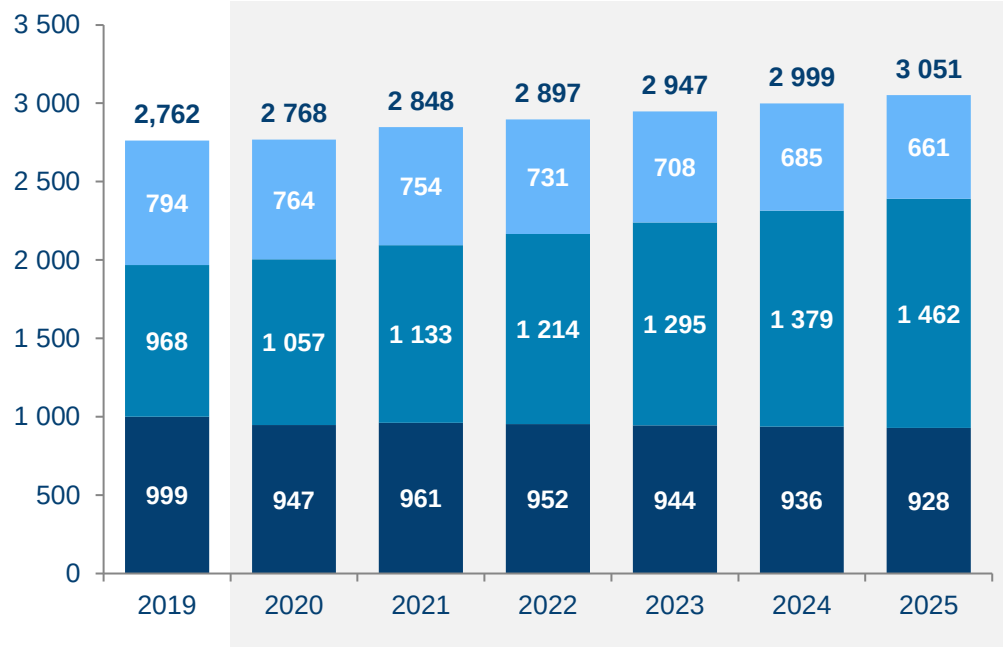
Sources: Smart Pharma Consulting

[1] *Compound annual growth rate*

A market approach based on the adjustment of historical sales projections can also be applied to estimate the dynamics of a brand on its market

3. Brand Objective

Example: Sales forecasting in the oncology market



Market approach

	CAGR[1] 2019-2025	Market share 2019	Market share 2022	Market share 2025
Total market	+1.7%			
Product A	-3.0%	28.8%	25.2%	21.7%
Product B	+7.1%	35.1%	41.9%	47.9%
Product C	-1.2%	36.2%	32.9%	30.4%

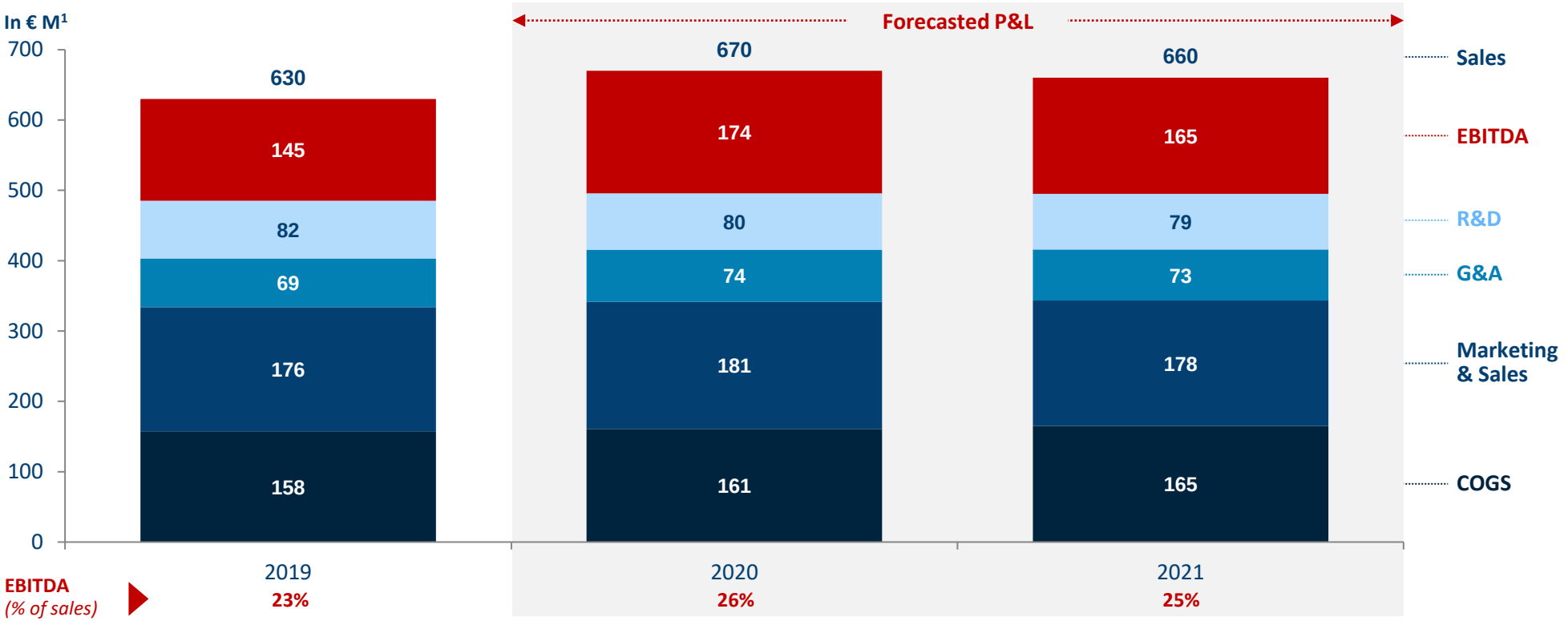
Sources: Smart Pharma Consulting

[1] *Compound annual growth rate*

Smart Pharma Consulting can develop for pharma companies' models to forecast the potential margin of selected products

3. Brand Objective

Example: Profit forecasting for a CNS product



Sources: Smart Pharma Consulting

[1] Constant ex-factory prices, excluding VAT

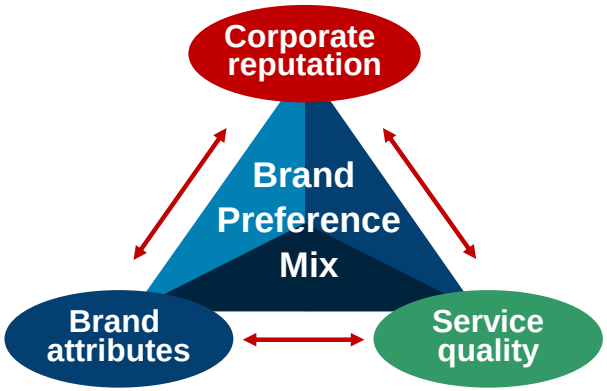
Smart Pharma Consulting proposes highly effective positioning and segmentation methods that are associated with specific data collection about customers

4. Brand Strategy

Positioning & Segmentation studies

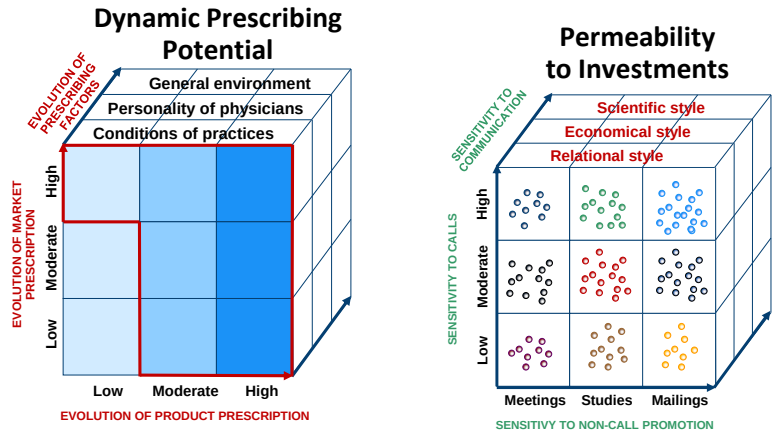
Applications to Physicians

Brand Preference Mix (BPM)[1] – Positioning



- The share of brand prescription is driven by physicians' preference level…
- … which is enhanced by acting on the BPM: (1) brand attributes, (2) service quality and (3) corporate reputation

Behavioral Prescriber Segmentation (BPS)[1]



- The BPS optimizes investment efficiency by considering:
  1. Factors that drive the dynamics of prescriptions[2]
  2. Prescribers' personalities
  3. Prescribers' permeability to investments[3]

Smart Pharma Consulting has developed methods and tools to gather each physician opinion on the 3 components of the Brand Preference Mix and information regarding the 3 dimensions of the Behavioral Prescriber Segmentation

Sources: Smart Pharma Consulting

[1] Developed by Smart Pharma Consulting (see position paper "Best-in-Class Pharma Marketers" on: www.smart-pharma.com) – [2] By market (competitors + brand) and by brand – [3] Medico-marketing-sales investments

The ELITE Program[1] enables med reps to interact more efficiently with prescribers and to optimize the prescription share of the brands they promote

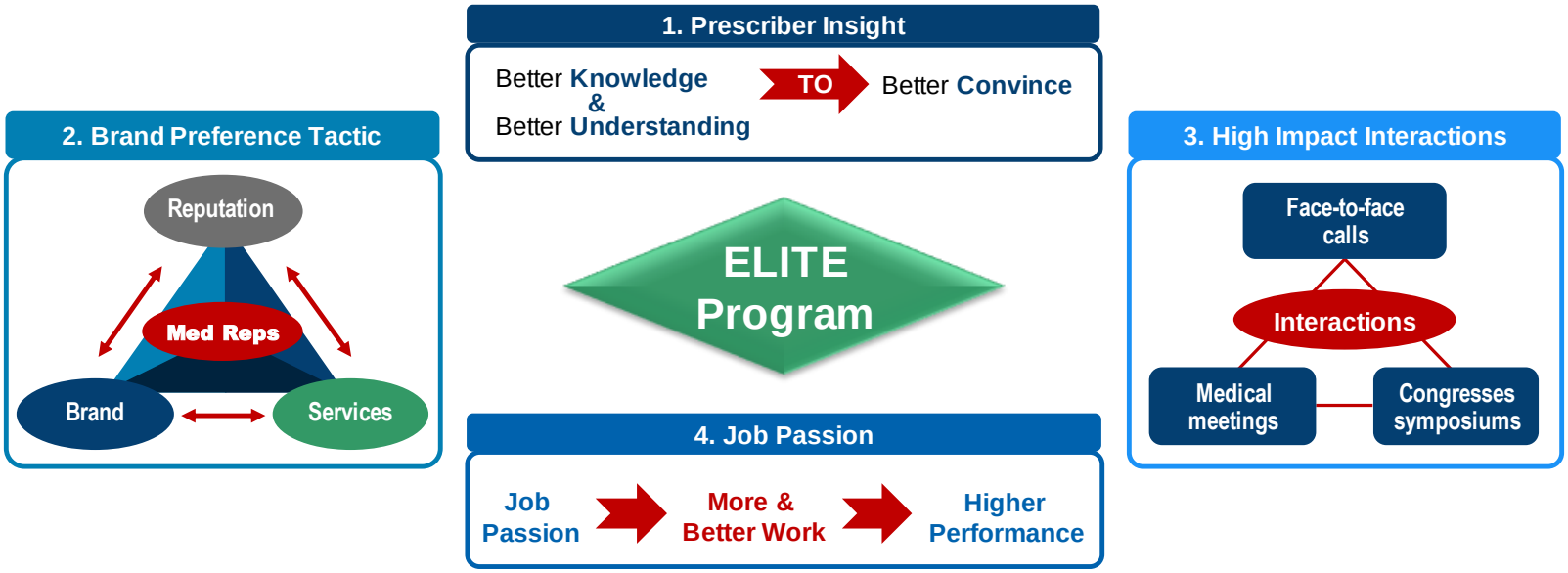
5. Brand Tactics

Sales force effectiveness studies

Applications to SFE[2]

The ELITE Program proposes a **holistic** and **practical** approach to **improve med reps' efficiency** and **efficacy**

The ELITE Program



Smart Pharma Consulting has created a series of tools and indicators to measure the impact of the ELITE Program on physicians' opinion and prescribing behavior, especially in terms of Brand Preference

Sources: Smart Pharma Consulting

[1] Developed by Smart Pharma Consulting (see position paper "Best-in-Class Medical Reps" on: www.smart-pharma.com) – [2] Sales Force Effectiveness

Smart Pharma
CONSULTING

Serving & Sharing with Passion

French Pharma Market 2020 – 2025

BUSINESS REPORT

Strategic implications for pharma companies

EXCERPTS October 2021

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

This position paper[1] analyzes the current situation and the key trends by the end of 2025 on the French Pharma market to provide pharma companies with key strategic insights

Introduction – Foreword

- Despite an ever-tougher environment, the French pharma market should remain a key priority for most of pharma groups
- Smart Pharma Consulting proposes to address the following key issues related to the French healthcare system and pharma market evolution by the end of 2025, to better grasp its strategic impacts for pharma companies

- How is the French healthcare system organized at national and regional levels?
- What are the key recent measures introduced by health authorities and their impact?
- What are the behavioral trends of key stakeholders and their impact by 2025?
- What are the estimated sales forecasts by strategic segment on the French pharma market by 2025?
- What could be the strategic and organizational implications for pharma companies by 2025?

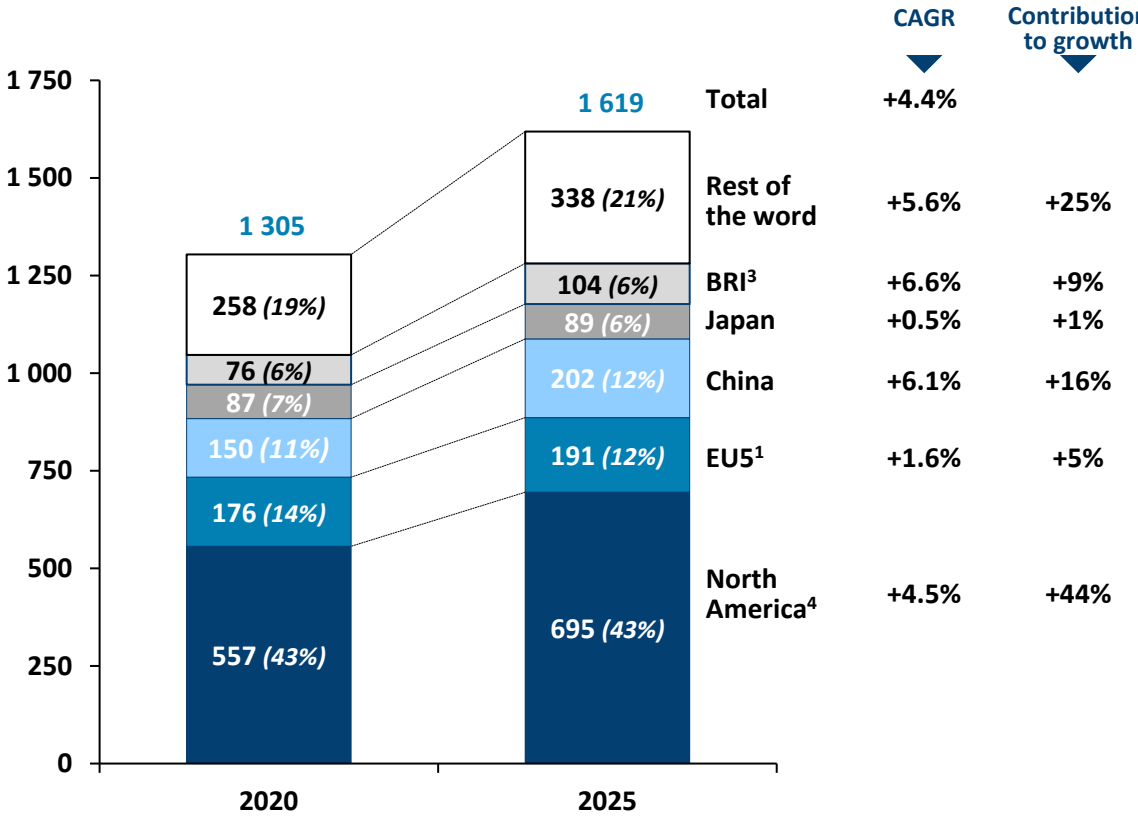
Sources: Smart Pharma Consulting

[1] This position paper represents an excerpt of a comprehensive report published in 2021 by Smart Pharma Consulting that can be ordered at the following address: jmpeny@smart-pharma.com

Sales of EU5[1] should grow slowly by 2025 due to stringent cost containment measures leading to a two-point decrease of their weight in the global pharmaceutical market

Introduction – Global pharma market (2020 – 2025)

Size and growth by geographic area



- The global pharma market is expected to grow with of a **CAGR of +4.4%** by 2025 including the impact of Covid-19, that should lead to **higher pressure** on **prices** worldwide in the next 5 years
- EU5 countries account together for only 14% of the global pharma market (Germany: 4%, France: 3%, Italy: 3%, UK: 2% and Spain: 2%) and should see their weight drop by 2 points by 2025, due to higher price pressure than in the average of the other countries
- North America should continue to weigh for 43% of the global pharma market in value and contribute to 44% to worldwide market growth over the 2020 – 2025 period

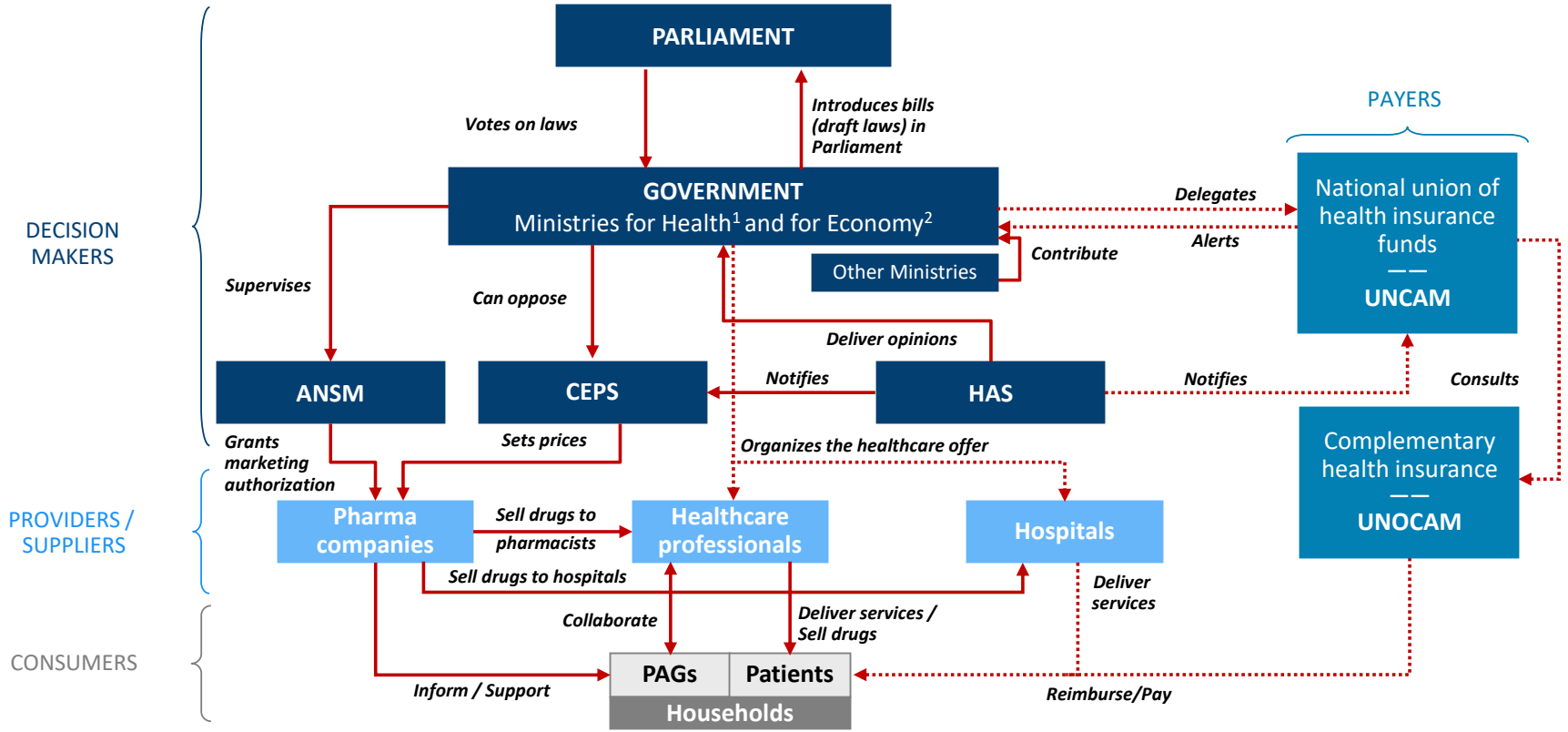
Sources: IQVIA Institute (March 2020) – Smart Pharma Consulting estimates

[1] France, Germany, Italy, Spain, UK – [2] Ex-factory price before rebates – [3] Brazil, Russia, India – [4] USA and Canada

Stakeholders in the French healthcare system can be divided according to their role as decision makers, payers, providers / suppliers and consumers

The French healthcare system – Key stakeholders

Mapping of key stakeholders



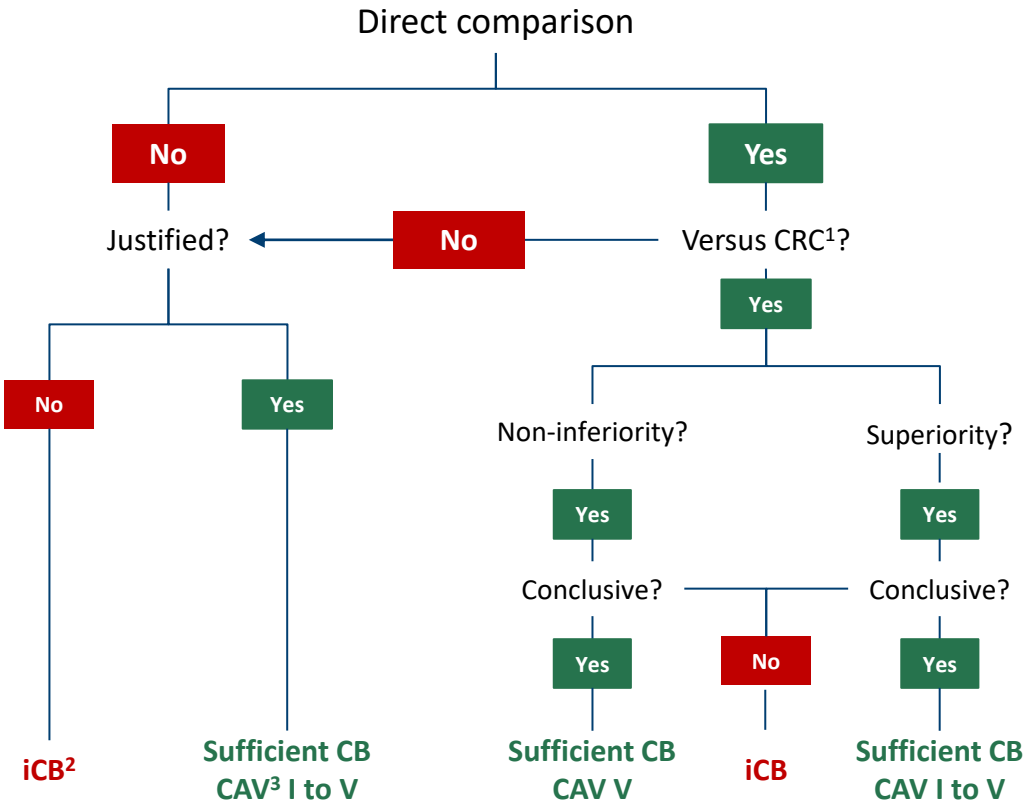
Sources: Smart Pharma Consulting

[1] The exact name of this ministry is: Ministry of Solidarity and Health – [2] The exact name of this ministry is the Ministry for the Economy and Finance which includes the budget and the industry

To assess the therapeutic progress of a product, the Transparency Committee will expect direct comparison – whenever possible – in terms of efficacy and safety with existing relevant therapies

The French healthcare system – Key stakeholders

Transparency Committee – Clinical added value (CAV) assessment



- The Transparency Committee (TC) will particularly pay attention to the following criteria, in view of medical need:
  - The quality of the demonstration:
    - The choice of comparator(s)
    - The methodological quality of the study
    - The appropriateness of the population included
    - The relevance and significance of clinical endpoints
  - The effect size in terms of clinical efficacy, quality of life and safety in view of the demonstration robustness
  - The clinical relevance of this effect compared to clinically relevant comparators
- Double-blind, randomized controlled studies is a prerequisite
- The absence of direct comparison to comparator must be justified and may be accepted by the TC in certain situations
- The absence of a direct comparison, which the TC believes was possible, may lead to an ASMR V
- The TC reasoning presented in this figure is not fixed and is adapted to the context of each evaluation

Sources: Transparency Committee doctrine December 2020 – Smart Pharma Consulting analyses

[1] Clinically Relevant Comparator – [2] Insufficient Clinical Benefit – [3] Clinical Added Value

The framework agreement signed between CEPS and Leem in March 2021 aimed at improving patient access to innovation, encouraging investments in France and simplifying access processes

The French healthcare system – Key stakeholders

CEPS – Framework agreement signed with the Leem (2021 – 2024)

Context & objectives

- Framework agreement signed on March 5, 2021, by Philippe Bouyoux (CEPS) and Frédéric Collet (Leem), in the presence of Olivier Véran (Minister of Health) and Agnès Pannier-Runacher (Delegate to the Minister of Economy in charge of Industry)
- This new agreement, that replaces the previous one which had been signed in 2016, has been concluded for a 3-year period, i.e., until March 5, 2024
- 3 main objectives pursued:
  - Improve patient access to innovation
  - Encourage productive investments in France
  - Simplify market access processes

Patient access to innovation

Innovative drugs

- Guidance on the duration of effect of comparators, the inclusion on uncertainty, the setting of rebates and the splitting of payments

Orphan drugs

- Possibility of renegotiating the terms of conventional rebates if target population evolves
- Commitment to come to a contractual amendment within 6 months with an adjusted budget package

Drugs that meet public health needs

- Possibility for ASMR IV drugs meeting a non- even partially-covered medical need to access to an EU price[1]

Productive investments in France

Support for investment and export

- Creation of a specific chapter intended to support for investment and export
- Authorization for investing pharma companies to proactively meet with the CEPS President to be informed of conventional terms

Pricing counterparties

- Possibility of granting a EU price[1] to ASMR I to III drugs whose manufacturing activities[2] are mainly carried out in France
- List price stability guaranteed over 2 years (renewable once) for products manufactured in Europe (notably in France) for which more than 60% of volumes are exported

Market access processes

Fast-track

- Access guaranteed within a maximum period of 15 days for:
  - ASMR I to III with dominant efficiency
  - ASMR IV with dominant efficiency & allowing savings
  - ASMR V with prices lower than comparators

Price stability and predictability

- 5-year stability of the EU price[1] for ASMR I to III drugs, covering both list and net prices

Transparency

- Statement by pharma companies of the amount of both R&D investment made, and public incentives received

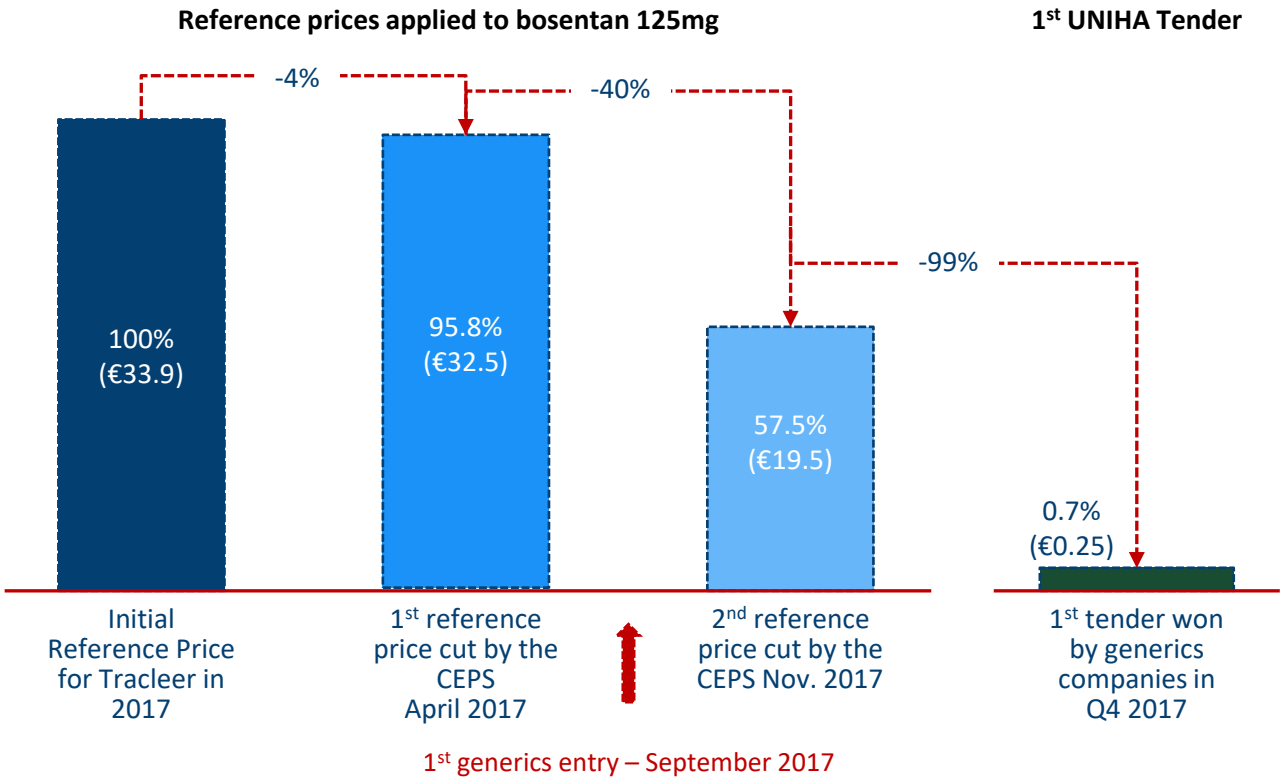
Sources: Framework agreement signed between CEPS and Leem (March 5, 2021) – Smart Pharma Consulting analyses

[1] In this case, French price cannot be lower than the lowest price in the rest of EU5 (Germany, UK, Italy and Spain) – [2] Including the manufacturing of active components, finished goods and/or packaging

Bosentan net price has dropped drastically as soon as the 1st call for tender, enabling the best bidder to discard competitors while taking the risk to make this "market" little or even non profitable

The French healthcare system – Key stakeholders

CEPS – Hospital generics pricing: Bosentan (Tracleer)



Comments

- For bosentan, the purchasers did not really value the quality of the dossier
- UNIHA[1] and the AGEPS[2] account for 80% of the total bosentan market
- The UNIHA market has been won at €0.25, Teva offered €0.50, and the originator price was €19
- The prices on generics should go up for the future calls for tender
- The prices should not remain at this level, which is unlikely to generate profits
- Such a drastic drop was not expected by Actelion (Janssen)
- Few small accounts do not list generics of bosentan
- Janssen doesn't discount beyond -75%

Sources: Business Intelligence – Smart Pharma Consulting analyses

[1] Purchasing group for the Regional Teaching hospitals and other public hospitals – [2] Purchasing group for largest public hospitals in Paris and close suburbs

The prices, margins and level of rebates are regulated by the CEPS throughout the value chain of the reimbursable products, either originators or generics

The French healthcare system – Key stakeholders

CEPS – Prices, margins and rebates for reimbursable drugs

	Originator without TFR[1]	Originator with TFR	Generic without TFR	Generic with TFR
Ex-factory price	▪ Price negotiated / set by the CEPS ▪ Generics are priced 60% below originator price at patent expiry ▪ After generics launch, originator price is cut by 20%			
Wholesalers' margins	▪ Minimum of € 0.30 per pack if ex-factory price below € 4.33 ▪ 6.93% of ex-factory price if ex-factory price from € 4.33 to € 468.97 ▪ 0% beyond € 468.97, representing a maximum of € 32.50 margin per sold unit			
Pharmacists' margins	▪ Variable margin: – 10.0% of ex-factory price below € 1.92 – 7.0% from € 1.92 to € 22.90 – 5.5% from € 22.91 to € 150.00 – 5.0% from € 150.01 to € 1,930.00 – 0% above € 1,930.00 ▪ Dispensing fees (VAT excluded): – € 1.00 per pack – € 0.50 per prescription including at least 1 reimbursable drug – € 1.00 per prescription with at least 5 medicines – € 1.55 if the patient is 3 years or under or over 70 years old – € 3.50 for specific drugs (e.g., immunosuppressive drugs)	Margin in absolute terms identical to the corresponding originator	Calculation identical to the originator's one	
Pharmacists' rebates[2]	▪ Maximum legal rebate: 2.5% of ex-factory price	▪ Maximum legal rebate: 40% of ex-factory price, since September 2014 (17% before)		
	▪ Possibility to add up to 100% of the wholesaler margin in case of direct sales			

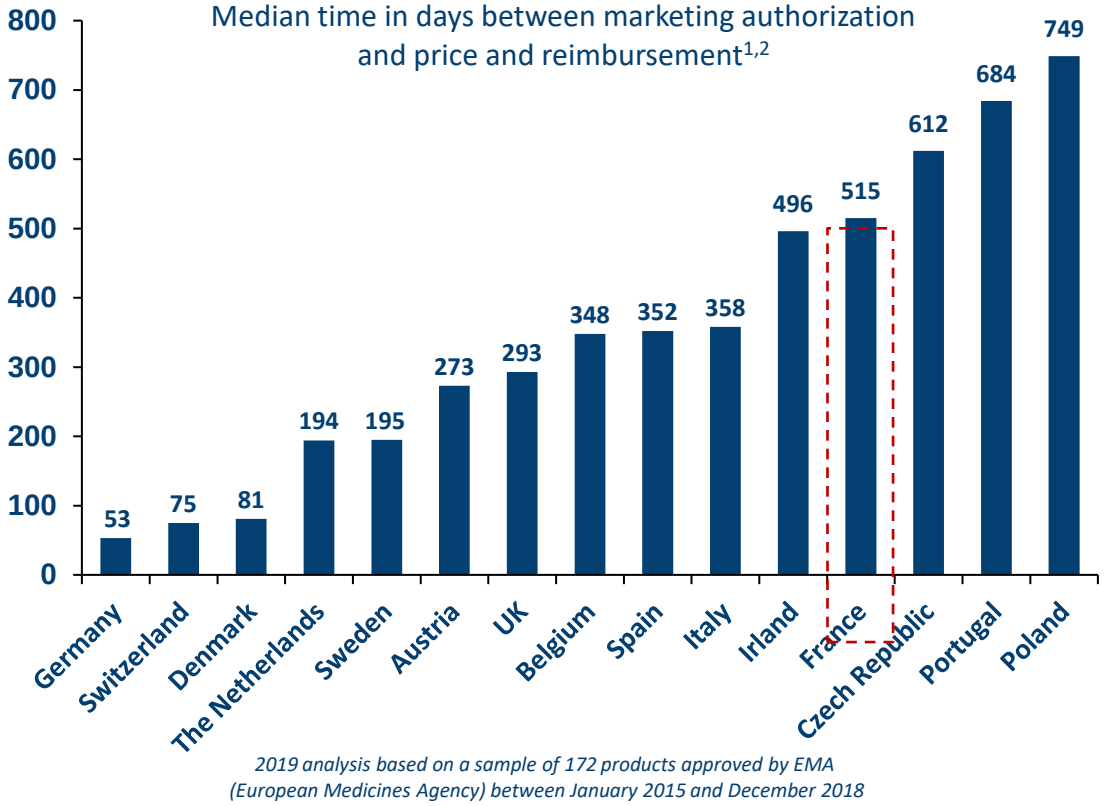
Sources: CEPS annual report (September 2020) – Legifrance (e.g., decree on September 14, 2020? intended to reevaluate wholesalers' margin from February 1, 2021) – Ameli – Leem –Smart Pharma Consulting analyses

[1] Tarif Forfaitaire de Responsabilité (Reference price) – [2] Including cooperation and other commercial rebates

In France, pharma companies and patients must wait ~17 months after marketing authorization to get a new drug reimbursed and launched[1]

The French healthcare system – Key stakeholders

Average time to market access – European comparisons



2019 analysis based on a sample of 172 products approved by EMA (European Medicines Agency) between January 2015 and December 2018

- 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

- In 2018, the Leem (French association of pharmaceutical companies) has carried out a study on 67 new products, showing an average time between marketing authorization and price & reimbursement of 563 days

Sources: Patients W.A.I.T. Indicator – EFPIA (June 2020) – Smart Pharma Consulting analyses

[1] Excluding early access programs for breakthrough innovations (e.g., ATU in France) –
[2] For drugs receiving their first marketing authorization between 2015 and 2017

Since the introduction of the T2A reform in 2004, the allocation of resources of public and private hospitals is based on the nature and on the volume of the activities carried out by hospitals

The French healthcare system – Key stakeholders

Hospital funding system: Activity-based financing (T2A) principles

Objectives

- Increase the efficiency of hospitals
- Address the inequity of resources allocation across structures
- Optimize the funding of the most active structures

Means

- Converge funding systems to be able to compare public and private sectors
- Gradually implement the T2A to facilitate the adaptation of both structures and players
- Harmonize funding arrangements between public and private sectors
- Expand the clarity and the visibility of the role of the players, for both managers and supervisors

Expected results

- Greater involvement of medical players in financing
- Accountability of health players
- Development of quality management and medico-economic tools
- Fairness of treatments between public and private sectors

Major drawback

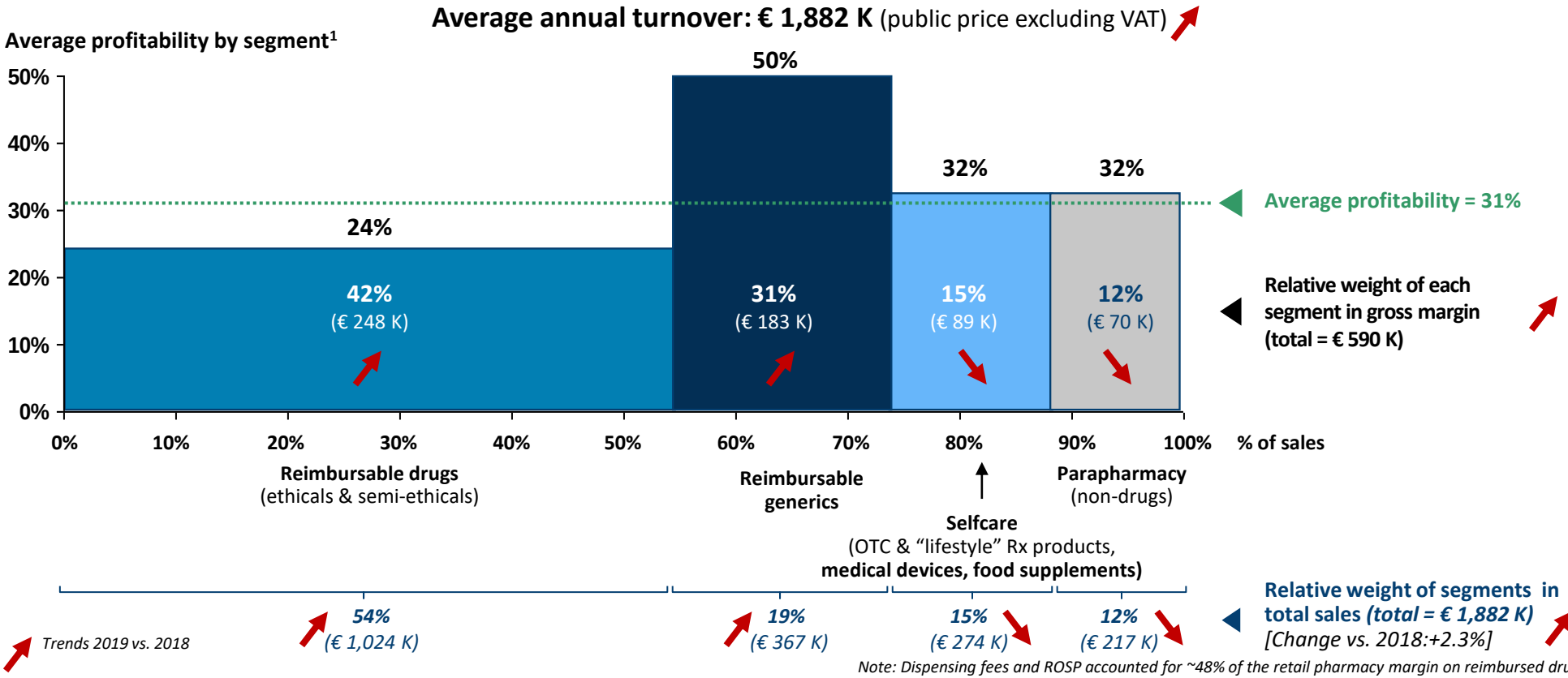
The T2A has led to an inflationary effect; hospitals being prompted to increase their level of activities and notably of the most profitable medical procedures, for maintaining adequate funding

Sources: French Ministry of Health, as of February 2021 – Smart Pharma Consulting analyses

In 2019, originators accounted for ~54% of the retail pharmacies sales on average and for ~42% of their gross margin

The French healthcare system – Key stakeholders

Economic structure of retail pharmacies in France (2019)



Note: Dispensing fees and ROSP accounted for ~48% of the retail pharmacy margin on reimbursed drugs

Sources: CGP Experts Comptables – KPMG – Smart Pharma Consulting estimates

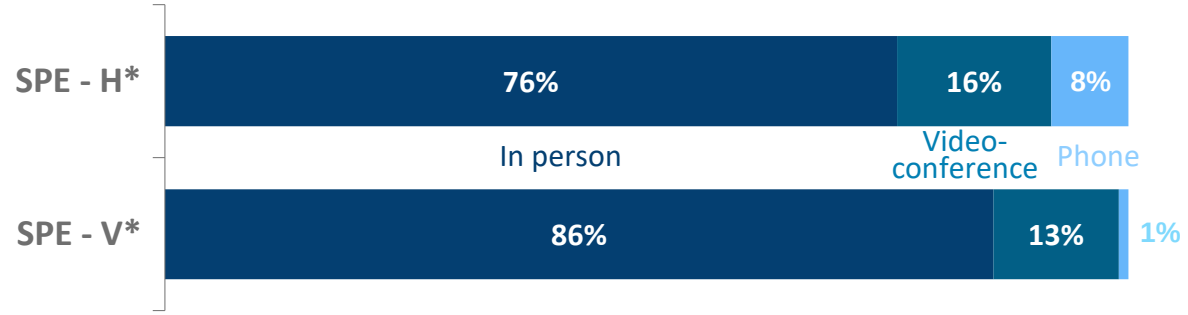
[1] Inclusive of legal margin, rebates, commercial agreements and remuneration for pharmaceutical services, notably those corresponding to the public health objectives (e.g., generics substitution objectives, pharmaceutical interviews with patients, etc.)

Specialists keep on preferring in person interactions with med reps to communicate about innovations and they remain attached to this communication channel

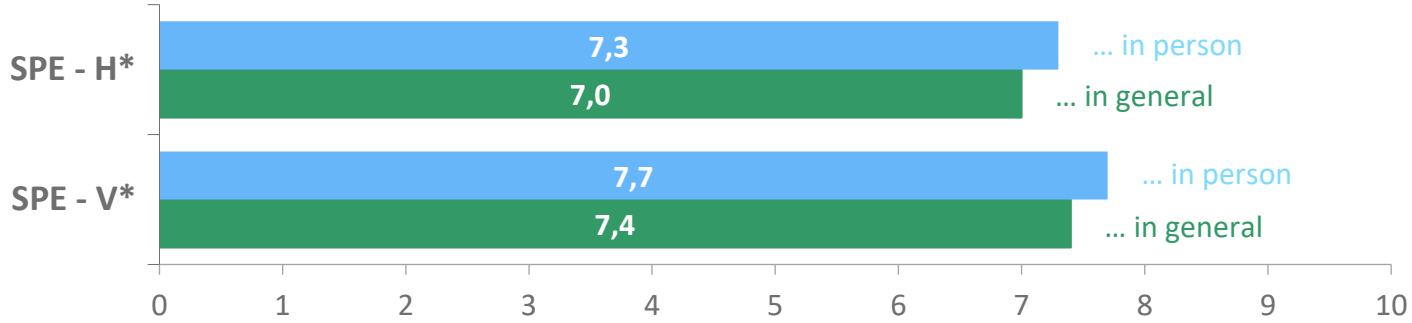
The French healthcare system – Key stakeholders

Access to HCPs in France (2020 – 2021)

Most appropriate channels for med reps to communicate about innovations (product, indications, dosage, etc.)[1]



Attachment to medical calls…



* : SPE-H (Hospital-based specialists) – SPE-V (Office-based specialists)

Sources: Leem (September 2020) – Smart Pharma Consulting analyses

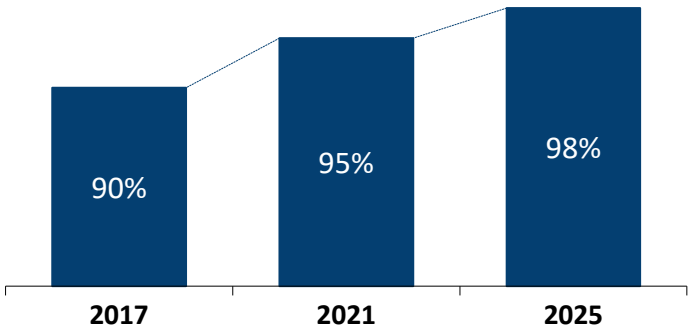
[1] *150 office-based specialists and 150 hospital-based specialists, whom 35 dermatologists interviewed on-line in June 2020*

Med reps are not viewed by physicians as a robust, updated and convenient source of scientific information, which means that they must bring high-value services to stay connected to them

The French healthcare system – Key stakeholders

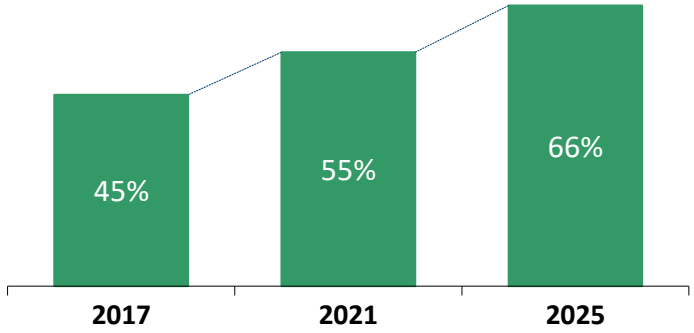
Access to HCPs in France (2017 – 2025)

Online scientific search by physicians
(% of total)



- Physicians becoming more familiar with the Internet, they are increasingly finding information online, as needed
- The Covid-19 crisis has accelerated the usage of digital channels by physicians to find scientific information
- Product-related is the most accessed website resource

Credit given to pharma websites by physicians
(% of total)



- 50% or more physicians using search engines, rely on pharma companies' digital resources
- Most of pharma companies have designed product-related websites, with objective and well-presented information
- Thus, these websites have a certain influence on physicians' prescribing decision

For scientific data, including those related to products, online websites are the first source of information, while pharma companies' websites are gaining credibility with physicians

Sources: Smart Pharma Consulting estimates and analyses based on multiple historical studies (e.g., DRGs – ZS – McKinsey)

LFSS 2020 modified the provisions to be granted an ATU, introduced constraints to prevent drug shortages and encouraged generics substitution, while quashing biosimilar substitutability law

The French healthcare system – Recent reforms

LFSS 2020 key articles regarding drugs and pharma companies

Safeguard clause for drugs (Article 24)

- For 2020, the safeguard clause to drugs, called the "M" rate, has been set at +0.5%, while it had been set at +1.0% for 2019

Financial sustainability of the ATU (early access program) (Article 44)

- This article concerns filings for ATUs applied before March 1, 2020, and modifies the conditions to obtain a nominative ATU (ATUn):
  - The drug efficacy should be important and clinically relevant
  - Refusal of ATUn if previous demands for cohort ATU (ATUc), clinical trial or in case of increased risk with the existing treatments have been rejected
  - Free pricing of ATUn is replaced by a compensation set by the government
- The receivability of a demand for an ATU is subject to the following conditions:
  - The number of ATUn for a given drug will be limited by a Ministerial Order
  - The drug has not yet been granted a marketing authorization or an ATUc
- Communication to the pharma company of the possible estimated amount that could be funded by the National Health Insurance Fund after the ATU ends
- The CEPS can set up a schedule a payment of discounts for a period beyond one year

Prevention of drug shortage (Article 48)

- Pharma companies must have buffer stock of 4 months located in Europe
- Financial penalty will be imposed to pharma companies in case of failure

Various measures regarding cost of drugs (Article 42)

- A ministerial order can set a maximum selling price for a drug to hospitals:
  - When there is risk of unjustified expenditure
  - In case of expensive health product
- Relaxation of the rules to substitute drugs with narrow therapeutic margins that will be clarified by an implementing decree
- Modification of the Article 66 (LFSS 2019) stipulating that if a patient refuses a generic[1], he will be reimbursed based on the price of the most expansive generic. This rule will start two years after the publication of the 1st generic's price and will be implemented on January 1, 2022, at the latest
- Repeal of the law authorizing biosimilar substitution by retail pharmacists[2]
- A working group will be set up to determine the inter-changeability between biologic drugs
- Manufacturers are authorized to file a registration dossier for a biosimilar before the patent expiry of the corresponding original biologic

Sources: LFSS 2020 – "Loi de Financement de la Sécurité Sociale pour 2020"
NILE Consulting – Smart Pharma Consulting analyses

[1] For non-valid reasons – [2] This law created by the LFSS 2014 has never been implemented in the absence of a decree defining the conditions of substitution

Launched in December 2019, the Health Data Hub[1] is a new French platform designed to cross-reference existing health databases for medical research purposes

The French healthcare system – Recent reforms

Health Data Hub

SNDS[2]
National Health Data System

- **PMSI**
  Information Systems Medicalization Program
  (Hospital data)
- **SNIIRAM**
  National Health Insurance Inter-Plan Information System
  (National Health Insurance Fund data)
- **CNSA**
  National Solidarity Fund for Autonomy
  (Disability data from MDPH)
- **CépiDC-Inserm**
  Electronic certification of causes of death
  (Medical causes of death)
- **Complementary health insurance companies**
  (Sample of data)

Aggregating and making these data available to promote studies, research or evaluation of a public interest nature and contributing to the :

- Information on health
- Implementation of health policies
- Knowledge of health expenditures
- Information of professionals and institutions about their activities
- Innovation in the fields of health and medico-social care

Definition
- New French health data platform, created in December 2019, that allows to cross-reference existing health database and thus facilitate their use for research and development purposes

Objective
- Based on the Artificial Intelligence, create a platform for accessing and sharing data, in the service of health research and innovation

Pros
- Health issues: improving research and development
- Competitive advantage at international level for research and innovation

Cons
- Sensitive and personal data that can be used if there is a public interest and after the CNIL's[3] consent
- Data hosted by Microsoft: exposure to US law (Cloud Act)

Implication for pharma companies
- Perspectives of interest at each stage of the drug or medical device value chain, from research to development, including monitoring the use of healthcare products in real life and organizing care pathways
- Access to data, not accessible as of today
- Additional place to forge new links and partnership relations with the players of the ecosystem, whether public or private

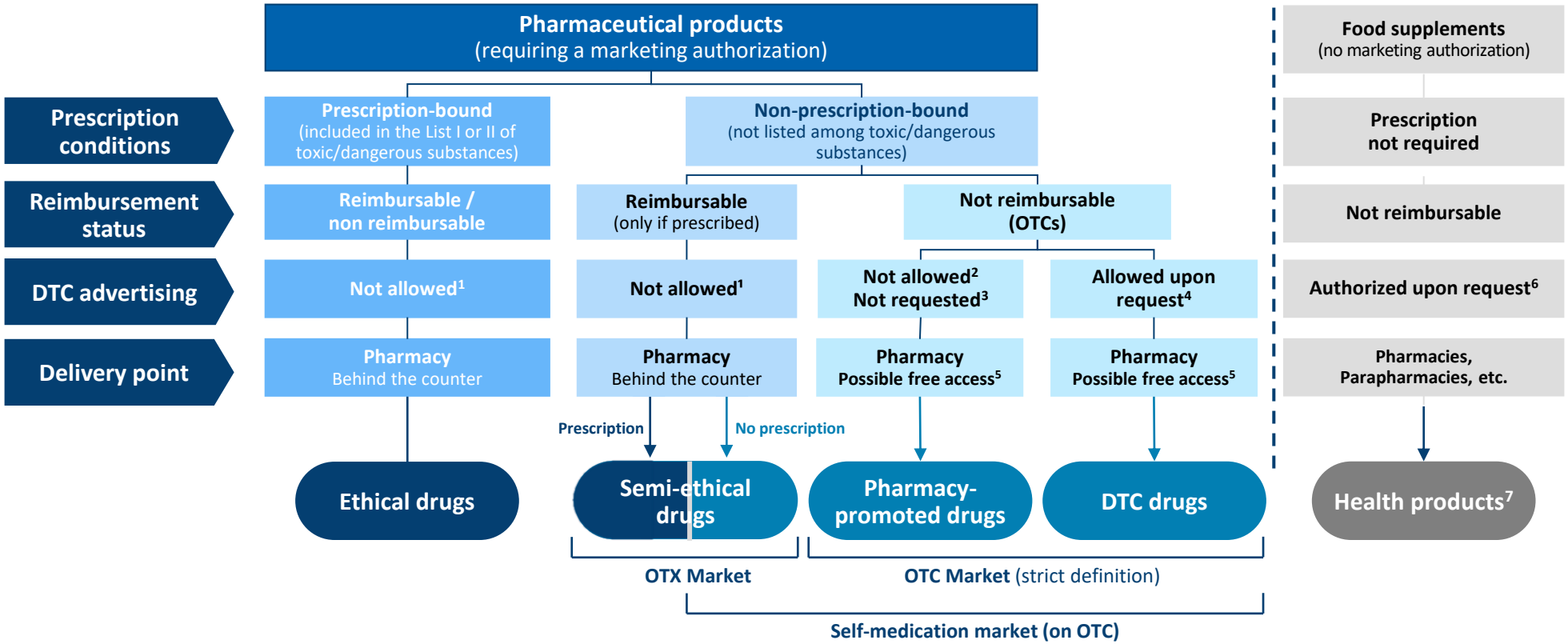
Sources: "La Plateforme des données de santé (Health Data Hub)", CNIL (February 2021) – "Health Data Hub : 6 questions sur la plateforme de données de santé et sa polémique", Numerama (June 2020) – "Le Health Data Hub : quelles opportunités pour l'industrie pharmaceutique ?", Alcimed (July 2020) – Smart Pharma Consulting analyses

[1] Also named PDS (Plateforme des données de santé) – [2] Système National des Données de Santé – [3] Commission Nationale de l'Informatique et des Libertés (National commission for information technology and civil liberties)

Pharmaceutical products can be split into prescription-bound and non-prescription-bound drugs, knowing that some of the prescribed drugs are not reimbursed

The French pharmaceutical market – Evolution of drugs sales

Classification of pharmaceutical products in France



Note: OTC = Over-the-counter, OTX = combination of prescription (RX) and over-the-counter (OTC), DTC = Direct to consumer

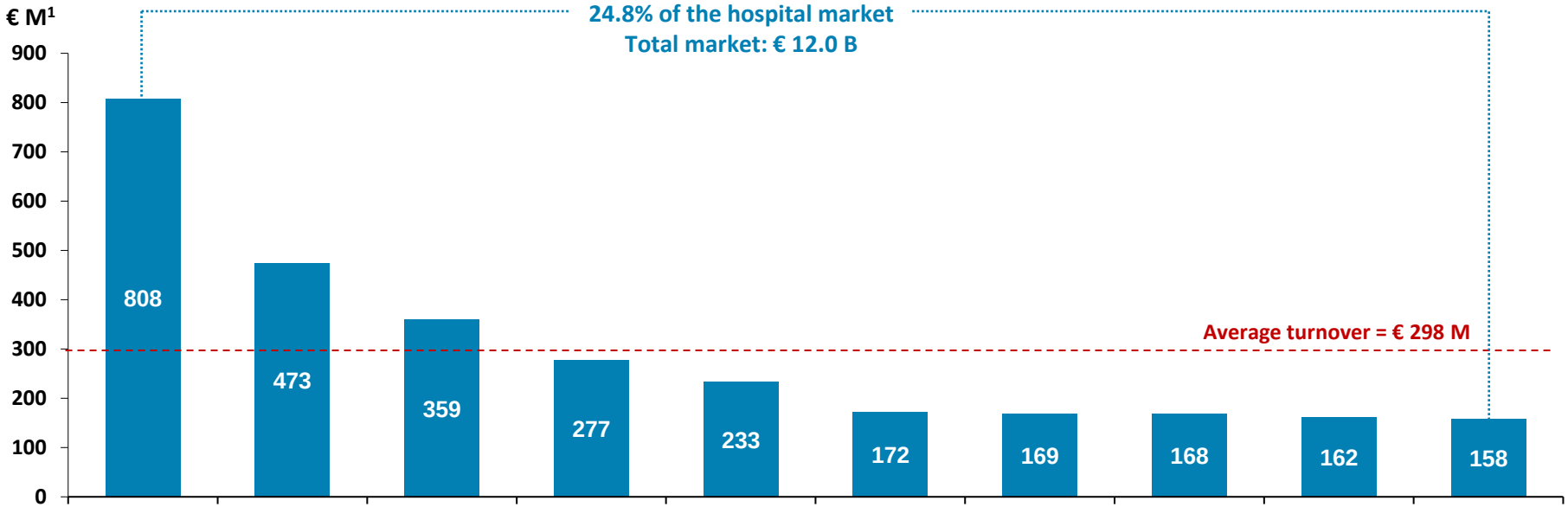
Sources: ANSM – DGCCRF – Smart Pharma Consulting analyses

[1] Rare exceptions (e.g., vaccines) – [2] Psychotropic or narcotic drugs – [3] When the pharma company does not wish to communicate to the general public – [4] Whatever the claims – [5] Possibility of "free access" within the retail pharmacy for certain OTC products – [6] Only for claims relating to healing, alleviating or preventing diseases – [7] Other than drugs and pharmaceutical products

With a growth rate of +82.6% in 2020, Keytruda has become the best-selling drug on the French hospital market, ahead of Opdivo and Revlimid

The French pharmaceutical market – Evolution of drugs sales

Top 10 products in value – Hospital sales (2020)



	Keytruda	Opdivo	Revlimid	Darzalex	Clairyg	Avastin	Lovenox	Privigen	Perjeta	Imnovid
Market share	6.7%	3.9%	3.0%	2.3%	1.9%	1.4%	1.4%	1.4%	1.3%	1.3%
2019 ranking	2 ⇗	1 ⇘	3 =	7 ⇗	6 ⇗	4 ⇘	9 ⇗	5 ⇘	8 ⇘	10 =
2019 - 2020 evolution	+82.6%	+2.5%	+7.4%	+61.1%	8.4%	-30.4%	3.9%	-28.0%	-1.9%	+4.1%

⇗: Rise - ⇘: Drop - = ***No change in 2020 vs. 2019 ranking***

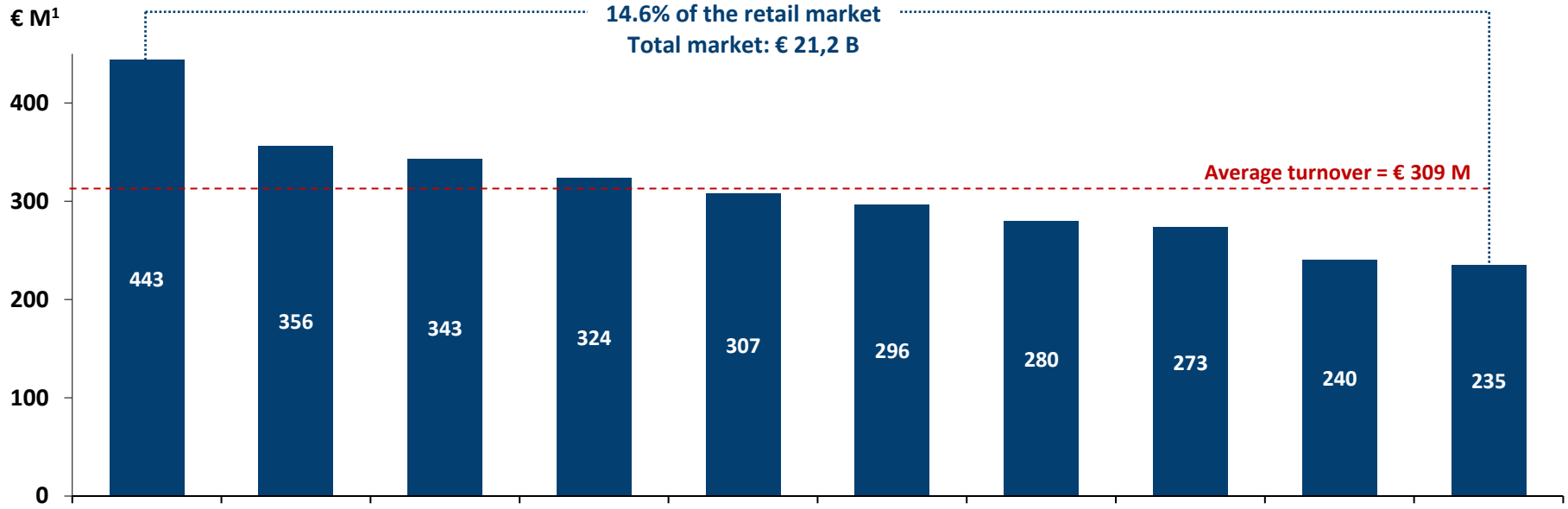
Sources: GERS – Smart Pharma Consulting analyses

[1] Constant ex-factory price, excluding rebates and taxes (including rebates, the hospital market amounted to ~€ 7.9 billion in 2020)

With a growth rate of +27.5% in 2020, Eliquis has become the leader of the French retail market, ahead of Lucentis and Humira

The French pharmaceutical market – Evolution of drugs sales

Top 10 products in value – Retail sales (2020)



	Eliquis	Lucentis	Humira	Eylea	Xarelto	Ibrance	Doliprane	Imbruvica	Zytiga	Xtandi
Market share	2.1%	1.7%	1.6%	1.5%	1.5%	1.4%	1.3%	1.3%	1.1%	1.1%
2019 ranking	3 ⇗	1 ⇘	2 ⇘	5 ⇗	7 ⇗	4 ⇘	6 ⇘	8 =	9 =	9 ⇘
2019 - 2020 evolution	+27.5%	-4.3%	-6.7%	+4.4%	+7.0%	-10.5%	-3.4%	+22.8%	+16.8%	+12.7%

⇗: Rise - ⇘: Drop - = ***No change in 2020 vs. 2019 ranking***

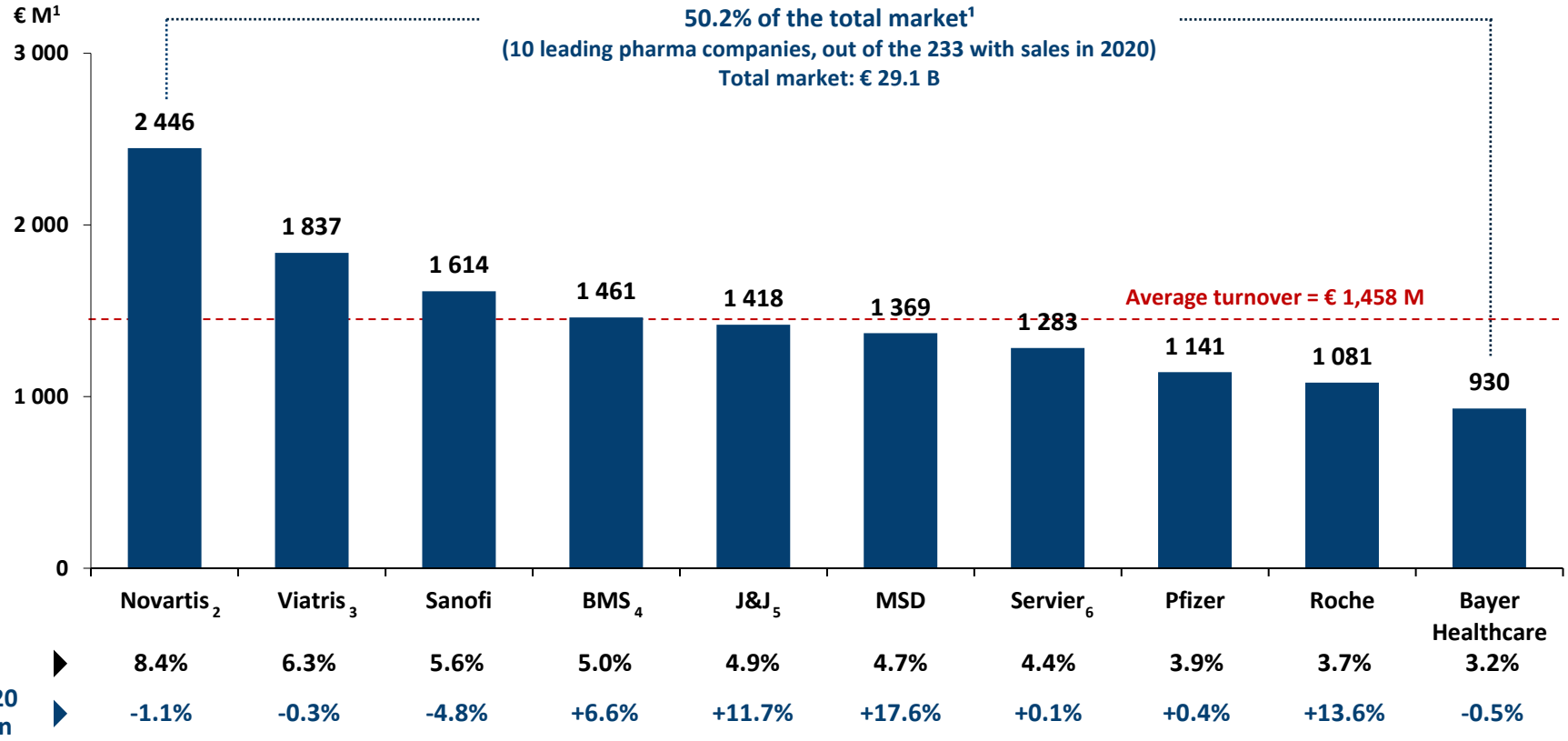
Sources: GERS – Smart Pharma Consulting analyses

[1] *Ex-factory price, excluding rebates and taxes*

In 2020, the top 10 pharma companies accounted for ~50% of the French pharma market, with Novartis, Viatris and Sanofi standing on the top

The French pharmaceutical market – Evolution of pharma companies' sales

Top 10 pharma companies on the hospital and retail markets – In value (2020)



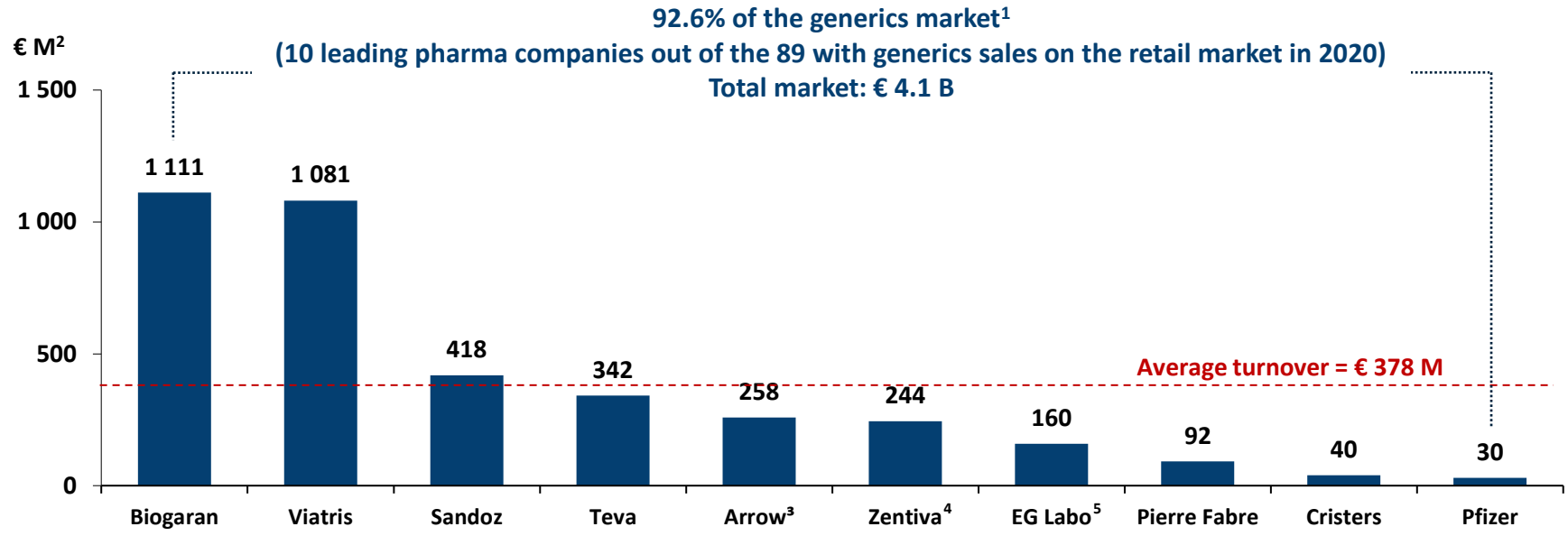
Sources: GERS – Smart Pharma Consulting analyses and estimates

[1] Constant ex-factory prices, excluding taxes and rebates, except for hospital sales for which rebated sales have been estimated – [2] Including Sandoz – [3] Company founded in November 2020 by the merger of Mylan, Mylan Medical and Pfizer Upjohn activities – [4] Including Celgene (acquired in 2019) but excluding UPSA (acquired by Taisho Pharmaceutical in 2019) – [5] Janssen and J&J Santé Beauté – [6] Including Biogaran

In 2020, Biogaran and Viatris generated more than € 2 B sales and represented together ~54% of the French retail generic market in value

The French pharmaceutical market – Evolution of pharma companies' sales

Top 10 generics companies on the retail market – In value (2020)



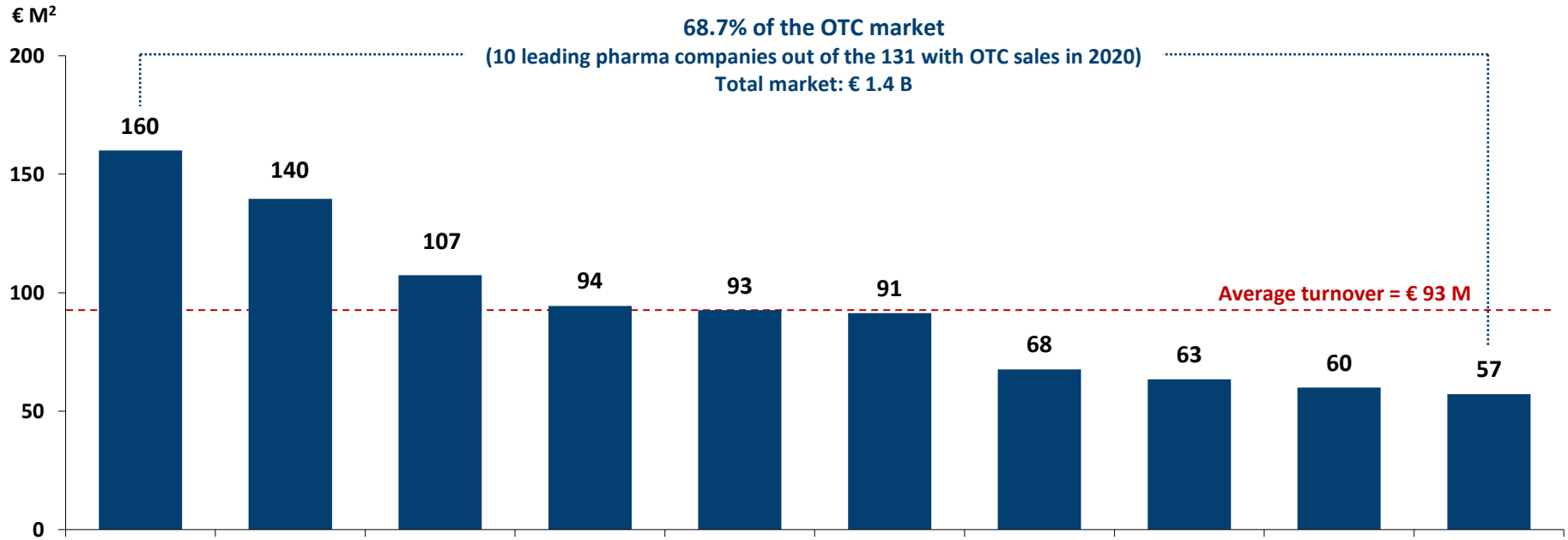
	Biogaran	Viatris	Sandoz	Teva	Arrow³	Zentiva⁴	EG Labo⁵	Pierre Fabre	Cristers	Pfizer
Market share	27.2%	26.5%	10.2%	8.4%	6.3%	6.0%	3.9%	2.3%	1.0%	0.7%
Generics weight in the retail portfolio	97.2%	96.3%	70.7%	65.5%	90.3%	98.6%	95.6%	27.4%	96.9%	3.2%
2019-2020 evolution	+5.0%	+3.8%	-3.3%	+11.6%	+5.0%	+33.9%	13,7%	-10.3%	5.1%	-17.2%

Sources: GERS – Smart Pharma Consulting analyses and estimates

[1] Reimbursable and non-reimbursable, listed in the ANSM generics Directory, including quasi generics – [2] Ex-factory price, excluding taxes and rebates – [3] Part of Aurobindo, since its acquisition of Actavis in 2014 – [4] Acquired by Advent International on September 30th, 2018 – [5] Subsidiary of Stada which was acquired by Bain Capital and Cinven in August 2017

The French pharmaceutical market – Evolution of pharma companies' sales

Top 10 companies on the OTC[1] market – In value (2020)



	Boiron	Sanofi	Cooper[3]	Bayer Healthcare	UPSA[4]	J&J (Santé Beauté)	Reckitt Benckiser	Pierre Fabre	Servier	Viatris[5]
Market share	11.8%	10.3%	7.9%	6.9%	6.8%	6.7%	5.0%	4.7%	4.4%	4.2%
2019-2020 evolution	+5.7%	-22.6%	-2.1%	-19.8%	-1.1%	-1.2%	-25.5%	-28.9%	+1.1%	-7.6%

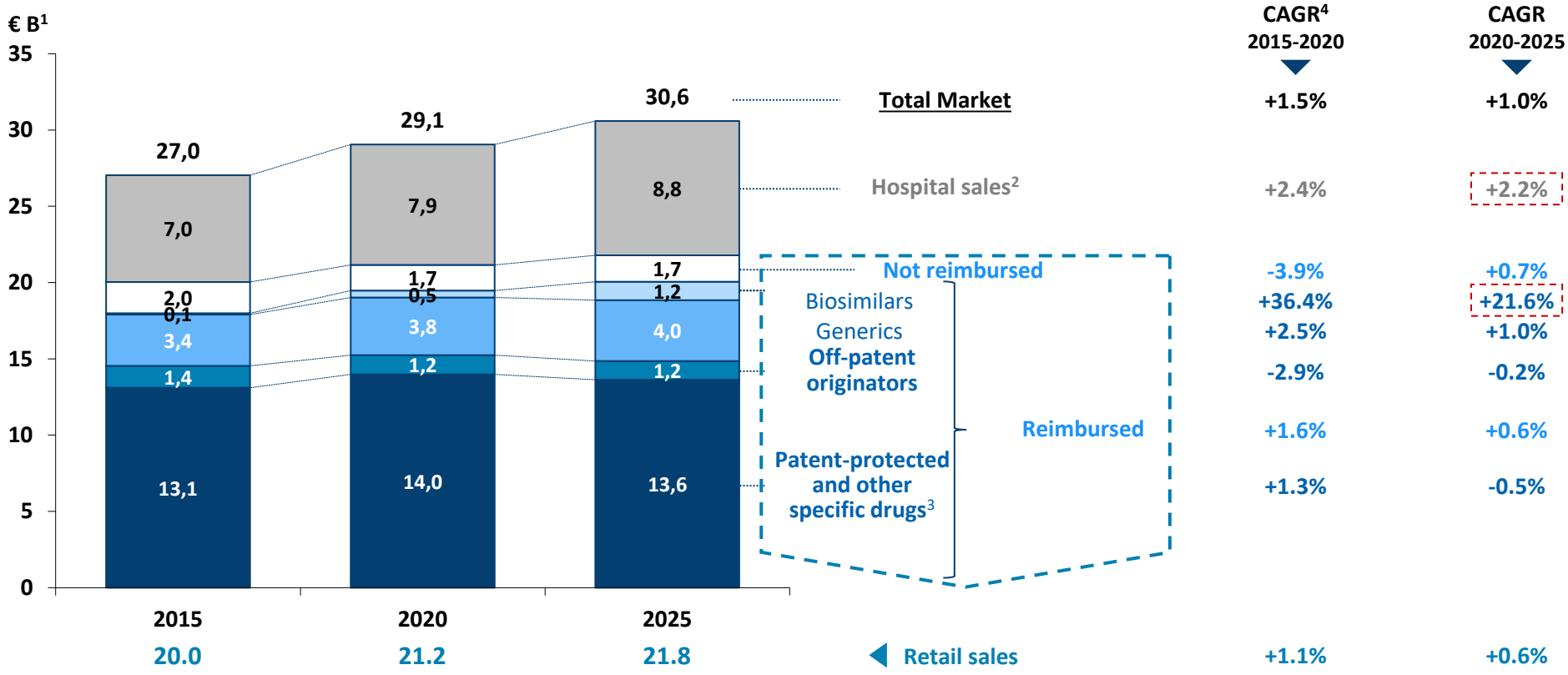
Sources: GERS – Smart Pharma Consulting analyses and estimates

[1] Non-listed, non-reimbursable products – [2] Ex-factory prices, excluding rebates and taxes – [3] Being sold by Charterhouse, which had acquired it from Caravelle in 2015 – [4] Acquired by Taisho Pharmaceutical in 2019 – [5] Company founded in November 2020 by the merger of Mylan, Mylan Medical and Pfizer Upjohn activities

By 2025, the French pharmaceutical market should be mainly driven by innovative hospital products and biosimilars

The French pharmaceutical market – Future market trends

Drugs sales forecast by segment (2015 – 2020 – 2025)

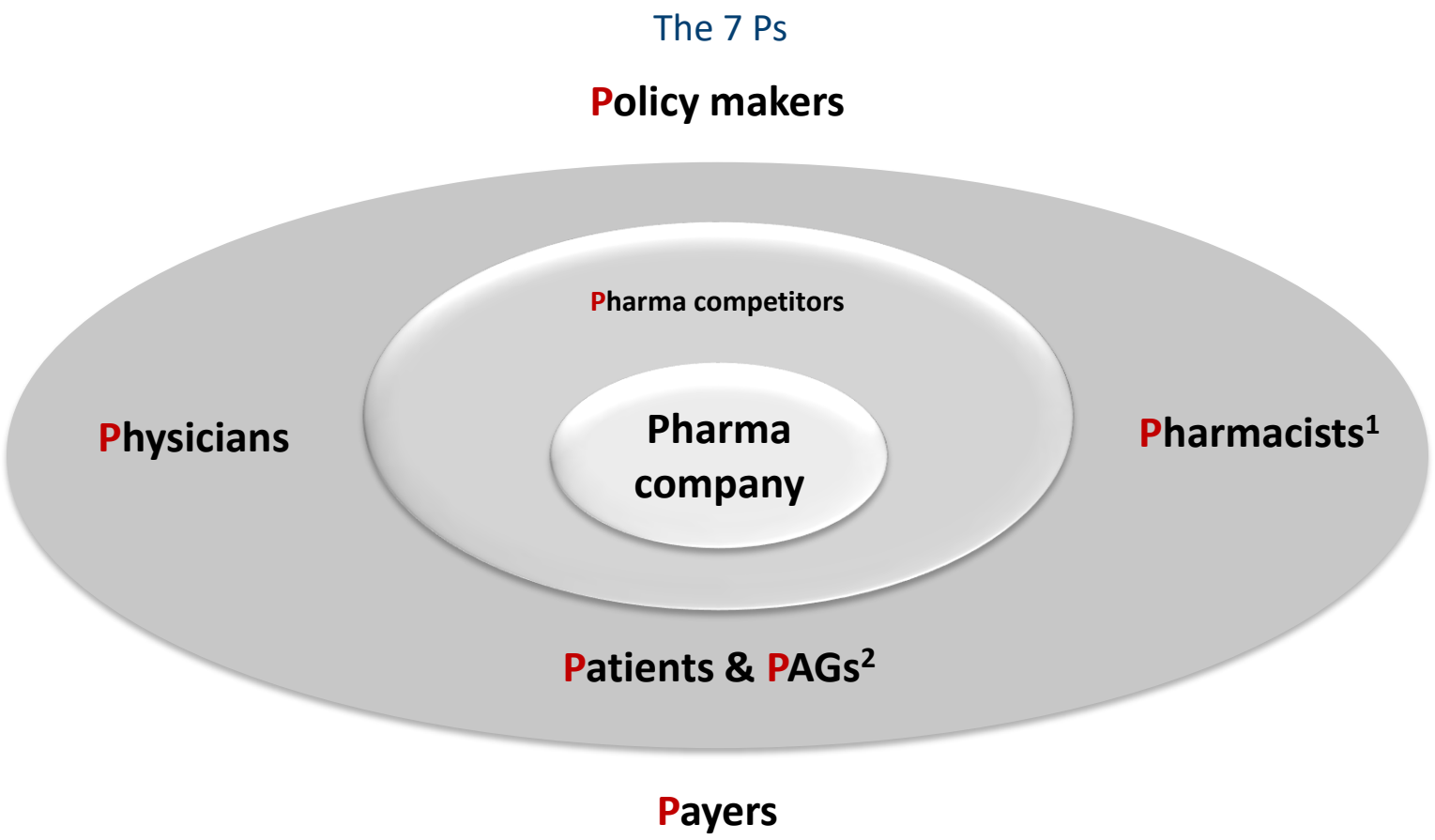


Sources: GERS dashboards – Smart Pharma Consulting estimates

[1] Constant ex-factory prices – [2] Estimated rebated sales including hospital sales of biosimilars, products invoiced on top of "T2A" and reassigned medicines
[3] Sales of drugs whose patents have not expired and of other specific products (calcium, sodium, potassium, paracetamol, etc.) – [4] Compound annual growth rate

Pharmaceutical companies' strategic priorities by 2025 will be linked with the behavior of the "7 Ps" stakeholders

Strategic priorities for pharma companies – Stakeholder mapping



Sources: Smart Pharma Consulting

[1] Pharmacists also play the role of purchasers, and their importance will keep on increasing in the upcoming years, either on the open care or the hospital segments – [2] Patient Advocacy Groups

Policy makers & Payers will work jointly to secure the sustainability of the healthcare system, implying its redesign and the introduction of new measures and possibly new taxes

Strategic priorities for pharma companies – Policy makers & Payers

Stakeholder behavioral trends: Global cost optimization

2020 – 2025 Trends

- Increase of the ONDAM in the range of +4.5% p.a. by 2025, compared to +2.5% on average between 2015 and 2020
- Research of new funding mechanisms to ensure a better sustainability of the healthcare system
- Reorganization of the healthcare system to improve its efficacy and efficiency
- Reduction / prevention of National Health Insurance Fund deficit

Driving factors

- Healthcare costs and economic turmoil induced by the Covid-19 outbreak should increase healthcare expenditure as a percentage of GDP, from ~11.2% in 2019 to 13.2% in 2025 and widen the National Health Insurance Fund deficit
- 78% of healthcare expenditure are funded by the National Health Insurance Fund; whose 90% of revenues are generated by social contributions
- € 19 B investment have been budgeted following the "Ségur de la Santé" consultation (June & July 2020) to improve the healthcare system
- The National Health Insurance Fund has cumulated a deficit reaching a total of € 193 B over the 2008-2020 period, 20% of which has been concentrated in the year 2020

Implications

- Increase of the CSG (+0.9% in 2021) and possibility to introduce new taxes to reduce dependency on social contributions and thus, on the employment
- Redesign of the healthcare system:
  - Shift from hospital to home care
  - Improve hospital / open care markets coordination
  - Improve patient journey efficiency
  - Set up a new framework for funding innovation in the healthcare system[1]
- Introduction of measures and tools:
  - Tighter control of hospital costs
  - Increase price pressure on reimbursed drugs
  - Reinforcement of the ROSP[2] contracts plan for physicians
  - Limitation of access to ALD[3]
  - Budgeting control generalization

Sources: Smart Pharma Consulting analyses

[1] As addressed in the Article 51 of the LFSS 2018 – [2] Bonus program to encourage physicians to comply with "best prescribing practices" for a better efficacy/cost ratio – [3] 100% cost coverage for chronic and long-lasting diseases

The Covid-19 crisis and the outcomes of the "Ségur de la Santé" consultation have led the government to invest heavily in public hospitals while maintaining a strong pressure on drug price

Strategic priorities for pharma companies – Policy makers & Payers

Stakeholder behavioral trends: Drug cost optimization & Hospital services prioritization

2020 – 2025 Trends	Driving factors	Implications
Drug cost optimization ▪ Stricter rules re. reimbursement and price of new drugs, more "aggressive price" regulation of marketed drugs, along with a several rebate mechanisms should limit their sales growth ≤ 1% p.a. ▪ Development of EU guidelines for better valuation of innovation[1]	▪ The cost of drugs spent which reached € 32.6 B in 2019 (i.e., 15.7 % of healthcare goods and services spent), is well controlled by health authorities ▪ Price cuts on drugs are technically easy to implement, politically and socially risk-free for the government ▪ The Covid-19 crisis did not significantly impact the global French drug market	▪ Accelerated price decrease over time ▪ Tighter reimbursement restrictions[2] ▪ Capping of drug cost per product (e.g., orphan drugs) or pathology (e.g., HCV) ▪ New measures to boost generics[3], hybrids and biosimilars[4] ▪ Development of simple managed care agreements for innovative drugs
Strong investment to increase hospital services and attractiveness *("Ségur de la Santé" consultation outcomes)* ▪ Hospital costs should shift from 46.7% in 2019 to almost 50% in 2025 of total healthcare goods and services spent ▪ Modification of the T2A system ▪ Better cost management of products on top of the T2A system	▪ € 19 B to be invested for hospital, ambulatory and medico-social care ▪ € 8.2 B budgeted p.a. to raise salaries of public hospital staffing ▪ 15,000 people to be recruited ▪ Reopening of 4,000 beds on need basis ▪ Regional health agencies and local branches of the National Health Insurance Fund apply a tighter control on drug prescribed by hospital HCPs	▪ Growing price pressure on drug costs which account for only 2.4% of the hospital budget (compared to 72% for personnel which is going to increase to almost 80% by the end of 2025) ▪ More restricted access to on top of T2A products with a… ▪ … regular price decrease by CEPS ▪ Day care / home care development

Sources: Smart Pharma Consulting analyses

[1] EUnetHTA – [2] Number of indications, volume per indication, patient profiles, etc. – [3] Physicians and pharmacists should be incentivized to meet objectives of prescriptions within the generic directory of the ANSM and of substitution rate by generics, respectively – [4] Physicians could be encouraged to prescribe biosimilars as it is yet the case with etanercept, insulin glargine, adalimumab

In addition to cost containment measures, the French government gives the priority to measures to improve patients' access to care and to reinforce the efficiency of the healthcare system

Strategic priorities for pharma companies – Policy makers & Payers

Stakeholder behavioral trends: Patient's care

2020 – 2025 Trends	Driving factors	Implications
Patient's care ▪ Assurance of an earlier and broader access to innovation: – Framework agreement between the CEPS and the Leem (March 2021) – Reform of the French Early Access Programs (ATU) in 2021 (LFSS 2021) – Plan Cancer III – Direct Acting Anti-HCV drugs[1] ▪ Willpower to offer all patients the same access to quality of care and to innovation ▪ Improvement of patient management and adherence to achieve better outcomes ▪ Adjustment of healthcare resources (i.e., facilities, HCPs, funds, etc.) according to the specific needs of the population	▪ Growing and ageing population induce an increase in demand for healthcare services ▪ Patients are more and more aware of innovations and want to benefit from them, as soon as possible ▪ Since 2016, one member of the Transparency Committee represents patients, PAGs and user associations ▪ Poor management of patients leads to a negative impact on clinical and financial outcomes ▪ The number of GPs and of certain specialists is insufficient compared to the needs of the population, especially in isolated areas	▪ New regulations, through which the reimbursement is secured until the price of innovative drugs is granted by the CEPS, during ATU (EAP[2]) and post-ATU periods ▪ ATU can be granted for a new innovative indication of a drug already marketed ▪ Introduction of a fast-track process to negotiate drug prices with the CEPS for the most innovative drugs ▪ Measures to reinforce healthcare networks and patients follow-up[3] ▪ Increasing importance given to: – Day care at hospital level – Home care (with the contribution of pharmacists, nurses, etc.) ▪ Redefinition and reorganization of healthcare territories to increase the efficiency of care

Sources: Smart Pharma Consulting analyses

[1] A universal coverage is provided by the National Health Insurance Fund for all patients, irrespective of the severity of the disease since April 2017 – [2] Early Access Program – [3] Resources allocated to coordinate healthcare networks (e.g., CPTS), creation of community hospitable territories (GHTs)

Additional measures will be introduced to restore the trust in the healthcare system, to drive R&D investment and to relocate the production of essential drugs in France, or at least in EU countries

Strategic priorities for pharma companies – Policy makers & Payers

Stakeholder behavioral trends: Restoration of trust & Search for investors

2020 – 2025 Trends	Driving factors	Implications
Restoration of trust ▪ Willingness to restore / enhance the trust of citizens in: – Health authorities – French healthcare system – Pharma industry and drugs	▪ Different scandals having affected the public opinion leading to more transparency and stricter regulations (e.g., the Covid-19 crisis management) ▪ Prices of innovative drugs are viewed as outrageous and not justified by health authorities, payers but also patients / citizens and PAGs	▪ Strengthening pharmaco-surveillance ▪ More frequent risk/benefits assessment[2] ▪ More robust data required before/after marketing authorization (e.g., RMP[3]) ▪ More transparency requested re. R&D cost of drugs, price agreements with the CEPS, drug profile
Search for investors ▪ Raising the attractiveness of France for pharmaceutical R&D investment (e.g., biotechnologies) ▪ Relocation of selected essential active pharmaceutical ingredients ▪ Support to public / private partnerships between universities, teaching hospitals, public research institutes[1] and pharma companies	▪ Several barriers limit R&D investment: – High labor & social costs – Limitation of partnerships between HCPs and pharma companies – Deterrent effect of administrative hurdles to carry out clinical trials ▪ The Covid-19 crisis has led the French government to support the relocation of industries, especially the drug industry, considered as strategic	▪ Leverage of France excellence (e.g., oncology) through mobilization of public and private funds ▪ Advertising on French R&D set-up and know-how (e.g., IHU[4]) ▪ Simplification of procedures to partner with hospitals re. clinical studies (introduction of the Sole Agreement) ▪ Price advantage for drugs manufactured in France or at least in EU countries

Sources: Smart Pharma Consulting analyses

[1] Such as Curie Institute, INSERM (Research in Health and Life Sciences), etc. – [2] With sanctions – [3] Risk Management Plan – [4] Instituts Hospitalo-Universitaires are public / private partnerships benefiting from a special grant from the government

Pharma companies must position their products, services and themselves to be perceived by Policy makers and Payers as offering superior value than competition

Strategic priorities for pharma companies – Policy makers & Payers

Strategic priorities induced by Policy makers & Payers behavioral trends

Behavioral trends	Strategic priorities for pharma companies
1 Stricter control of reimbursed drug expenditure 2 Measures to boost generics & biosimilars	Enhance the global value proposition (incl. corporate identity, product and service offering) through: – Dedicated corporate reputation programs targeted at policy makers and government – Generation of data vs. standards of care, real world data and … – … high quality medico-economic studies (whenever relevant) – Initiation / support of specific projects to improve patient care
3 Shift from hospital to ambulatory care	Participate to working groups with health authorities and other stakeholders to: – Facilitate the change management (e.g., development of tools, processes, proposition of training programs) – Ensure it will benefit or be neutral on pharma company performance
4 Promotion of investments in France	Increase or maintain R&D activities to be in a more favorable position to negotiate drugs' price, and weigh – very carefully – the pros and cons before deciding to produce in France

Sources: Smart Pharma Consulting analyses

Pharma companies will strive for portfolio and geographic coverage optimization and focus on customer preference vs. satisfaction to generate sustainable value

Strategic priorities for pharma companies – Pharma competitors

Strategic orientations

2020 – 2025 Trends	Driving factors	Implications
▪ Consolidation of business activities through partnerships and/or acquisitions ▪ Optimization of portfolio structure (diversification vs. concentration) and of geographic coverage (dispersion vs. concentration)	▪ Increasing regulatory and price constraints by health authorities ▪ Increasing competitive intensity (vs. generics companies, vs. biosimilars, vs. low-cost companies from emerging countries[1], etc.) ▪ Higher shareholders expectations	▪ Need to focus on therapeutic areas for which the unmet medical needs are the highest, to get higher prices ▪ Need to focus on the most attractive countries from an economic point of view (i.e., offering the highest profit potential over the mid- to long-term)
▪ Pharma companies are trying to put patients at the heart of their strategic thinking… ▪ …through "customer-centric" initiatives, but they are held back by the French regulations which prohibit pharma companies from communicating to or interacting directly with patients for prescription-bound and/or reimbursed products	▪ Need to improve stakeholders[2] experience and especially patients experience under treatment ▪ Need to better know and understand patients and other stakeholders to provide them unique products and services they will prefer and be loyal to, over the long term ▪ Technology development facilitating information sharing	▪ Investment in patients' programs (e.g., AbbVie, Janssen, Novartis, Roche, UCB) that are unique and recognized as superior to competitors ones by the other stakeholders ▪ Development of healthcare networks with patients and PAGs ▪ Use of new technologies to optimize relationship with stakeholders

Sources: Smart Pharma Consulting analyses

[1] Such as Accord Healthcare, subsidiary of the Indian generic company Intas or Samsung Bioepis which markets biosimilars in partnerships with Biogen and Merck & Co – [2] Policy makers, Payers, Physicians, Pharmacists, Patients, PAGs, etc.

Due to increasing regulatory constraints, higher competitive intensity and the Covid-19 crisis, pharma companies try to become more flexible and agile to adapt to environment changes

Strategic priorities for pharma companies – Pharma competitors

Organizational orientations

2020 – 2025 Trends	Driving factors	Implications
▪ Search for more flexible and more agile structures (less bureaucracy, less hierarchy, less complexity, project management models, matrix organization, holacracy organization, etc.) to better meet the change of the environment… ▪ … but limitations due to external regulatory constraints and internal compliance rules, set up by pharma companies, themselves ▪ Increase of teleworking and virtual meetings which are modifying the working interactions within pharma companies, in a sustainable manner ▪ Search for efficiency instead of efficacy, in order to maximize profits	▪ Increasing regulatory constraints by health authorities ▪ Increasing competitive intensity (vs. generics companies, vs. biosimilars, vs. low-cost companies from emerging countries, etc.) ▪ Strengthening bargaining power of payers on pharma companies, implying a greater pressure on prices ▪ Willpower of pharma companies to become more responsive and competitive in a limited number of specific therapeutic areas ▪ More flexibility to adapt rapidly to the change of the environment which has shown to be particularly unstable and unpredictable (e.g., Covid-19 outbreak)	▪ Creation of fully integrated franchises with dedicated resources and independent procedures to be more flexible and agile (e.g., Sanofi, which has created a fully integrated diabetes franchise to better face Novo Nordisk, and thus mimicking Novartis which adopted the same approach for its oncology business) ▪ Simplification of processes ▪ Implementation of transversal management processes ▪ Pharma companies will rethink their organization to better address patient needs and offer them better experiences (creation of patient care business units like AbbVie with “AbbVie Care”)

Sources: Smart Pharma Consulting analyses

Reinforced by the success stories of the anti-Covid-19 vaccines, more and more R&D projects will be conducted through partnerships to increase success rates and mitigate risks and costs

Strategic priorities for pharma companies – Pharma competitors

R&D and Registration

2020 – 2025 Trends	Driving factors	Implications
▪ Strong increase of partnerships, whether public-private or private-private with academics, research institutes or biotech startups ▪ Collaboration with CROs, or CDMOs especially for biologicals, to speed up the access to market	▪ Increasing R&D costs (~USD 2.7 B[1]) ▪ Increasing financial risk of R&D due to decreasing success rates ▪ Tightening of market access processes and requirements ▪ Higher competition vs. generics, hybrids, biosimilars and vs. companies from emerging countries ▪ Successful collaborations while developing anti-Covid-19 vaccines[2]	▪ Pharma companies will increase their level of outsourcing to share costs and risks and to benefit from external expertise or discoveries: – Acquisition of research projects in early clinical development phase – Acquisition of companies involved in early stage of development
▪ Search for innovative drugs in oncology, immunology, neurology, diabetes / metabolism and virology for which unmet needs are important and the prevalence increases in the worldwide ▪ The value of AI to select best drug candidates will lead to a significant increase of their use	▪ Innovate products addressing important unmet medical needs will benefit from an early access and higher prices ▪ The great majority of these products are prescribed by a restricted target of specialists in specialized centers which enables to limit associated marketing and sales costs	▪ High valuation of projects in oncology, neurology and cardio-metabolism (accounting for 62% of the value of the Top 10 pharma research projects in 2019) ▪ Priority given to secondary care treatments for which prices are in general higher and marketing costs lower

Sources: Smart Pharma Consulting analyses

[1] Per marketed drug, including cost of capital – [2] Examples of Pfizer / BioNTech and Moderna which received a fund from the US government agency BARDA (Biomedical Advanced Research and Development Authority) to accelerate the development of their mRNA vaccine and to support the manufacturing process scale-up

Pharma companies should slow down the delocalization of their production in emerging countries and even relocate; while their medical activities should be strongly reinforced

Strategic priorities for pharma companies – Pharma competitors

Manufacturing & Medical

2020 – 2025 Trends	Driving factors	Implications
Manufacturing ▪ Some pharma companies may relocate certain drugs in Europe, but it is likely to be limited due to the negative impact of such a move on cost of good sold and thus on their profitability ▪ Biological products – either original or biosimilars – (e.g., Biocon in India, Lonza in Switzerland, Samsung Bioepis and Celltrion in South Korea)	▪ Financial and regulatory incentives are getting introduced at the EU level and in France to encourage relocate certain essential drugs ▪ Tax environment may also play a major role to relocate production of pharmaceutical products in Europe	▪ Pharma companies will further streamline their production capabilities by shutting down, spinning off[1] or selling plants[2] ▪ To de-risk the supply chain, pharma companies will favor partnerships[3] with: – CDMOs having an international presence – Multiple CDMOs in parallel Moving from fee-for-service deals to complex joint ventures
Medical ▪ Medical affairs are increasingly essential to generate and disseminate high-quality data for health authorities and HCPs (e.g., data vs. comparators, RWD) ▪ They gather information on patient unmet needs to direct the R&D ▪ Reinforcement of pharmaco-surveillance processes	▪ Health authorities are more and more concerned by medical risks associated with prescription of drugs ▪ Therefore, adopting the precautionary principle, they ask for more efficacy and safety data to pharma companies ▪ Medical advisers and MSLs[4] facilitate the proper use of drugs by HCPs and patients	▪ The on-going decreasing efficacy of marketing and sales activities to engage HCPs will make Medical Affairs more and more important, to do so ▪ Medical Affairs should help key stakeholders prioritize the increasing abundance of scientific data, incl. clinical and real-world evidence data, to make better therapeutic decisions

Sources: Smart Pharma Consulting analyses

[1] For instance, Sanofi has recently announced that it will spin off its API business into a separate company by 2022 – [2] In general, to Contract Development and Manufacturing Organizations (CDMOs) – [3] Production outsourcing production should increase from ~25% to ~30% of the volumes, over the period – [4] Medical Science Liaisons

To positively influence HCPs, med reps should be able to carry out regular and highly valued interactions – either in-person or digital – and propose useful services

Strategic priorities for pharma companies – Pharma competitors

Marketing & Sales

2020 – 2025 Trends	Driving factors	Implications
▪ The number of interactions between HCPs and med reps (either in-person or remotely) will further decrease ▪ HCPs will require high-value marketing content and service offering, while interacting with pharma companies' collaborators ▪ The marketing battle will be focused on raising HCPs brand preference by leveraging the drug value, the quality of associated services and the corporate reputation ▪ Decreasing impact of sales calls ▪ Growth of investment in digital channels ▪ Demand for more transparency in terms of promotional and sales practices (including conditions and rebates)	▪ HCPs complain about the low added value of med reps calls and thus, limit the call frequency or refuse to be called upon (especially the young physicians) ▪ The Covid-19 crisis has reinforced the low value granted to medical calls by HCPs ▪ HCPs are more and more reluctant to attend medical meetings – including e-meetings - after working hours (knowing that Internet gives them easier access to quality information) ▪ The pressure from the government to better regulate the links of interest tends to reduce the variety and number of interactions between med reps and HCPs	▪ Rethink of the role of med reps (e.g., how to redefine their activities and train them so that they bring HCPs the information they are looking for or that they need) ▪ Content communicated must be adapted to each HCP fields of interest and needs to offer him a high value ▪ To keep on interacting with HCPs, med reps must create bespoke service-led interactions ▪ Med reps should orchestrate their interactions, combining different channels, according to the content to convey and to each HCP preference ▪ Necessity to adapt to regulatory constraints in terms of promotional activities (e.g., collective reps calls at hospital centers such as at the AP-HP)

Sources: Smart Pharma Consulting analyses

Support functions will be involved in the implementation of crafted strategies and in the search for flexibility and agility required by pharmaceutical companies

Strategic priorities for pharma companies – Pharma competitors

Support functions

2020 – 2025 Trends	Driving factors	Implications
Regulatory – Finance – Human Resources, etc. ▪ Integration of support functions in the building of the "customer-centric" strategies ▪ Increase of competencies and agility through the recruitment of new profiles (e.g., familiar with digital technologies, with customer centricity, with key account management) ▪ Focus on managerial skills rather than on an expertise in a specific domain ▪ Increasing importance of remote interactions amongst collaborators and with stakeholders	▪ Willpower to become more responsive and competitive in a particular therapeutic area ▪ More empowerment to make faster decisions and to be able to compete with digital companies that may enter the pharma market (mainly through partnerships, as a first step) ▪ Increasing regulatory constraints by health authorities ▪ Higher expectations of shareholders ▪ Need to improve stakeholders experience and to better serve patients ▪ The Covid-19 crisis has led pharma companies to introduce new operating procedures (e.g., teleworking, virtual meetings)	▪ Increase flexibility of pharma companies to adapt their organization to the evolving needs of employees and to the Covid-19 pandemic (e.g., flexible scheduling, teleworking) ▪ Importance to better communicate to employees regarding: – The strict compliance with the regulations – The strategic priorities of the company such as "customer-centric initiatives" ▪ Recruit talents or hire agencies coming from non-pharma sectors (e.g., FMCG, NICT) to leverage digital solutions ▪ Introduce an "employee journey" to collect all the changes (ways of working, tools, etc.) and collaborators expectations

Sources: Smart Pharma Consulting analyses

Pharma companies must differentiate from competition by offering highly valued products and services benefiting patients, HCPs and other stakeholders

Strategic priorities for pharma companies – Pharma competitors

Strategic priorities induced by Pharma competitors' behavioral trends

Behavioral trends	
1 Consolidation of business activities	Develop partnerships, especially in R&D, medical and manufacturing activities to increase efficiency and limit financial risks
2 Integrated customer-centricity strategy	Put the customers at the center of the strategy and of the organization to offer products and services that they will need, value correctly and prefer to competitors ones
3 Research of flexibility and agility	Learn from fast-growing industries (such as digital) to build more agile organizations (flexible structures and faster decision-making processes) to cope with changes
4 Adaptation of promotional channels	Invent a new kind of interactions with physicians and other key stakeholders to offer them unique experiences that will be likely to raise their preference for the brands marketed by the company

Sources: Smart Pharma Consulting analyses

The French pharmaceutical market will remain attractive despite a stronger pressure on drug prices, partly outweighed by earlier and broader access to patients

Competitive environment on the French pharma market – 2020-2025

Market Opportunities

- Despite the Covid-19, the **pharma market** should **increase by 1%** p.a., on average, over the 2020-2025 period; and remain the 6th largest market in value terms
- **Access** to **innovation** and to high **quality healthcare** is the **top priority** of the French government and citizens
- **Shift** from hospital **to ambulatory care** should **increase** the number of **patients** treated and better **protect** drug **prices**
- **Support** of **innovative projects** by the government which could **facilitate market access** and **penetration** of **new drugs**

Market Threats

- **Increasing price pressure** on reimbursed drugs, especially "me-too" and on mature products to give better prices to highly-valued innovations
- Generalization of **capping** per **product**, per **pathology** and/or **therapeutic class** to control drug costs
- Array of measures to boost prescription of low-cost copies[1]
- Increasing **difficulties** to **interact with HCPs** to inform them or create partnerships due to lack of interest and time, to regulatory constraints, and the lasting effect of the Covid-19

Implications

- The **French pharma market** will **remain** amongst the **leading markets** in the world in terms of **sales**, although its **profitability** is likely to **be** further **reduced** (unless pharma companies adjust accordingly their expenditures)
- Drastic **budget constraints** of payers and willingness of governments to give patients **early and broad access** to **innovations** will lead pharma companies to **accept lower prices** than in the past that should be partly **offset by higher volume sold**

Sources: Smart Pharma Consulting analyses

[1] *Generics, hybrids and biosimilars*

The future of pharma companies in France should remain attractive enough, provided they adopt a focused strategy, keep on improving their operational efficiency and design a lean organization

Pharma Companies Perspectives in France – 2020-2025

Pharma Companies Strengths

- **Breakthrough innovative** drugs to come by the end of 2025
- Better **clinical studies quality** and development of **real-world evidence data** contributing to optimize drugs benefit and use
- **Portfolio management** with focused strategy on the most attractive therapeutic areas and on drugs responding the best to medico-marketing and sales investments
- **Selection** of a limited number of **services offering** an important **benefit** to **HCPs**, **patients** or **healthcare settings**

Pharma Companies Weaknesses

- **Clinical developments not** often **adapted** to the needs of the French HTA[1] (i.e., controlled studies vs. standard of care)
- **Weak negotiating power** of pharma companies' vis-a-vis the drug pricing committee (CEPS)
- **Rigidity** and **complexity** of internal **processes** preventing pharma companies from optimally seizing opportunities and addressing threats
- **Underperforming marketing** and **sales** investments

Implications

- The **potential** for **efficiency** and **efficacy improvements** of pharma companies operating in France is important, especially in **market access**, **marketing** and **sales operations**
- Pharma companies' organizations should further **simplify their processes** and **become** more **agile**

Sources: Smart Pharma Consulting analyses

[1] Commission de la Transparence (Transparency Commission)

Best performing pharma companies will have in common to market better drugs, offer highly valued services and have a good reputation, driving the preference of their stakeholders

One-page Strategic implications

Strategic Priority: Fight for Key Stakeholders Preference

Innovative Product Portfolio

- Develop innovative 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 payers
- Endeavour to enter first markets with innovations and avoid me-too products with no or minimal incremental added value
- Carry out robust clinical studies to raise early confidence of key stakeholders:
  - Health authorities and payers to ease market access
  - HCPs for earlier adoption
- Complete clinical studies with RWE[1] data

Highly Valued Services

- Offer services highly valued by key stakeholders (e.g., policy makers, payers, HCPs, patients and/or PAGS[2])…
- … and related to the company products (services around the pills) to enhance the perceived value of the latter
- Thus, these services, targeted at HCPs, patients or healthcare settings, should be useful, interesting, convenient and properly executed
- Better communicate about high added-value of services proposed, so that to enhance stakeholders' preference for the drug sold by the company

Good Corporate Reputation

- Build a stronger corporate reputation[3], better than competition, by:
  - Offering highly valued drugs at an affordable price
  - Offering highly valued services to key stakeholders
  - Communicating on R&D activities and product pipeline
  - Investing in selected R&D projects[4] in France
  - Strengthening the skills and ethical behavior of collaborators
  - Developing a good working atmosphere …
  - … and possibly going beyond CSR[5] legal obligations

Sources: Smart Pharma Consulting analyses

[1] Real-world Evidence data – [2] Patient advocacy groups – [3] See the position paper "How to create a superior Pharma Corporate Reputation?": https://smart-pharma.com/wp-content/uploads/2019/07/Pharma-Corporate-Reputation-VF.pdf – [4] And to a lesser extent in distribution or manufacturing facilities – [5] Corporate Social Responsibility

Smart Pharma
CONSULTING

Serving & Sharing with Passion

Global Pharma Market
& Covid-19 Impact

MARKET INSIGHTS

2019-2024 perspectives

"Wrong decisions are often due to weak market insights"

POSITION PAPER July 2020

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Smart Pharma Consulting proposes to share insights regarding 8 topics that are essential to play and to win in the pharmaceutical industry

Introduction

- This position paper provides specific insights for those who want to anticipate the global pharma market evolution over the 2019-2024 period, while considering the impact of the Covid-19
- We have selected 8 topics for which we share our knowledge and thoughts:

Part A - Pharma Market Insights

1. Size and Dynamics by Geography
2. Size and Dynamics by Business
3. Attractiveness
4. Access to Market

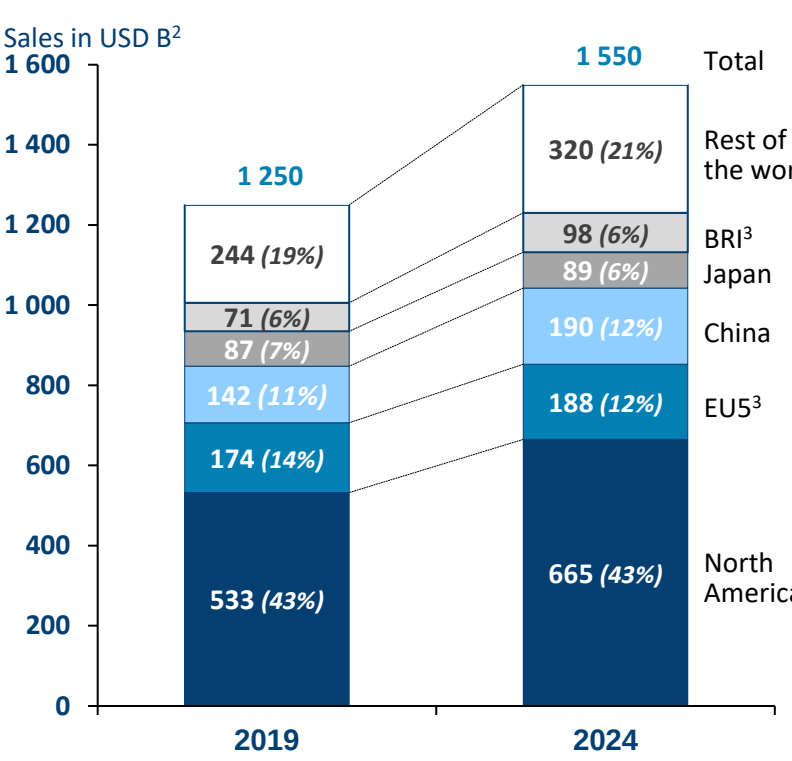
Part B - Pharma Company Insights

5. Strategic Directions
6. R&D Operations
7. Manufacturing & Supply Chain Operations
8. Medico-Marketing & Sales Operations

Sources: Smart Pharma Consulting

Sales of EU5[1] should grow slowly by 2024 due to stringent cost containment measures leading to a two-point decrease of their weight in the global pharmaceutical market

Part A – Pharma Market Insights – 1. Size and Dynamics by Geography



	CAGR	Contribution to growth
Total	+4.4%	
Rest of the word	+5.6%	+25%
BRI[3]	+6.6%	+9%
Japan	+0.5%	+1%
China	+6.1%	+16%
EU5[3]	+1.6%	+5%
North America[4]	+4.5%	+44%

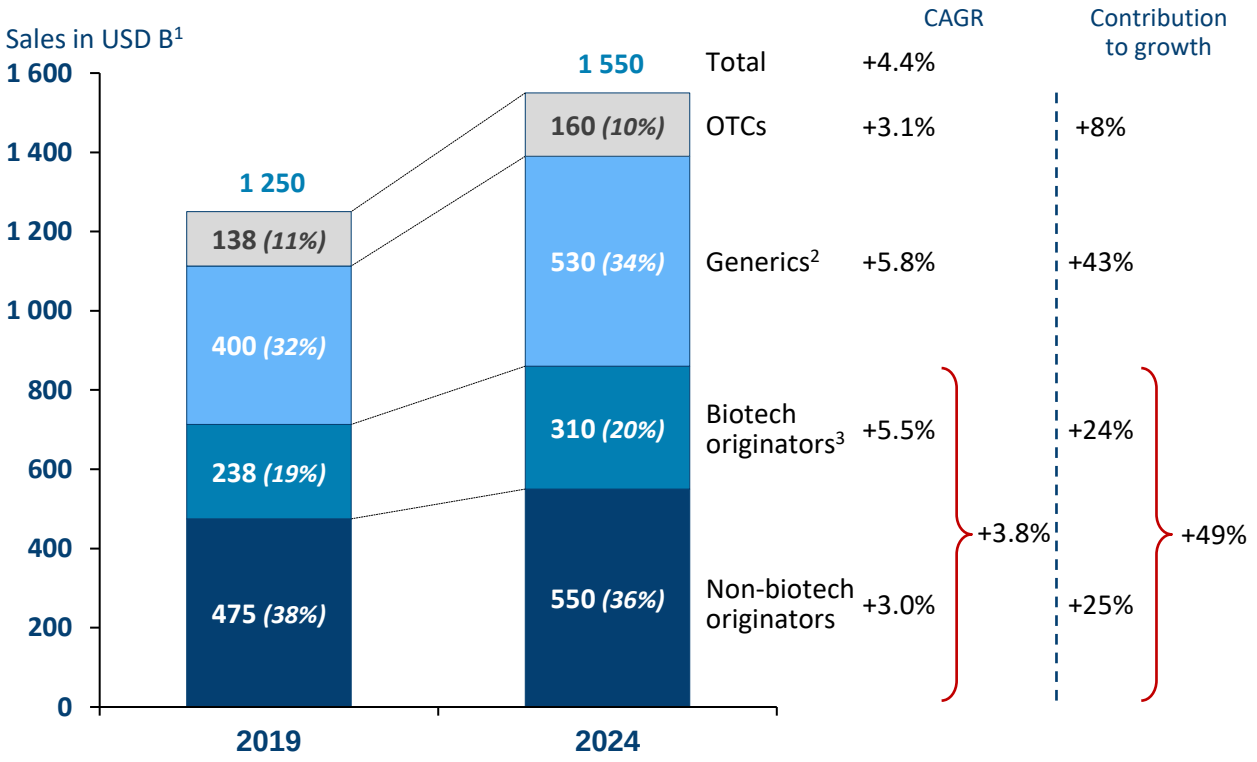
- The global pharma market is expected to grow with of a CAGR of +4.4% by 2024 including the impact of Covid-19, that should negatively impact volumes over 4 to 6 months in 2020 and lead to higher pressure on prices worldwide in the next 5 years
- EU5 countries account together for only 14% of the global pharma market (Germany: 4%, France: 3%, Italy: 3%, UK: 2% and Spain: 2%) and should see their weight drop by 2 points by 2024, due to higher price pressure than in the average of the other countries
- North America should continue to weigh for 43% of the global pharma market in value and contribute to 44% to worldwide market growth over the 2019 – 2024 period

Sources: IQVIA Institute (March 2020) – Smart Pharma Consulting estimates

[1] France, Germany, Italy, Spain, UK – [2] Ex-factory price before rebates – [3] Brazil, Russia, India – [4] USA and Canada

All the business segments of the pharma market will be affected by the Covid-19 crisis through a volume effect in 2020 and a strong price pressure over the 2019-2024 period

Part A – Pharma Market Insights – 2. Size and Dynamics by Business



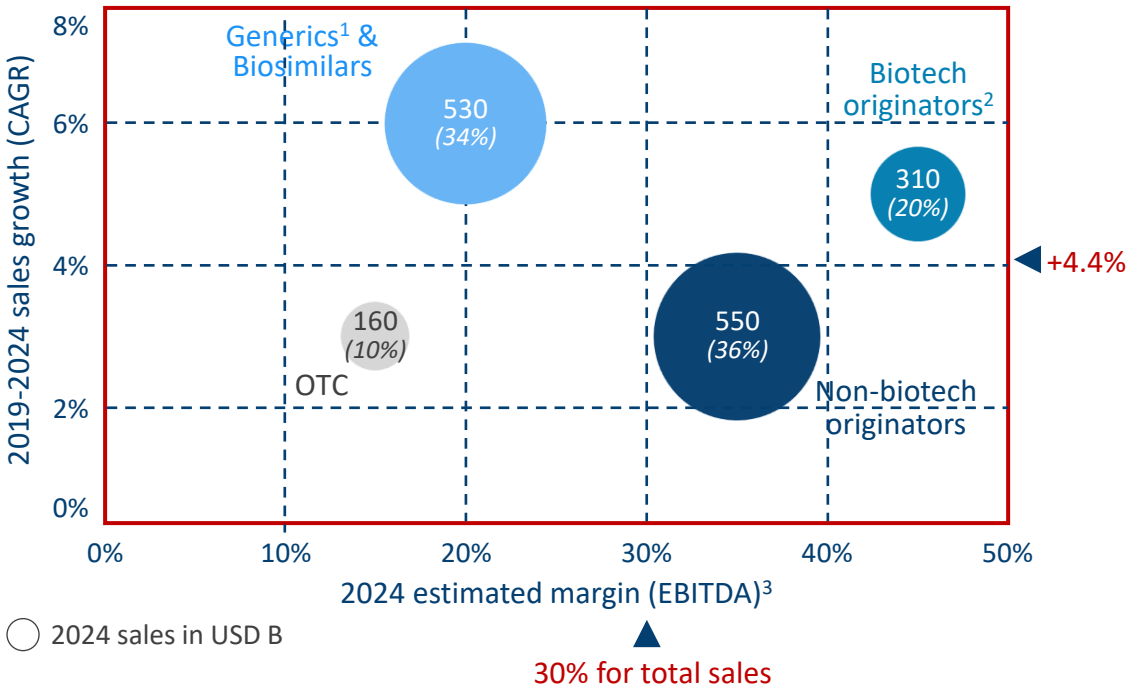
- OTCs, which should remain the smallest segment of the global pharma market, has been significantly affected by the Covid-19 crisis, especially during the lockdown period and the following months
- Generics and biosimilars should continue to grow in volume due to patents expiry, but pressure on prices should intensify on this market segment
- Biotech originators should become the main driver of innovation in the next 5 years
- Non-biotech originators should be less dynamic, but they should remain the largest segment of the global pharma market

Sources: IQVIA Institute (January 2019) – Smart Pharma Consulting estimates

[1] Ex-factory price before rebates – [2] Including branded and unbranded generics and biosimilars, excluding OTC – [3] Excluding biosimilars, already included in the "Generics" segment

By 2024, 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

Part A – Pharma Market Insights – 3. Attractiveness



- By 2024, the global pharma market should reach USD 1,550 B and grow at a pace of +4.4% per year, i.e. 1.8 point of percentage above the forecasted worldwide economic growth, but 0.6 point below the pre-Covid-19 estimates
- The average EBITDA of the Pharma industry should decrease from ~32% in 2019 to ~30% in 2024, mainly as a result of increasing price pressure
- In 2024, the average profitability of pharma companies should remain more than 4 times higher than the average of all other business sectors
- The biotech segment will remain very attractive but biosimilar competition will ramp up
- The OTC segment appears to be the least attractive

Worldwide economic growth – CAGR 2019-2024: +2.6%

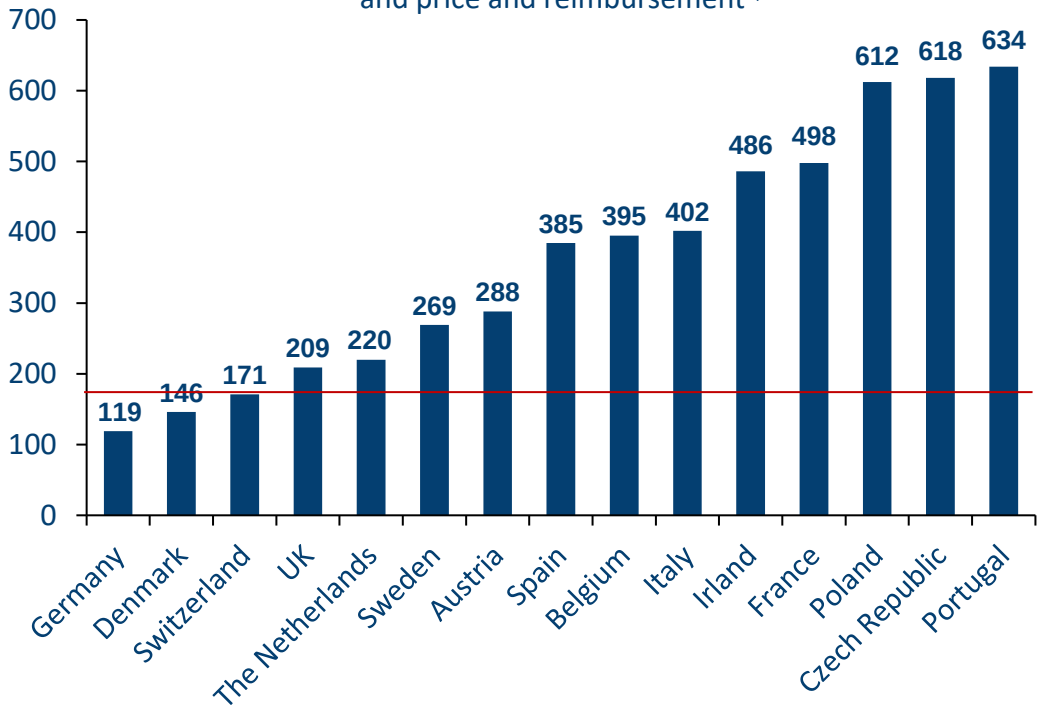
Sources: IQVIA Institute (January 2019) – Smart Pharma Consulting estimates

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

The Covid-19 crisis will have a negative impact, irrespective of the countries, over the 2019-2024 period due to lockdown restrictions and its economic consequences

Part A – Pharma Market Insights – 4. Access to Market

Median time in days between marketing authorization and price and reimbursement[1,2]



2018 analysis based on a sample of 121 products approved by EMA (European Medicines Agency) between January 2015 and December 2017

- The Covid-19 pandemics should defer the availability of new medicines in all countries, due to:
  - Lockdown measures having delayed the assessment of drug registration and market access negotiations
  - The induced economic crisis which will lead to stricter cost containment measures
- In most European countries, delays between marketing authorization and drugs availability exceed the 180 days recommended by the European Commission
- The UK and Germany have no delay since reimbursement and price negotiations occur once the product is in the market
- Delays vary widely, due to the time required to obtain their inclusion on reimbursement list and to agree on a price
- Delays are harmful for pharma companies which face a loss of revenues[1] and patients who do not have access to innovation
- The slowing down of the pricing and reimbursement approval process is used by several countries to contain the cost of new drugs with a price likely to be higher than the existing ones
- The delay is also often due to the difficulties for the drug pricing committee and the pharma company to come to an agreement

Sources: Patients W.A.I.T. Indicator – EFPIA (April 2019) – Smart Pharma Consulting analyses

[1] Excluding early access programs for breakthrough innovations (e.g., ATU in France) – [2] For drugs receiving their first marketing authorization between 2015 and 2017

Drug price pressure imposed by public or private payers is going to intensify, more than ever, irrespective of the value created

Part A – Pharma Market Insights – 4. Access to Market

Historical Trends

- Payers[1] put in place increasingly drastic measures to control drug cost growth
- Drugs account for ~20% of the total healthcare costs[2], but are used by payers as the main lever of cost-containment[3]
- HTA[4] agencies and drug pricing committees control drug cost through:
  - The definition of the target population
  - The positioning of the drug in the therapy
  - The price set per unit of the drug
  - A capping of the drug turn-over reimbursed
- Progressive shift from pay-per-product to pay-per-performance pricing model

2020 Impact

- Delays in drug assessment due to lockdown (part-time activities, backlog assessment put on hold)
- Redirected priorities to assess technologies related to the Covid-19
- Price negotiations becoming tougher due to tighter budgets resulting from financial disruption, across the board
- Considering the anticipated worldwide financial recession, HTAs and payers should put more emphasis than ever on assessing the value of drugs for patients and healthcare systems

2021 – 2024 Impact

- Strong squeezes drug (innovative, me-toos, biosimilars, generics, vaccines) prices which are likely to affect by ~2 points the average profitability of the pharma sector
- Value-based pricing models, incl. pay-per-performance, will become the rule, especially for innovative drugs, if the implementation is not too complex
- Generalization of a budget approach by disease (e.g. € 700M budgeted for antidiabetic drugs on a given year) with a mechanism of drawbacks per drug prescriber for that disease

Sources: Smart Pharma Consulting

[1] Either public or private – [2] After the OECD publication "Health at a Glance" (2019) – [3] Cost-containment measures applied to drugs are easy to implement and well accepted by citizens, unlike those applied to hospital, ambulatory care, long-term care, which have a significant deleterious social impact (layoffs, pay cuts) – [4] Health Technology Assessment

Best performers are focused on innovative Rx-bound drugs and generate an important share of their revenues from the USA, which is the most profitable and dynamic market

Part B – Pharma Company Insights – 5. Strategic Directions

Top 20 pharma companies Strategic Mapping[1]

- Activities concentrated in the USA, EU5[2] and Japan
- Portfolio mainly centered on the innovative branded ethical segment

Higher profitability
Lower growth perspectives

- Activities concentrated in the USA, EU5[2] and Japan
- Broad portfolio incl. generics, OTCs, food supplements, medical devices, vaccines, services, etc.

Moderate profitability
Moderate growth perspectives

- Strong presence, incl. in Latin America, Africa and Asia[3]
- Portfolio mainly centered on the innovative branded ethical segment

Moderate profitability
Higher growth perspectives

- Strong presence, incl. in Latin America, Africa and Asia[3]
- Broad portfolio incl. generics, OTCs, food supplements, medical devices, vaccines, services, etc.

Lower profitability
Higher growth perspectives

Geographical coverage \ Strategic segments	Rx branded Focused	Diversified
Focused	AbbVie, Allergan, Amgen, BMS, Celgene, Eli Lilly, Gilead, Novo Nordisk	J&J
Diversified	AstraZeneca, Boehringer, MSD, Pfizer, Roche, Sanofi, Takeda	Bayer, GSK, Novartis, Teva

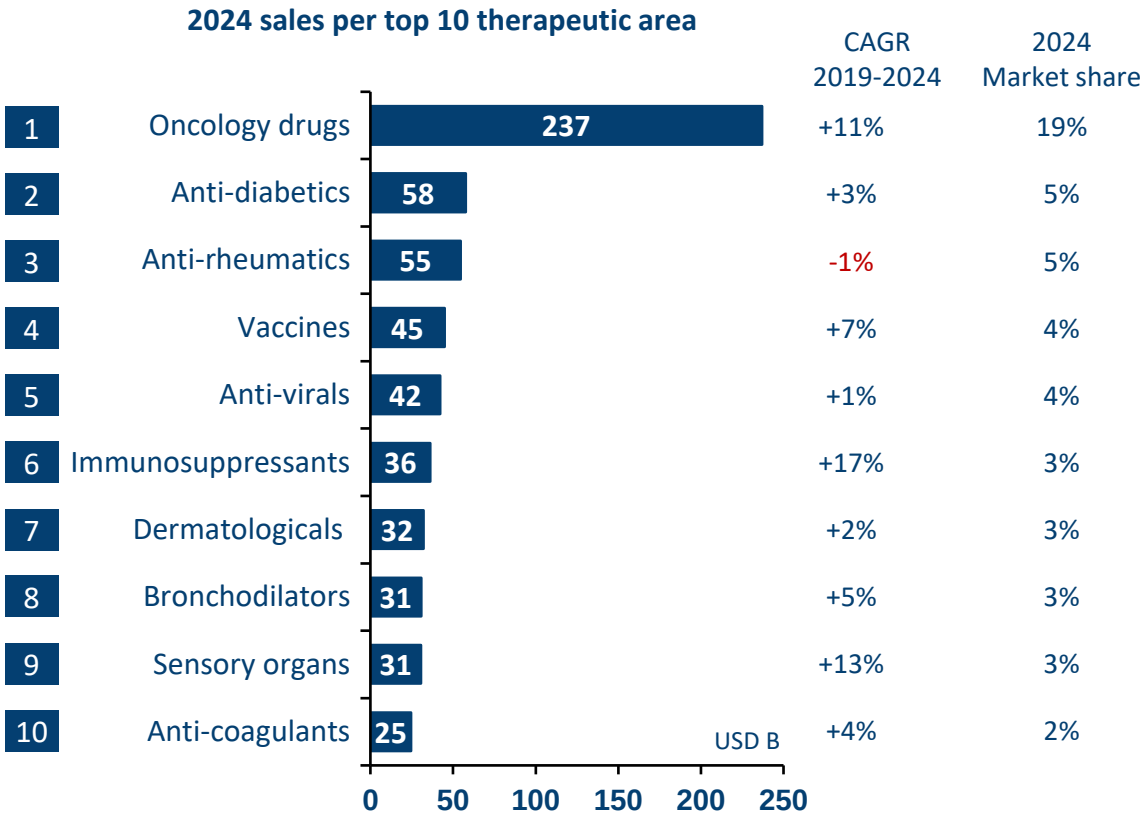
Note: Rx Branded focused: Original Rx-bound drugs and vaccines ≥ 75% of total product sale – Geographically focused: >50% of sales in a single geographical region (e.g. USA, Europe, Japan, etc.)

Sources: Companies annual reports (2018) – Smart Pharma Consulting analyses

[1] Top 20 pharma companies based on their prescription sales – [2] France, Germany, Italy, Spain, UK – [3] Including segments of the population with lower income and/or from rural areas

The important growth in oncology will be mainly driven by anti PD-1 products while immunosuppressants will benefit from an increased incidence of chronic diseases

Part B – Pharma Company Insights – 6. R&D Operations



- The 2024 therapeutic area forecasts shows the steadily increasing weight of specialty products, sustained by the development of new biological drugs
- Oncology prevails as the leading therapeutic area and will be notably driven by the growth of PD-1 inhibitors
- Immunosuppressants will have the highest CAGR through 2024, driven by the incidence of chronic diseases and the use of immunotherapeutic agents in clinical development for other therapeutic areas
- Biosimilars are beginning to make their mark on the anti-rheumatic segment, which should see a decline in its CAGR despite the high drive in sales from JAK inhibitors
- If a vaccine and/or a treatment for the Covid-19 were discovered, the Vaccines and the Anti-virals segments could be boosted over the period

Sources: World Preview 2019 – Outlook to 2024 , Evaluate Pharma (June 2019) – Smart Pharma Consulting estimate

The Covid-19 crisis should contribute to accelerate AI use and further increase partnerships between pharma players to speed up the development of new drugs

Part B – Pharma Company Insights – 6. R&D Operations

Historical Trends

- A lot of hope has been placed in the potential contribution of Artificial Intelligence (AI) to streamline the development of drugs
- In January 2021, for the 1st time, the UK firm, Exscientia, managed to move a drug from the pre-clinical to the clinical stage in 12 months by using AI; which is five times less than what it would have taken without AI
- The use of AI can potentially accelerate timeline and reduce cost of R&D, but most pharma companies are not yet using it

2020 Impact

- The Covid-19 pandemic appears to be a tipping point for the use of AI in accelerating the R&D timeline to find a vaccine or a treatment
- For example, BenvolentAI, in three days, selected six out of more than 370 drug candidates that could be active on the Covid-19, with an AI-based discovery platform
- The Covid-19 crisis has led numerous collaborations, as surprising as the one between the "enemy brothers", Sanofi and GSK, to co-develop a vaccine

2021 – 2024 Impact

- The value of AI to select the drug candidates likely to have the best efficacy / safety ratio will lead to a significant increase of their use
- Big pharma companies will increase their partnerships with other pharma companies, with public and private research centers and data centers to improve their R&D productivity
- The articles[1] published in the New England Journal of Medicine and the Lancet and then withdrawn due to lack of data reliability will lead much stricter peer review processes

Sources: Smart Pharma Consulting analyses – Exscientia website – BenvolentAI website

[1] Two articles related to the Covid-19

The Covid-19 crisis might lead to relocate the manufacturing of certain essential drugs in Europe, while CMOs[1] should account for ~30% of the drugs produced by the end of 2024

Part B – Pharma Company Insights – 7. Manufacturing & Supply Chain Operations

Historical Trends

- Pharma companies have tried to control or even reduce their manufacturing costs, which account for ~27% of their revenues, by implementing strategies such as:
  - Relocation in low manufacturing cost countries like India or China
  - Outsourcing to CMOs which are flexible and/or have specific assets and expertise (e.g. in biologicals)
  - Shifting from conventional batch to continuous manufacturing system
  - Digitalization of production and distribution to increase efficiency

2020 Impact

- With China and India representing 70 to 80% of the APIs manufactured in the world, the EU, under the pressure of the German and French governments, is going to develop a plan to increase EU sovereignty on medical and pharmaceutical products
- If financial and regulatory incentives are introduced at the EU and/or national levels, some pharma companies may relocate certain drugs in Europe, but it is likely to be limited due to the negative impact of such a move on cost of good sold and thus on their profitability

2021 – 2024 Impact

- Pharma companies will keep on streamlining their manufacturing capabilities by shutting down, spinning off[2] or selling plants[3]
- The outsourcing of drug production should increase from ~25% to ~30% of the volumes, over the period
- To de-risk the supply chain, pharma companies will favor partnerships:
  - With CMOs having an international presence
  - With multiple CMOs in parallel

  Moving from fee-for-service deals to complex joint ventures

Sources: Smart Pharma Consulting analyses – E. Wilson, NS Healthcare, May 25, 2020

[1] Contract Manufacturing Organizations – [2] For instance, Sanofi has recently announced that it will spin off its API business into a separate company by 2022 – [3] In general, to CMOs

Medical Affairs will become, more than ever, essential to engage KOLs and other key stakeholders to take the full benefit of the products pharma companies offer

Part B – Pharma Company Insights – 8. Medico Marketing & Sales Operations

Medical Affairs Operations

Historical Trends

- Medical Affairs operations are increasingly essential to generate and disseminate high-quality scientific data related to:
  - Diseases and corresponding treatments
  - Pharma company's products
- Medical Affairs play a key role in engaging KOLs[1] and other stakeholders[2] by showing how their products improve patient outcomes with clinical and real-world evidence data
- They also gather information on patient unmet needs to direct the R&D

2020 Impact

- The Covid-19 outbreak, and the related lockdown restrictions have led to:
  - Limited interactions with KOLs and other stakeholders
  - Cancellations or transformations of medical meetings[3] into e-meetings
  - Disruptions in the recruitment and follow-up of patients in clinical studies / IISs[4]
- Interactions between Medical Affairs, KOLs and other stakeholders are progressively resuming with the lifting of the lockdown restrictions

2021 – 2024 Impact

- The on-going decreasing efficacy of marketing and sales activities to engage HCPs will make Medical Affairs more and more important, to do so
- Medical Affairs should help key stakeholders prioritize the increasing abundance of scientific data, incl. clinical and real-world evidence data, to make better therapeutic decisions
- Medical Affairs, Market Access and Commercial teams should work closely and in a coordinated way to optimize the perceived value of their products

Sources: Smart Pharma Consulting

[1] Key Opinion Leaders – [2] Such as healthcare professionals, patient advocacy groups, health authorities, payers, etc. – [3] Congresses, symposiums, ad boards, etc. – [4] Investigator-Initiated Studies

Pharma marketing strategies should, more than ever, focus on offering high-value content and building strong relationships, so that to raise HCPs preference for marketed brands

Part B – Pharma Company Insights – 8. Medico Marketing & Sales Operations

Marketing Operations

Historical Trends

- The number of marketing interactions per HCP has significantly decreased
- Marketing initiatives have become much more customer-focused, as shown by the development of services[1] for:
  - Institutions and HCPs to facilitate diagnosis and treatment choices
  - Patients, often through PAGs[2], to improve adherence, quality of life, etc.
- Invitations of HCPs to congresses and to other medical meetings have also significantly dropped and been even stopped by certain pharma companies

2020 Impact

- During the lockdown period[3] and the following months, congresses and other meetings have been digitalized, postponed or even cancelled
- The number of commercial interactions will be lower than in 2019…
- … while the importance of digital channels will significantly increase vs. conventional ones
- Pharma companies are crafting multi- or omni-channel strategies in the hope of securing regular interactions with HCPs, across the year

2021 – 2024 Impact

- AI will be more systematically leveraged to gather actionable insights
- HCPs engagement will take greater account of their individual profile
- HCPs will require high-value marketing content and service offering, while interacting with pharma companies' collaborators
- The marketing battle will be focused on raising HCPs brand preference by leveraging the drug value, the quality of associated services and the corporate reputation[4]

Sources: Smart Pharma Consulting

[1] Conventional or digital, including Apps – [2] Patient Advocacy Groups – [3] Two or three months, depending on the countries – [4] See the "Brand Preference Mix" concept and tools developed by Smart Pharma Consulting: https://smart-pharma.com/wp-content/uploads/2019/07/Stakeholders-Brand-Preference-Mix-2016-EN-web.pdf

To positively influence HCPs, med reps should be able to carry out regular and highly valued interactions – either in-person or digital – and propose them useful services

Part B – Pharma Company Insights – 8. Medico Marketing & Sales Operations

Sales Operations

Historical Trends

- Strong decrease in face-to-face interactions between HCPs and med reps (40 to 50% over the last 10 years)…
- … partially outweighed by virtual contacts
- The youngest generation of physicians (below 40-45 years old) considers medical calls (either in-person or remotely) as useless, most of the time
- Coordination between med reps and MSLs is increasing but remains limited, due to regulatory and compliance barriers
- Sales activities are mainly in-person and still very focused on quantitative aspects

2020 Impact

- During the lockdown period (~2-3 months) in-person and remote interactions between HCPs and med reps have been largely restricted
- 10-15% of HCPs are likely to not accept anymore calls from medical reps, following the Covid-19 crisis
- The proportion of remote vs. in-person calls will increase but their sum will be significantly reduced vs. previous years
- HCPs are more than ever expecting useful and interesting contents from medical reps

2021 – 2024 Impact

- The number of interactions between HCPs and med reps (either in-person or remotely) will further decrease[1]
- To keep on interacting with HCPs, med reps have no choice but to create bespoke service-led interactions[2]
- Content communicated must be adapted to each HCP fields of interest and needs to offer him a high value
- Med reps should orchestrate their interactions, combining different channels, according to the content to convey and to each HCP preference

Sources: Smart Pharma Consulting

[1] By 30% to 40% between 2019 and 2024 – [2] See our position paper: https://smart-pharma.com/wp-content/uploads/2019/12/Service-led-Medical-Calls-VW.pdf

The Global Pharmaceutical Market will remain very attractive despite a much stronger pressure on drug prices, partly outweighed by early and broader access to patients

Conclusions

Global Pharma Market Perspectives 2019-2024

Market Opportunities

- Despite the Covid-19, the pharma market should increase by 4.4% p.a., on average, over the 2019-2024 period
- Access to high quality healthcare is the top priority of governments and citizens
- Boosted opportunities to discover new treatments – such as for a Covid-19 vaccine – through partnerships:
  - Public-Private with academics[1] or public funds[2]
  - Private-Private with other pharma companies[3]

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 regulations re. R&D and registrations, 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

Implications

- The Global Pharma Market will remain one of the most dynamic and profitable industrial sectors over 2019-2024, despite a decrease from 5.0% to 4.4% of its CAGR and from 32% to 30% of its profitability, due to the Covid-19 pandemic
- Drastic budget constraints of payers and willingness of governments to give patients, early and broad access to innovations, will lead pharma companies to accept lower prices than in the past that should be partly offset by higher volume sold

Sources: Smart Pharma Consulting

[1] AstraZeneca and Oxford University in the UK – [2] Sanofi and the BARDA (Biomedical Advanced Research and Development Authority) in the USA – [3] Sanofi and GSK biologicals

The future of pharma companies should be bright, provided they adopt a focused strategy, keep on improving their operational efficiency and design a lean organization

Conclusions

Global Pharma Companies Perspectives 2019-2024

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 2024
- Increased manufacturing efficiency with Artificial Intelligence
- Better clinical studies quality and development of real word evidence data contributing to optimize drugs benefits
- Reduction or removal of marketing and sales investments having no or limited business impact

Pharma Companies Weaknesses

- Weak negotiating power of pharma companies vs. public 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]
- Underperforming marketing and sales investments

Implications

- R&D-based companies should focus on a limited number of attractive TAs and countries with the USA being the top priority
- The potential for efficiency and efficacy improvements along the value chain of pharma companies is important, especially in R&D, marketing and sales operations
- Pharma companies' organizations should need to simplify their processes and become further agile

Sources: Smart Pharma Consulting

[1] See the position paper "Best-in-class Pharma Strategy Crafting": https://smart-pharma.com/wp-content/uploads/2019/07/Best-in-class-Pharma-Strategy-WFV.pdf

Best performing pharma companies have in common to market better drugs, offer highly valued services and have a good reputation, driving the preference of their stakeholders

Conclusions

Strategic Priority: Fight for Key Stakeholders Preference

Innovative Product Portfolio

- Develop innovative 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 payers
- Endeavour to enter first markets with innovations and avoid me-too products with no or minimal incremental added value
- Carry out robust clinical studies to raise early confidence of key stakeholders:
  - Health authorities and payers to ease market access
  - HCPs for earlier adoption
- Complete clinical studies with RWE[1] data

Highly Valued Services

- Offer services highly valued by key stakeholders (e.g. policy makers, payers, HCPs, patients and/or PAGS[2])…
- … and related to the company products (services around the pills) to enhance the perceived value of the latter
- Thus, these services should be useful, interesting, convenient and properly executed
- Better communicate about high added-value services proposed, so that to enhance stakeholders' preference for the drug sold by the company

Good Corporate Reputation

- Build a stronger corporate reputation[3], better than competition, by:
  - Offering highly valued drugs at an affordable price
  - Offering highly valued services to key stakeholders
  - Communicating on R&D activities and product pipeline
  - Investing in R&D projects[4] in strategic markets
  - Strengthening the skills and ethical behavior of collaborators
  - Developing a good working atmosphere …
  - … and possibly going beyond CSR[5] legal obligations

Sources: Smart Pharma Consulting

[1] Real World Evidence data – [2] Patient advocacy groups – [3] See the position paper "How to create a superior Pharma Corporate Reputation?": https://smart-pharma.com/wp-content/uploads/2019/07/Pharma-Corporate-Reputation-VF.pdf – [4] And to a lesser extent in distribution or manufacturing facilities – [5] Corporate Social Responsibility

Smart Pharma
CONSULTING

Serving & Sharing with Passion

French Retail
Pharmacies

MARKET INSIGHTS

2019-2023 perspectives

POSITION PAPER January 2020

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In this position paper, Smart Pharma Consulting proposes an analysis of recent changes that have affected French retail pharmacies and an assessment of their perspectives by 2023

1. Introduction

Context and objectives

In this position paper, Smart Pharma Consulting proposes to answer the following questions

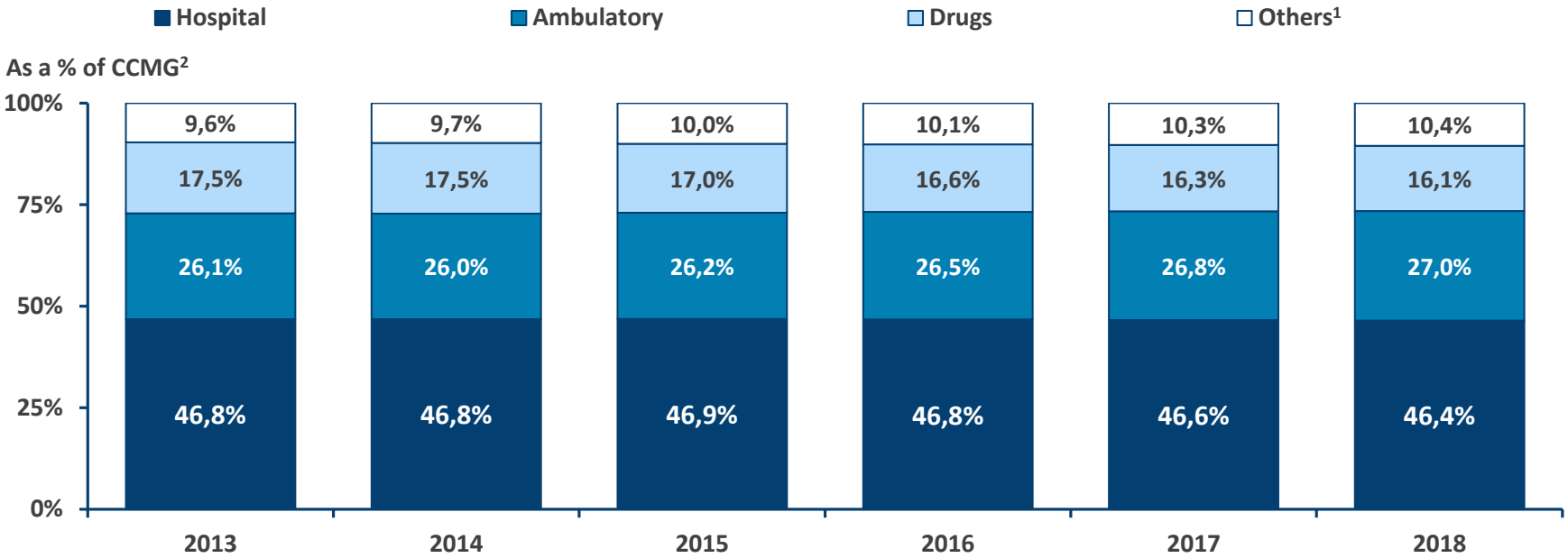
- How is organized drugs distribution in France?
- What is the regulatory framework applicable to retail pharmacies in France and how should it evolve?
- What are the recent dynamics, changes and trends on the French retail pharmacies market?
- What is the level of performance of retail pharmacies in France and what are the main levers to boost it?

Sources: Smart Pharma Consulting

Although drugs expenditure is only the third largest source of spending in France, it is under a higher pressure as it is politically and technically the easiest to reduce

1. Introduction

Breakdown of public and private healthcare expenditure



	2013	2014	2015	2016	2017	2018
Total (€ B)	185.2	190.2	190.0	196.8	199.3	203.5
CCMG as a % of GDP	8.7%	8.8%	8.8%	8.8%	8.7%	8.6%
CEH[3] as a % of GDP	11.9%	12.0%	11.9%	11.9%	11.9%	11.7%

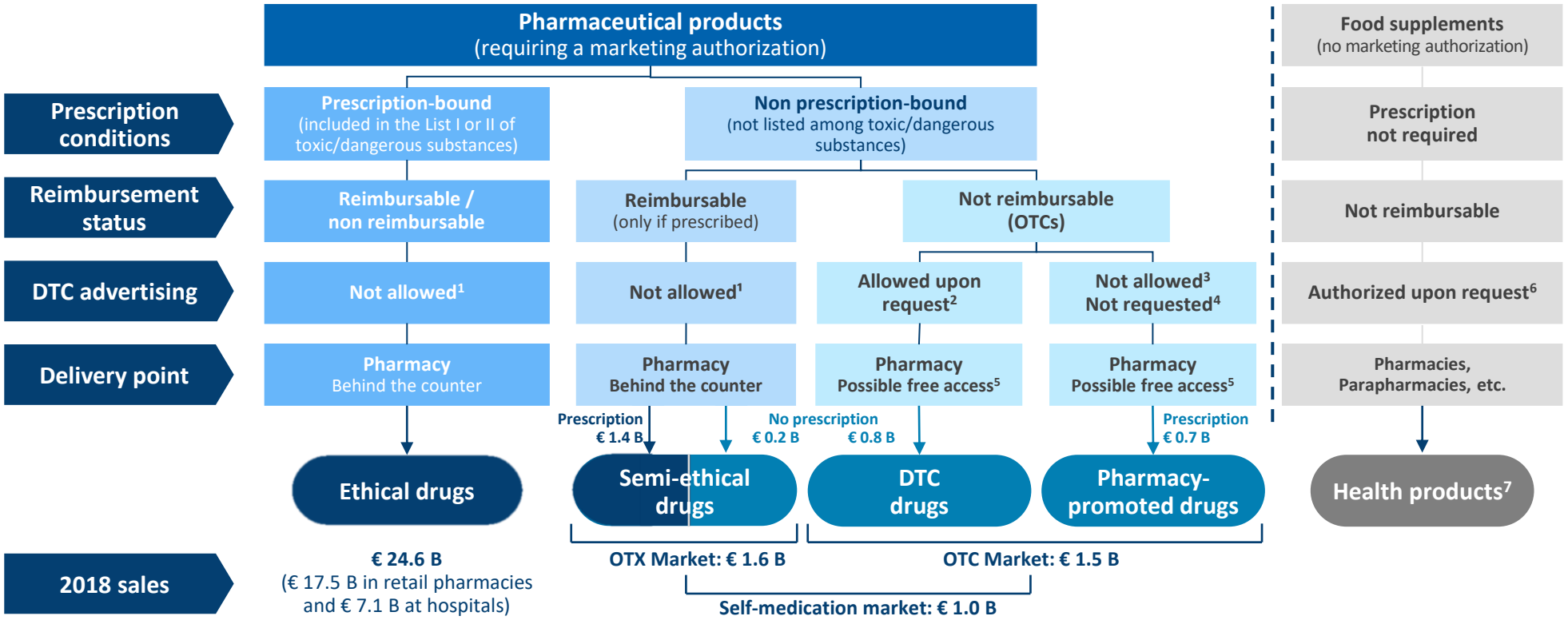
Sources: "Les dépenses de santé en 2018", DREES (2019) – INSEE – Smart Pharma Consulting analyses

[1] Other healthcare goods and services, including patient transportation and other medical goods – [2] CCMG: Consumption of care and medical goods – [3] CEH: Current expenditure on health

Pharmaceutical products can be split into prescription- and non-prescription-bound drugs, knowing that some of the prescribed drugs are not reimbursed

1. Introduction

Classification of pharmaceutical products



Note: OTC = Over-the-counter, OTX = combination of prescription (RX) and over-the-counter (OTC), DTC = Direct to consumer

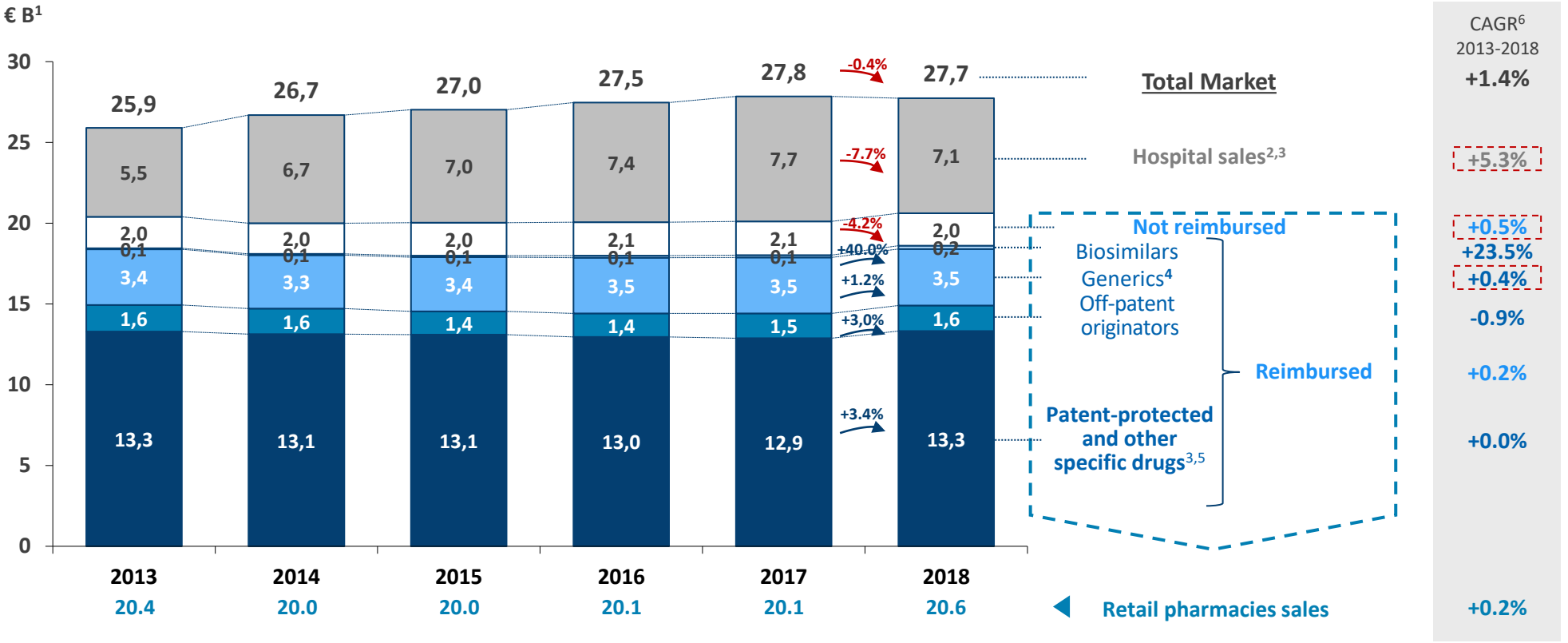
Sources: ANSM – DGCCRF – Smart Pharma Consulting analyses

[1] Rare exceptions (e.g. vaccines) – [2] Whatever the claims – [3] Psychotropic or narcotic drugs – [4] When the pharma company does not wish to communicate to the general public – [5] Possibility of "free access" within the retail pharmacy for certain OTC products – [6] Only for claims relating to healing, alleviating or preventing diseases – [7] Other than drugs and pharmaceutical products

Since 2013, spending on drugs has been mainly driven by hospital sales and by non-reimbursed drugs and generics sold in retail pharmacies

1. Introduction

Evolution of drugs sales by segment (2013 – 2018)



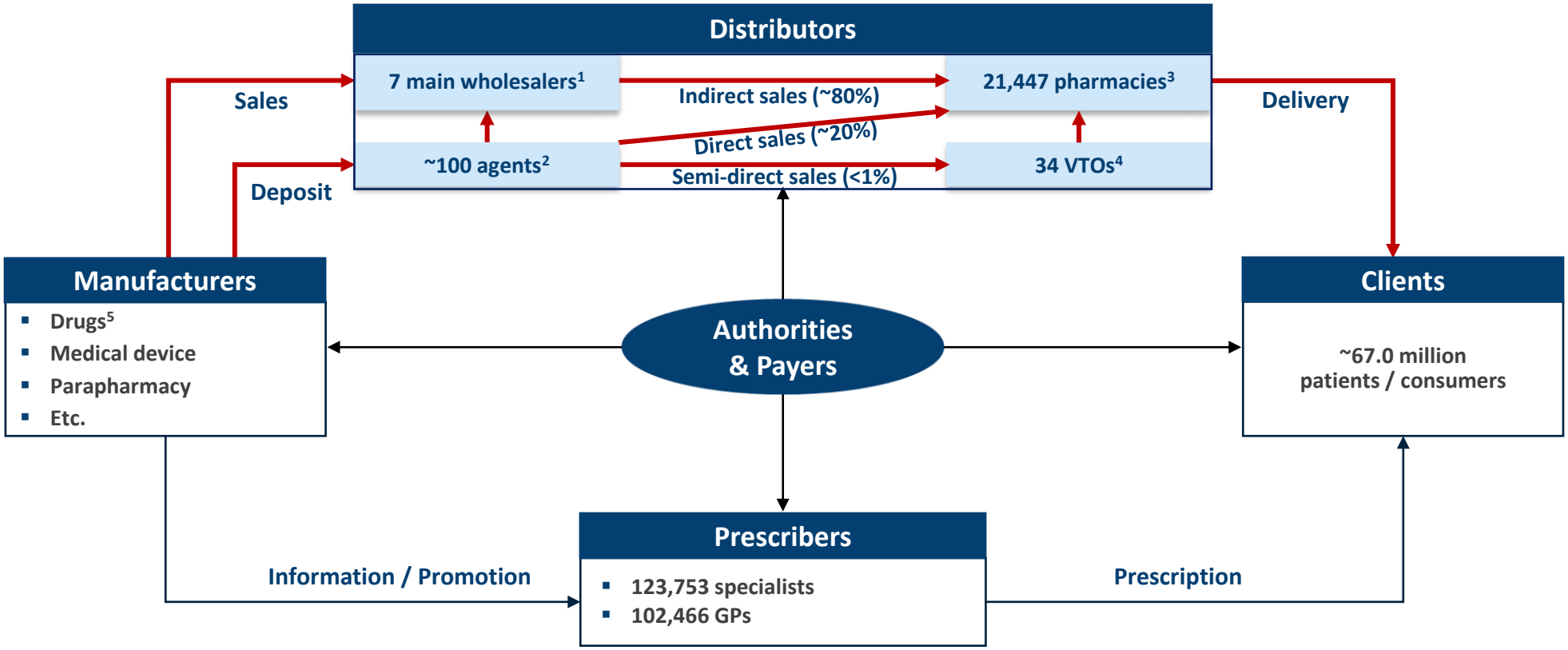
Sources: GERS dashboards – Smart Pharma Consulting estimates

[1] Constant ex-factory prices – [2] Estimated rebated sales including hospital sales of biosimilars, products invoiced on top of "T2A" and reassigned medicines – [3] In 2018, classes of drugs (e.g. hepatitis C) have been transferred from the hospital to the retail market – [4] Reimbursable generics and quasi-generics – [5] Sales of drugs whose patents have not expired and of other specific products (e.g. calcium, sodium, potassium, paracetamol) – [6] Compound Annual Growth Rate

The drug supply chain organization involves 4 categories of stakeholders which are highly dependent on the decisions made by healthcare authorities and payers

2. Drugs distribution

Key stakeholders



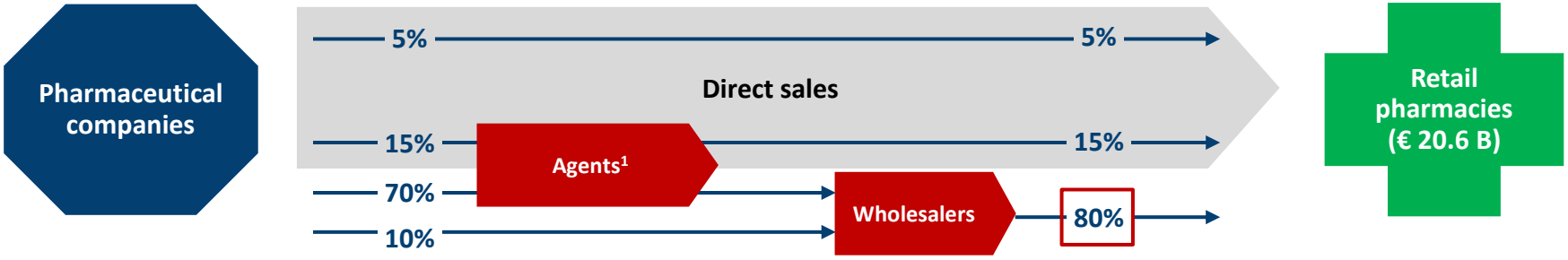
Sources: CSRP – LEEM – GERS – French Council of Pharmacists – ANSM – DREES –Ameli and RPPS database –Smart Pharma Consulting analyses

[1] Accounting for ~97.7% of the wholesalers market in 2018 – [2] Pre-wholesalers –[3] Including 620 pharmacies located in French overseas departments – [4] Of which 17 with more than 500 members individually – [5] Mandatory or optional medical prescription, reimbursed or not

~80% of the value goes through wholesalers, who are the cornerstone of the supply chain between pharma companies and retail pharmacies

2. Drugs distribution

Share of direct sales in the retail market



Agents (~20%)

- **Independent health specialists:**
  - CSP
- **Subsidiaries of integrated distribution groups and health specialists:**
  - Alloga / Directlog (Alliance Healthcare)
  - Eurodep (CERP)
  - IvryLab (PharmaVie / Phoenix Pharma)
  - Movianto[1] (Owens & Minor, USA)
  - Sogiphar (Giphar)
- **Subsidiaries of integrated distribution groups; non health specialists:**
  - FM Health (FM Logistic)
  - Arvato Services Healthcare (Bertelsmann group)
  - Pharmalog (Geodis)
  - Rhenus (previously Wincanton)
- **Subsidiaries of pharmaceutical companies:**
  - AstraZeneca
  - Pierre Fabre
  - Sanofi Pasteur
  - Servier

Wholesalers (~80%)

	Market share[2]
CERP network	**36.2%**
– CERP Rouen (Astera)	20.7%
– CERP Rhin Rhône Méditerranée	11.8%
– CERP Bretagne Atlantique	3.7%
OCP (McKesson)	**31.3%**
Alliance Healthcare France (Alliance Boots)	**19.2%**
Phoenix Pharma (Phoenix Group)	**8.4%**
Giphar	**2.6%**
Others[3]	**2.3%**

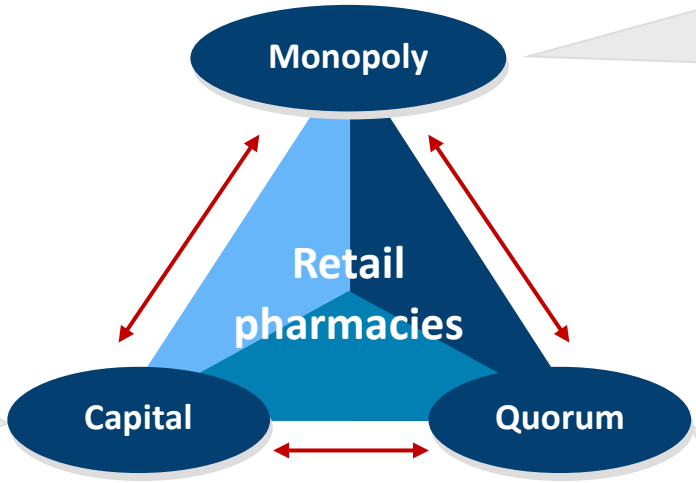
Sources: Xerfi – LEEM – GERS – CSRP –ANSM – Register of the French pharmaceutical establishments – Smart Pharma Consulting analyses

[1] Pre-wholeselling to wholesalers or VTOs or directly selling to retail pharmacists – [2] Market share in value (2018) – [3] Non-members of the "Chambre Syndicale de la Répartition Pharmaceutique (CSRP)"

Amongst the three fundamental pillars of retail pharmacies, only the monopoly on the dispensing of self-medication products could be called into question

3. Regulatory environment

The 3 fundamental pillars of retail pharmacies in France



✖ **Pillar most threatened, notably under the pressure of the mass-market retailing**

Challenged by the competition authority and the IGF[1]

Start of crumbling with online sales

✔ **Decision to open the capital of retail pharmacies left to each EU member State by the European Commission**

The current French government seems opposed to the opening of the capital of French pharmacies

✔ **Consensus between authorities and representatives of the profession to maintain the territorial network based on demo-geographical criteria**

✔ Not questioned ✖ Questioned

Sources: Interviews with retail pharmacists and representatives from VTOs and professional unions (September 2019) – Competition authority report (April 2019) – "La pharmacie d'officine: nouveaux défis, nouvelles opportunités de croissance", Les Echos Etudes (2017) – Smart Pharma Consulting analyses

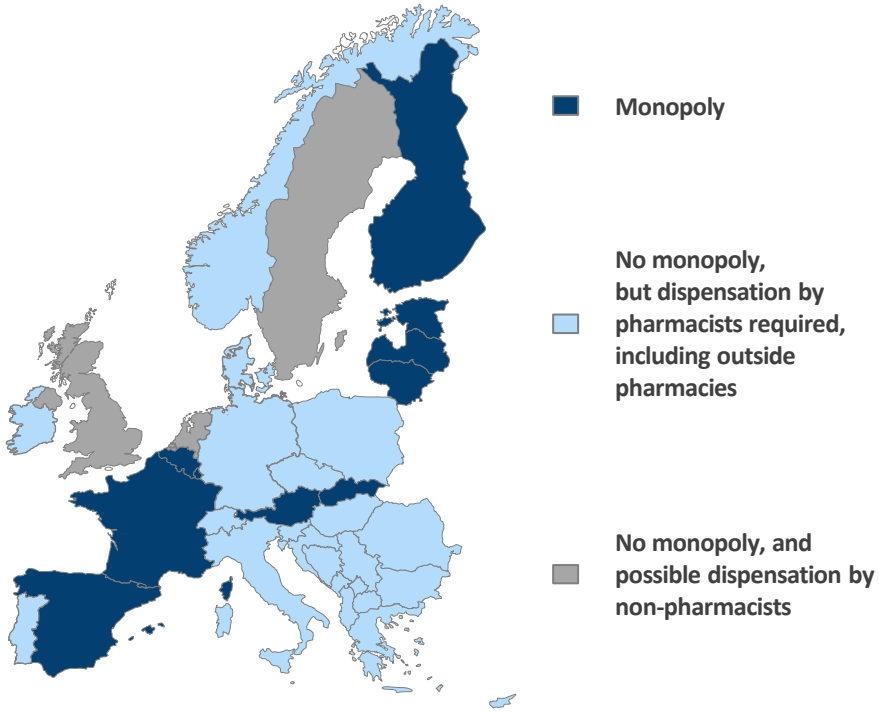
[1] "Inspection Générale des Finances": General Inspectorate of Finance

Although questioned by distribution chains and reports, French governments and people have always shown an attachment to retail pharmacists' monopoly

3. Regulatory environment

Monopoly – Situation in Europe

Situation of the monopoly for non-prescription bounds



Comments

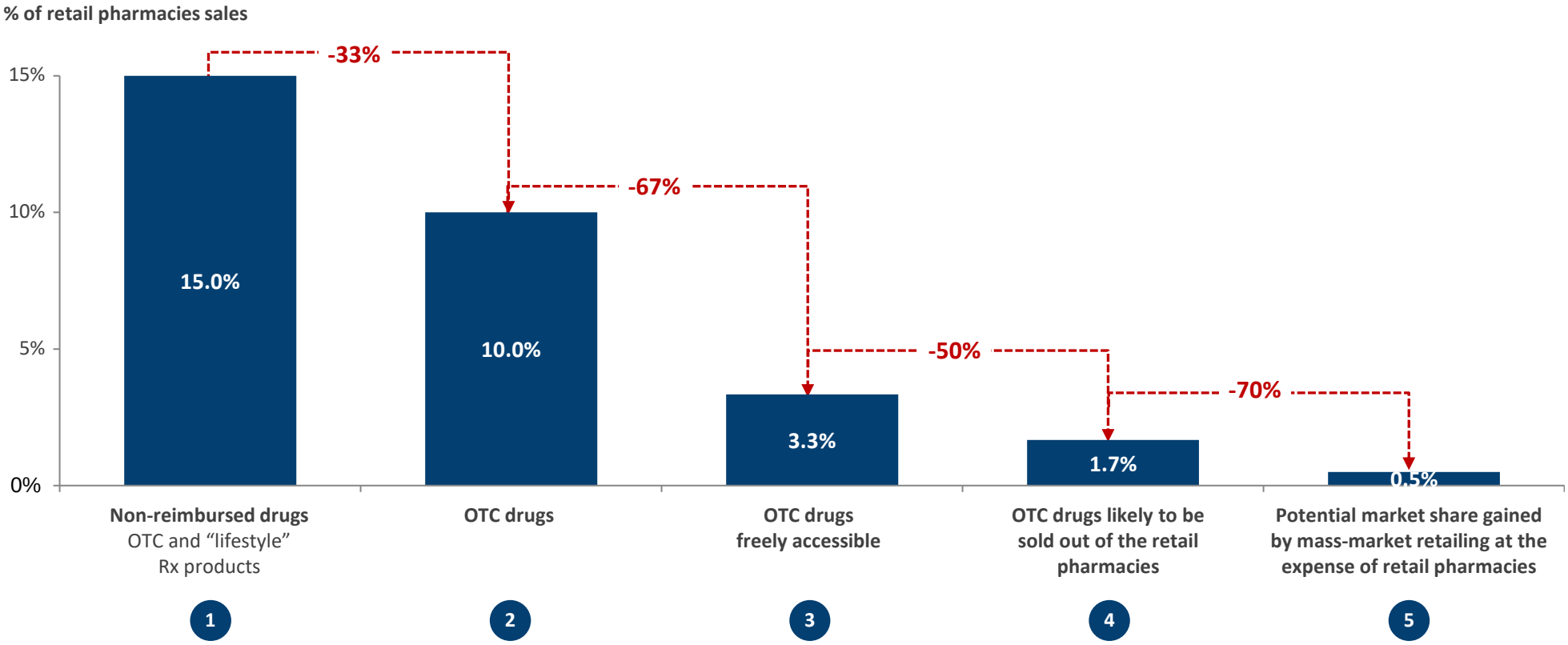
- In **Europe**, the **opening** of the **monopoly** is generally **partial** and never concerns prescription drugs
- Drug sales in **mass-market retailing** (e.g., **supermarkets**, **drugstores**, **specialized stores**) is most often limited to a list of **self-medication drugs**, as those currently proposed in free access in French retail pharmacies
- In France, many **reports** challenged the monopoly on self-medication drugs (e.g., the Attali report in 2008, the General Inspectorate of Finance report in 2013 or the French Competition Authority reports in 2014 and, more recently, in 2019)
- **E-Leclerc** chain also regularly calls for the end of the monopoly on self-medication products. This has been especially the case since **2013**, when the authorization to sell non-prescription drugs **online** was granted to **retail pharmacists** only
- However, the successive **French governments** have always expressed their **reluctance** to sell drugs in supermarkets as it may question the **continuity of care**, especially in **rural areas**. Besides, as expressed by Agnès Buzin (the current Ministry for Health) after the latest French Competition Authority report was released in April 2019: *"drugs are **not object of everyday consumption**. There may be always **side effects** and **pharmacists** are there for that"*
- In 2014, **6 million patients** had also signed a **petition** against the opening of the monopoly that had been launched by the USPO Pharmacists Union

Sources: Desk research – Competition Authority report (April 2019) – Smart Pharma Consulting analyses

If the monopoly is challenged, we estimate that the maximum impact for French retail pharmacies would be less than 1% of their total sales, i.e., ~5% of their OTC sales

3. Regulatory environment

Monopoly – Estimated impact of French retail pharmacies monopoly loss



Sources: Smart Pharma Consulting analyses and estimates

Since January 2nd, 2013, non-prescription-bound medicines can be sold online by pharmacies under some specific conditions…

3. Regulatory environment

Monopoly – Online drugs sales – Regulation

Date of authorization	The online sale of medicines is **allowed** in France since **January 2nd, 2013**[1]
Authorized drugs	All **non-prescription-bound medicines**, either **reimbursable** if prescribed or **not reimbursable** drugs (+/- 4,300 references)
Conditions of creation and activity	▪ The **website** must be **attached** to a **physical retail pharmacy** and **managed** by the **pharmacy owner** ▪ It must be authorized by the **Regional Health Agency** (ARS) before being opened and declared to the **French Council of Pharmacists** (Ordre National des Pharmaciens) ▪ **Patients** must fill a **health status questionnaire** before placing the first order on a given website ▪ Drugs can be **either directly** sent to the patient or delivered to the **pharmacy** to which the website is attached ▪ Comply with **online commerce rules** and **good practices** set by a decree issued by the **Ministry of Health**
Evolution of the regulation	▪ In **March 2015**, a ministerial decree **limiting** the **promotion** of online pharmacies was canceled by the State Council, authorizing the **online promotion** of non-prescription bound medicines ▪ Since **July 1st, 2015**, a **unique logo** for the entire European Union appears on websites authorized to sell drugs online ▪ On **December 1st, 2016**, 2 ministerial decrees on good practices and technical rules applicable to Internet websites for the online commerce of medicinal products was published on the Official Gazette and entered into force on February 1st, 2017

Sources: Ministry of Health – French Council of Pharmacists – AFIPA – GERS – Decree of December 19th, 2012 – Competition Authority reports – Smart Pharma Consulting analyses

[1] *Published in the Official Gazette on December 21st, 2012*

… but corresponding sales remain limited, as online purchases are estimated to represent about 2% of the total self-medication purchases

3. Regulatory environment

Monopoly – Online drugs sales – Key Facts & Figures

Number of authorized websites

- As of **January 2021, 689** websites[1] are officially authorized by Regional Healthcare Agencies (ARS) and published by the French Council of Pharmacists (Ordre National des Pharmaciens)

Performance

- According to French Council of Pharmacists, online purchases represented in 2017 **about 2% of the total self-medication** purchases in France
- In comparison, the online channel represents up to **18% of the total self-medication** purchases in **Germany** or in the **UK** (where online drug purchases have been authorized since 2004 and 2000, respectively)

Patients' behavior

- Experience of online purchases: according to various studies, **~10% of French people** have already bought non-prescription-bound medicines online
- Willingness to purchase online in 2015: **45% of patients** declared to consider drugs purchase online vs. **30% in 2013** and **13% in 2012**

Key drivers for online purchases

- **Convenience**: home delivery in **24 to 48 hours**
- Possibility to **compare prices (with platforms like Unooc)**
- **Lower prices** than those in physical retail pharmacies

Sources: French Council of Pharmacists – IRACM – IFOP for Giphar (April 2016) – Quotidien du Pharmacien (July 2019) – Smart Pharma Consulting analyses

[1] Compared to 431 on September 2017

Various government reports have advocated the opening of the capital of pharmacies but it does not seem that there is any real political will to adopt such a law

3. Regulatory environment

Capital – Situation

Current regulation

- In **Europe**, although some countries have made the choice to reduce the ownership of retail pharmacies capital **to pharmacists**, as in **France**, other countries have chosen to open the capital of retail pharmacies to **non-pharmacists**, leading to the creation of drug chains (e.g., **UK**, **Netherlands**, etc.)
- In this context, and since the early 2000s, various **government reports** aimed at modernizing the French economy (e.g., Beigbeder, Attali and Longuet reports) **recommended** the **opening** of the **capital** to **non-pharmacists** …
- … like the **European Commission** which, in March 2007, put France and other countries in need of **liberalization**
- Subsequently, the **European Court of Justice** was solicited on similar cases in Italy and Germany. It ruled that a pharmacist *"is supposed to operate the pharmacy **not for a purely economic purpose**, but also for a **professional purpose** related to his **medical training**. The **subordination** of pharmacists, as **employees**, to an **outside operator** could make it **difficult** to **oppose** the **instructions** given"*
- More recently, in October 2014, the **Ferrand report** submitted to the Minister of the Economy, recommended *"to allow the **opening** of the capital of the liberal exercise societies (SEL) within the health professions, subject to the respect of the rules of incompatibility"*
- The negotiations following the Ferrand report are today in the spirit of **compromise**, with the possibility of opening up the capital to the **employees of the pharmacy only**

Sources: Press release n° 44/09 from the Court of Justice of the European Communities –Ferrand report (October 2014) – La distribution au détail du médicament au sein de l'Union Européenne: un croisement entre santé et commerce, CAIRN – Le Quotidien du Pharmacien (13/10/2014) –Smart Pharma Consulting analyses

Since November 2019, retail pharmacists must report to the French Council of Pharmacists all agreements / amendments signed with their related parties (including lenders)

3. Regulatory environment

Capital – Recent measure

The "Transparency" amendment (July 2019)

- On July 24th, 2019, the article L4221-19 of the French Public Health Code was amended to increase transparency on the agreements that may signed between pharmacy owners and non-pharmacists (e.g., investment funds)
- The amended article is written as follows:
  - *"Pharmacists must **communicate** to the French Council of Pharmacists, in addition to the statutes of their pharmacy and their endorsements, all **agreements** and corresponding **amendments** related to their operations with related parties, including **partners** and, when applicable, **lenders** contributing to the funding of their pharmacy"*
  - *"These documents must be communicated **within one month** after the signature of the agreement or amendment"*
  - *"Contractual provisions which are **incompatible** with the rules of the profession, or which may **deprive** the contracting parties of their professional **independence** render them liable to the **disciplinary sanctions** provided for in Article L. 4234-6 of the French Public Health Code"*[1]
- This amendment came into force from **November 1, 2019**

Sources: Legifrance –Smart Pharma Consulting analyses

[1] *Penalties up to the prohibition from exercising*

The authorization to set up a pharmacy in a city depends on the number of inhabitants and any creation, grouping or transfer is subject to the issue of a license

3. Regulatory environment

Quorum – Situation

Current regulation

- In France, the **authorization** to **establish** a **retail pharmacy** in a city depends on the **number of inhabitants** identified in the city where it will be located, in accordance with the ***numerus clausus***
- The **opening** of a pharmacy, by **transfer** or **creation**, is possible in cities with **over 2,500 inhabitants** (or 3,500 in Guyana, Moselle and Alsace and 7,500 for Mayotte). Then, the opening or transfer of new pharmacies is allowed for every **4,500 inhabitants**. Thus, a **second** pharmacy can in a city with more than **7,000 inhabitants**
- The establishment of a pharmacy in a city of **less than 2,500 inhabitants** is **not allowed unless** the city previously had a pharmacy that served more than 2,500 inhabitants
- The **transfer** of a pharmacy to **another city** is possible only if the city of origin has **fewer than 2,500 inhabitants**, if there is only **one pharmacy** or a population of less than **4,500 inhabitants per additional pharmacy**
- Any transfer, grouping or creation of pharmacies is subject to the issue of a license by the **Regional Health Agency** (ARS)
- In some cases, the **regional Prefect** may also impose a minimum distance between the pharmacies of the district where the transfer takes place

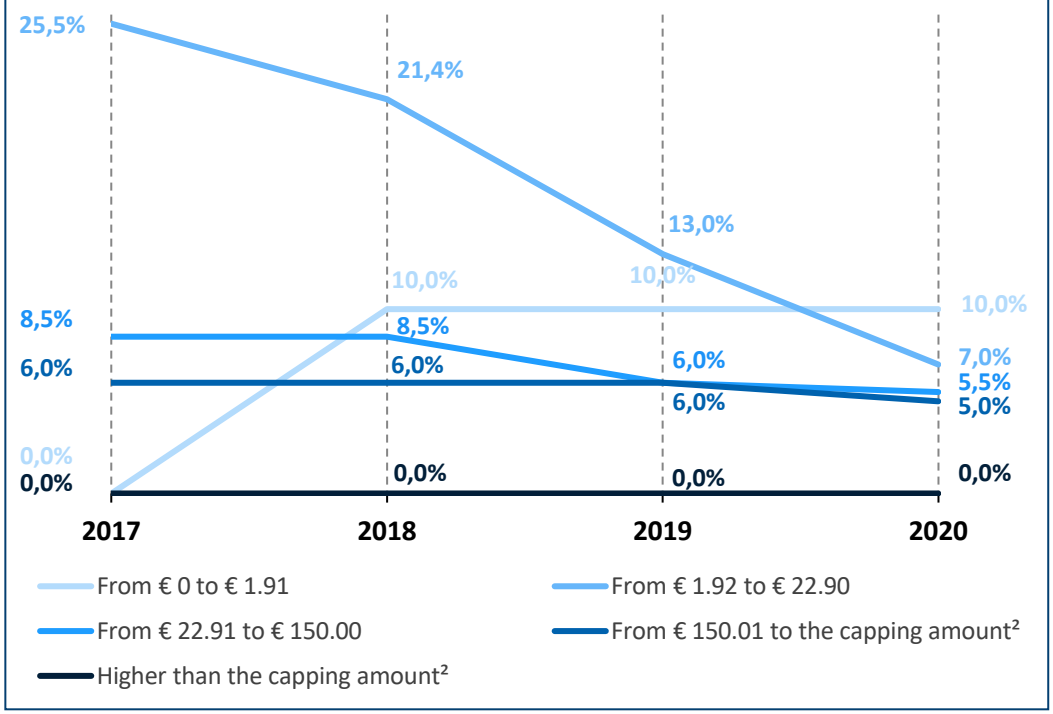
Sources: Public service website (September 2019) – Smart Pharma Consulting analyses

The revision of the smoothed digressive margin is part of a decorrelation process between the economy of retail pharmacies and the price of reimbursed drugs

3. Regulatory environment

Retail pharmacists' margins and fees for reimbursed drugs – Excluding rebates

Evolution of the smoothed digressive margin on ex-factory price[1] (2017-2020)



- The main priority of the 11th amendment[3] to the National Pharmaceutical Agreement is to change the remuneration of retail pharmacies and make them **less dependent on the price and volume of reimbursable drugs**
- Thus, it proposes **progressive transfer** to **new forms of remuneration** related to dispensing and to the improvement of patients' management

New dispensing fees	2019[1]	2020[1]
Fees for the delivery of a prescription	€ 0.50	€ 0.50
Fees related to the age of the patient (youth children and elderly people)	€ 0.50	€ 1.55
Fees for the delivery of specific drugs (e.g., immunosuppressive drugs)	€ 2.00	€ 3.50

New missions	Remuneration (2019)
Medication reports for elderly people taking more than 5 drugs	€ 60 for the initial interview and then € 30[4] or € 20[4]
Belonging to a primary care team	€ 420 per year
Share medical file	€ 1 per open medical file

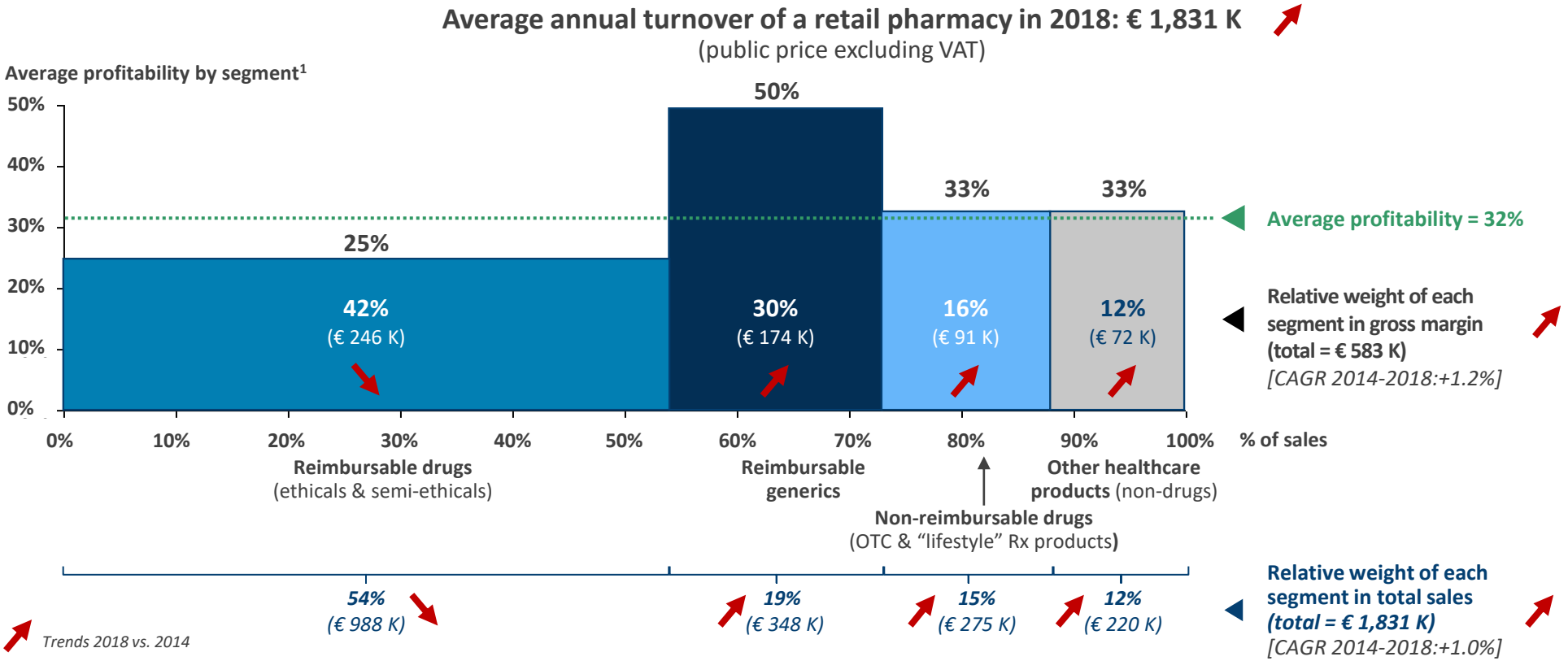
Sources: 11th amendment to the National Pharmaceutical Agreement (July 2017) – Official Gazette (September 2015, December 2017 and November 2018) – 11th Meeting of the USPO (January 2019) – Le Moniteur des pharmacies (December 2019) – Smart Pharma Consulting analyses

[1] VAT excluded – [2] Amount from which the margin is capped: €1,500 in 2017, € 1,515 in 2018, € 1,600 in 2019 and €1,930 in 2020 – [3] The amendment was signed by only 1 of the 3 French pharmaceutical unions – [4] Whether new treatments are initiated in subsequent years or not

In 2018, reimbursable originators accounted on average for ~54% of retail pharmacies sales and ~42% of their gross margin

4. Sector financial performance

Economic structure of retail pharmacies in France (2018)



Sources: CGP Experts Comptables – KPMG – Smart Pharma Consulting estimates

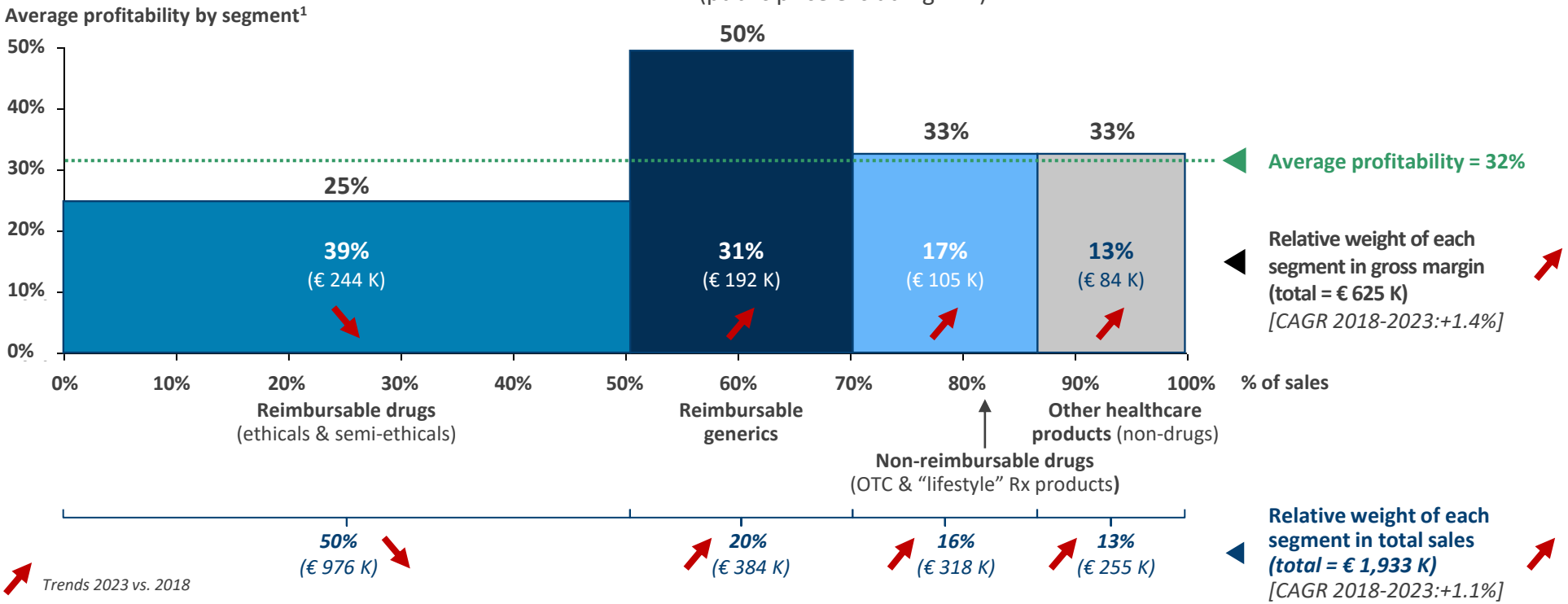
[1] Inclusive of legal margin, rebates, commercial agreements and remuneration for pharmaceutical services, notably those corresponding to the public health objectives (e.g., generics substitution objectives, pharmaceutical interviews with patients, etc.)

In 2023, reimbursable originators should account on average for ~50% of retail pharmacies sales and ~39% of their gross margin

4. Sector financial performance

Economic structure of retail pharmacies in France (2023)

Average annual turnover of a retail pharmacy in 2023: € 1,933 K
(public price excluding VAT)



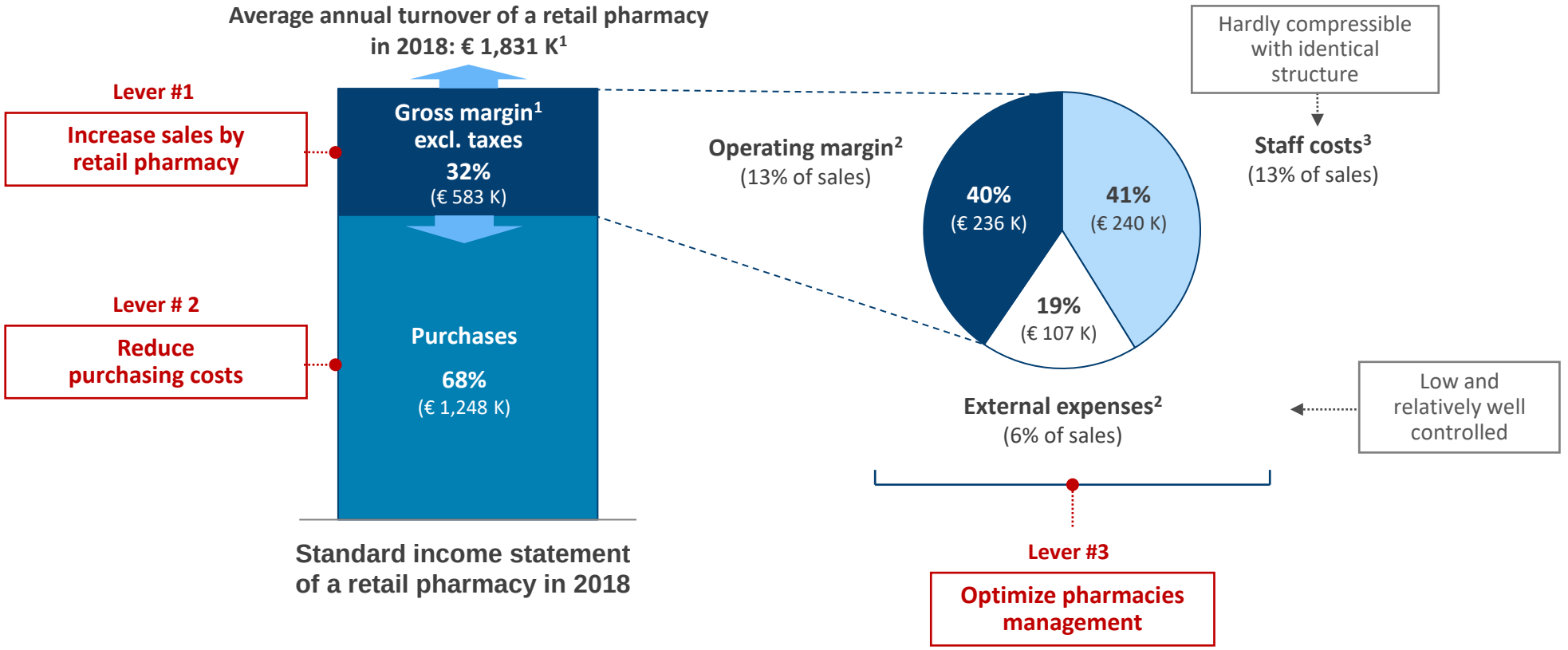
Sources: CGP Experts Comptables – KPMG – Smart Pharma Consulting estimates

[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.)

The revitalization of sales (by the expansion of products and services offering) as well as cost and management optimization are the key levers to protect / increase profits

4. Sector financial performance

Optimization levers by retail pharmacy



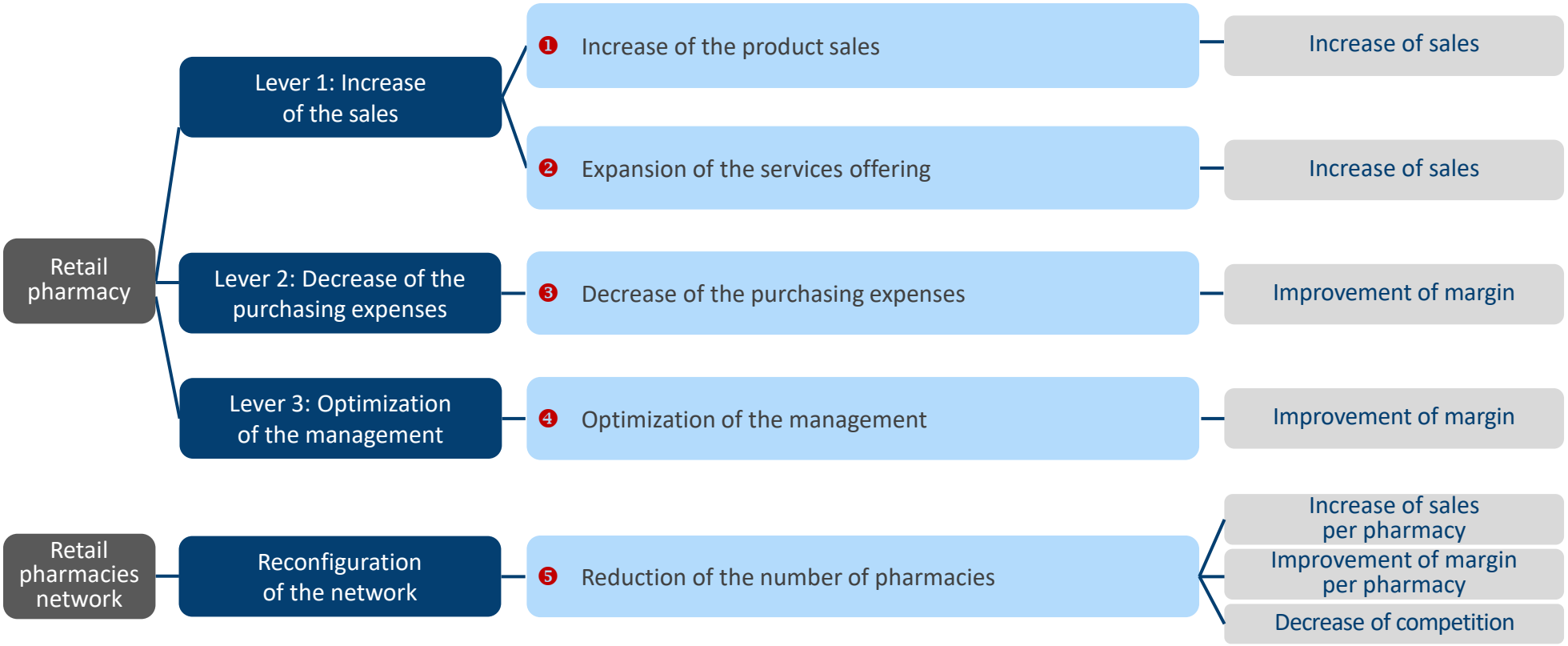
Sources: CGP Experts Comptables (2019) – Smart Pharma Consulting analyses

[1] Including dispensing fees and other remunerations (e.g., ROSP) which averaged ~€ 187 K per retail pharmacy in 2018 – [2] Before amortization, financial expenses and dues paid to the pharmacist owner – [3] Including social charges and contribution for non-salaried workers

The room for improvement of retail pharmacies performance is important but requires to rethink and reshape the role and the organization of pharmacies

5. Optimization levers

Overview of levers and solutions to improve retail pharmacies performance



Sources: Smart Pharma Consulting analyses

Retail pharmacies sales by product segment can be boosted by rigorously and systematically activating a certain number of levers

5. Optimization levers

1 Increase of the product sales

Exemples of levers

Reimbursable drugs

- **Partnership with EHPADs** (Medico-social facilities housing the elderly dependent patients for whom care at home is no longer possible)

Non-reimbursable drugs

- **Self-medication:**
  - **Free access**
  - **Pharmaceutical advice**

Non-prescription-bounds (i.e. OTX and OTC)

- **Online sales**

Other healthcare products (non-drugs)

- Orthopedics
- Compression stockings
- Pregnancy tests
- Baby products
- Self-tests
- First aid
- Veterinary products
- Food supplements
- Hygiene and dermo-cosmetics
- Pain patches and compresses
- Urinary incontinence
- Medical devices (e.g., insulin pumps)
- Connected objects (e.g., electronic pillbox)
- Acoustics and Optics
- Home support (MAD)

Sources: Interviews with retail pharmacists and representatives from VTOs and professional unions (September 2019) – Smart Pharma Consulting analyses

In addition to their core business focused on drugs dispensation, pharmacists should carry out new missions, notably for patients suffering from chronic diseases

5. Optimization levers

2 Expansion of the services offering

Extension of services

- **Regulatory framework:**
  - HPST law (2009)
  - National Pharmaceutical Agreement (2012)
  - National agreement on inter-professionality (2018)
  - "My Health 2022": Territorial reorganization of care (2019)

- **Supports** (tools – means – structures)**:**
  - Shared patient file (DP)
  - Connected health / Telemedicine / Telecare
  - Multidisciplinary Health Centers (MSP)
  - Healthcare networks

Prevention – Screening – Vaccination – Therapeutic education – Follow-up

- **In particular for patients suffering from chronic diseases** (e.g., patients receiving anti-vitamin K treatments (AVK) or direct-acting oral anticoagulants (AOD), long-term illness (ALD), diabetes, asthma, high blood pressure, COPD, overweight, etc.)
- **Services paid by various stakeholders:**
  - National Health Insurance / Private insurers / Mutual health organizations
  - Regional health agencies (ARS)
  - Regional unions of HCPs (URPS)
  - Pharma companies

Sources: Interviews with retail pharmacists and representatives from VTOs and professional unions (September 2019) – Smart Pharma Consulting analyses

With SRAs and CAPs, the lawmaker proposed a solution to regularize retrocession practices between retail pharmacies

5. Optimization levers

3 Decrease of the purchasing expenses

	SRA	CAP	SRA + CAP
	Grouped procurement structure	**Buying group**	**SRA supported by a CAP**
Principle	▪ The SRA has no delivery points	▪ The CAP has delivery and storage points	▪ The SRA negotiates and invoices ▪ The CAP stores and delivers
Negotiation	▪ The agent negotiates maximum purchasing conditions	▪ The CAP sales manager negotiates purchasing conditions	▪ The commissioner / agent negotiates maximum purchasing conditions
Procurement	▪ The agent purchases on behalf of its pharmacy members	▪ The CAP purchases on its behalf	▪ The commissioner / agent purchases on behalf of its pharmacy members
Delivery	▪ The pharma company delivers each retail pharmacy	▪ The pharma company delivers the CAP	▪ The pharma company delivers the CAP
Billing	▪ The pharma company invoices the SRA	▪ The pharma company invoices the CAP	▪ The pharma company invoices the SRA
Relationship with members	▪ The SRA invoices each pharmacy member	▪ The CAP delivers and invoices each pharmacy member	▪ The SRA relies on the CAP to store, delivers and invoices each pharmacy member

Note: The current regulations do not allow a retail pharmacist to buy large quantities of drugs to resell to colleagues

Sources: Decree 2009-741 (June 2009) – Le Moniteur des pharmacies (April 2012) – Smart Pharma Consulting analyses

Retail pharmacists can improve the operating result of their pharmacy by professionalizing their management methods

5. Optimization levers

4 Optimization of the management

1. Margin and price strategy

- Don't limit it to a linear multiplying coefficient policy by product class and apply:
  - A **lower coefficient** on **"sensitive" products** whose price is well known by customers, in particular those in free access
  - A **higher coefficient** on **prestige** products or on products requiring a pharmaceutical **advice**
- The selling price must include a **profitability objective** and take into account the **competition** on the **catchment area**

2. Rationalization of the activity and organization according to the catchment area

- **Adapt** the **offer** of products and services
- Adapt **opening hours** to customer expectations and competition
- **Optimize** the **layout** of the retail pharmacy to boost sales and improve circulation of customers in the selling point, based on supermarkets and hypermarkets model
- **Streamline staffing**, organization and staff time
- Assess the opportunity of **automating inventory management** (i.e., robots)

3. Professionalization of pharmacy management

- **Monitor the performance** of the retail pharmacy thanks to few relevant KPIs[1]
- Follow, if needed, a postgraduate **training** of **retail pharmacy management** (e.g., MBA, master, university diploma, certificate)

4. Financial, accounting and tax optimization

- Improve **control** over **operating costs** and **stock rotation**
- Reduce **borrowing costs** (individual contribution, short-term loan, renegotiation of the loan, if needed)
- Evaluate **tax optimization** opportunities

5. Cost sharing

- **Mutualize the cost** of **support functions** (e.g., procurement, IT, quality management, management control, treasury) with other retail pharmacies thanks to:
  - The membership in VTOs[2]
  - The creation of holdings of SELs (e.g., SPFPL)

Sources: Interviews with retail pharmacists and representatives from VTOs and professional unions (September 2019) – Smart Pharma Consulting analyses

[1] Key Performance Indicators – [2] Voluntary Trade Organizations

French pharmacists are currently experiencing a revolution which will turn them from drugs dispensers to providers of high-quality health and wellness services

6. Conclusion

Strategic priorities for retail pharmacists (1/2)

2019 – 2023 trends

1. **Government pressure** on **prices** and **volumes** of **reimbursable drugs**
2. Progressive **transfer** of the **pharmacist regulated margin** on the **price of drugs** to **fee for service**
3. **Younger generations** of **physicians** seeking to **limit** the **number** of **drugs prescribed**

Implications for retail pharmacists

- Shift from "**neighborhood pharmacists**" focused on **drug delivery**…
- … to "**health center pharmacists**" delivering **high quality services**:
  - **Prevention** / **screening** (e.g., colorectal cancer)
  - **Education** and **monitoring** of **patients** (e.g., interviews on compliance, safety, etc.)
  - **Vaccination** (e.g., influenza)
- …offering **attractive prices** for non reimbursed products (e.g., OTC, hygiene and cosmetic products)
- … and developing **customer loyalty programs** (for non-reimbursed products purchase) to retain their customers

1

Sources: Interviews with retail pharmacists and representatives from VTOs and professional unions (September 2019) – Smart Pharma Consulting analyses

Pharmacists will be more and more at the cornerstone of a coordinated management of patients, notably in rural areas deserted by physicians

6. Conclusion

Strategic priorities for retail pharmacists (2/2)

2019 – 2023 trends

4 **Shift** from **hospital** to **ambulatory** care

5 **Aging** of the population / Increase of **chronic diseases**

6 **Medical desertification** in some **rural** areas

7 **IT developments** (e.g., shared patient file, telemedicine, telecare)

2

Implications for retail pharmacists

- Need for an **efficient coordination** of pharmacists with **all key stakeholders** involved in the management of patients at **local** level, notably:
  - Physicians (GPs and specialists)
  - Nurses
  - Physiotherapists
  - Occupationnel therapists
  - Medical devices providers
- **Business extension** on dynamic segments, such as:
  - Home care
  - Home delivery
  - Insulin pumps
  - Treatments for sleep apnea
- Partnership with **EHPADs**[1]

Sources: Interviews with retail pharmacists and representatives from VTOs and professional unions (September 2019) – Smart Pharma Consulting analyses

[1] Medico-social facilities housing the elderly dependent patients for whom care at home is no longer possible

Smart Pharma
CONSULTING

Serving & Sharing with Passion

French
Biosimilars Market

MARKET INSIGHTS

Key Success Factors

POSITION PAPER June 2019

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Tel. +33 6 11 96 33 78
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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

Masterclass

- 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

Sources: Smart Pharma Consulting

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

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

Rx

Dispensation

Patients

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

Retail pharmacists

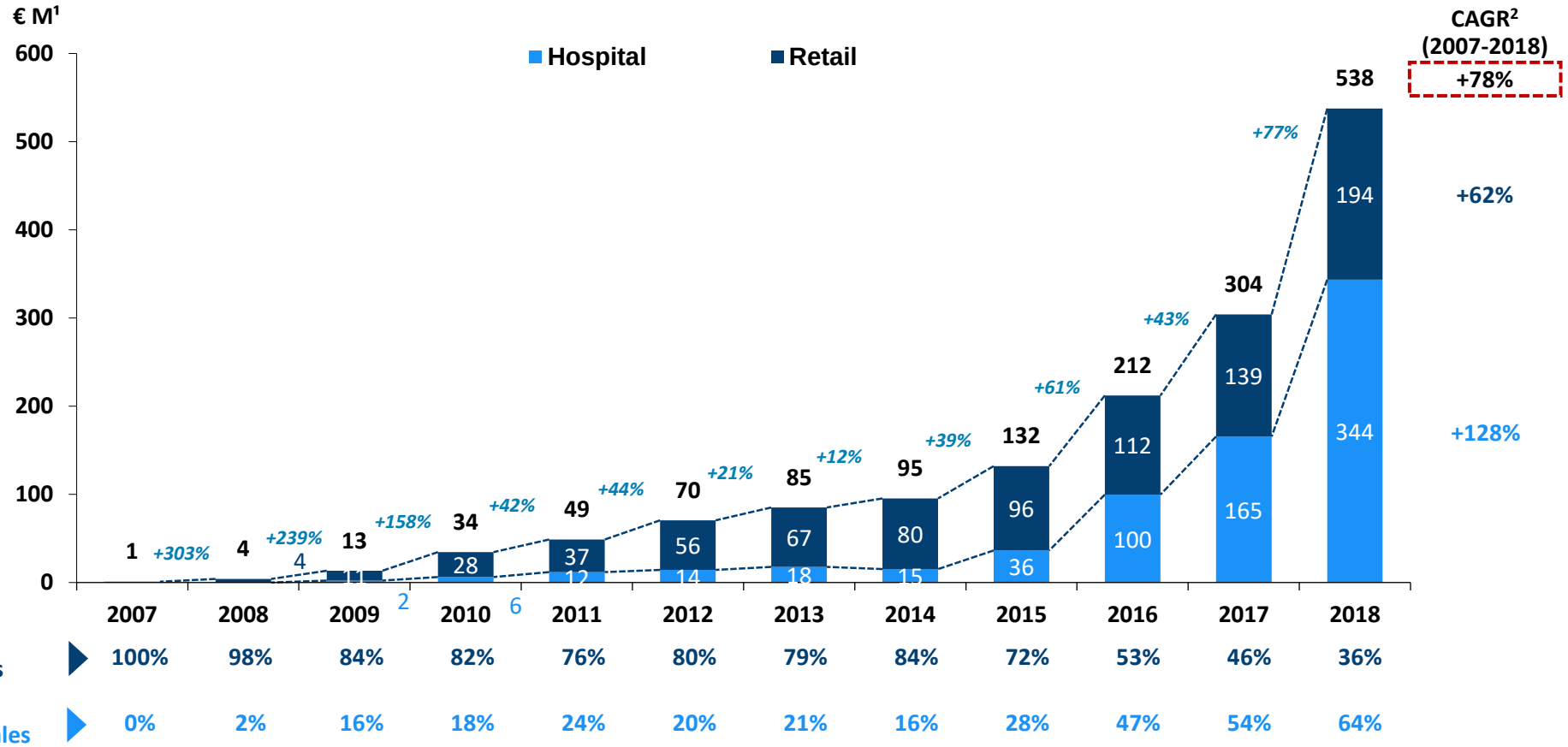
- Retail pharmacists are divided regarding the substitution of biological drugs

Sources: Smart Pharma Consulting

[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)

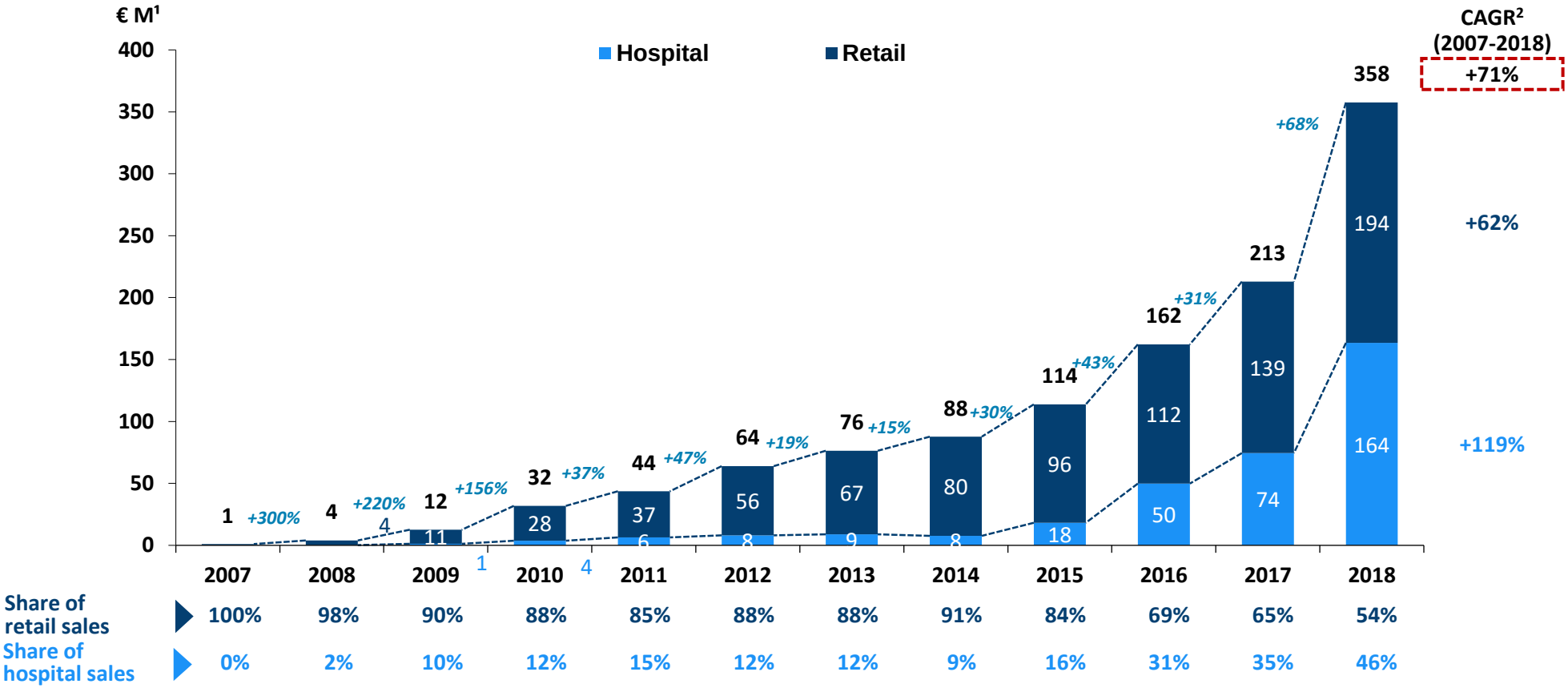


Sources: GERS – Smart Pharma Consulting analyses

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



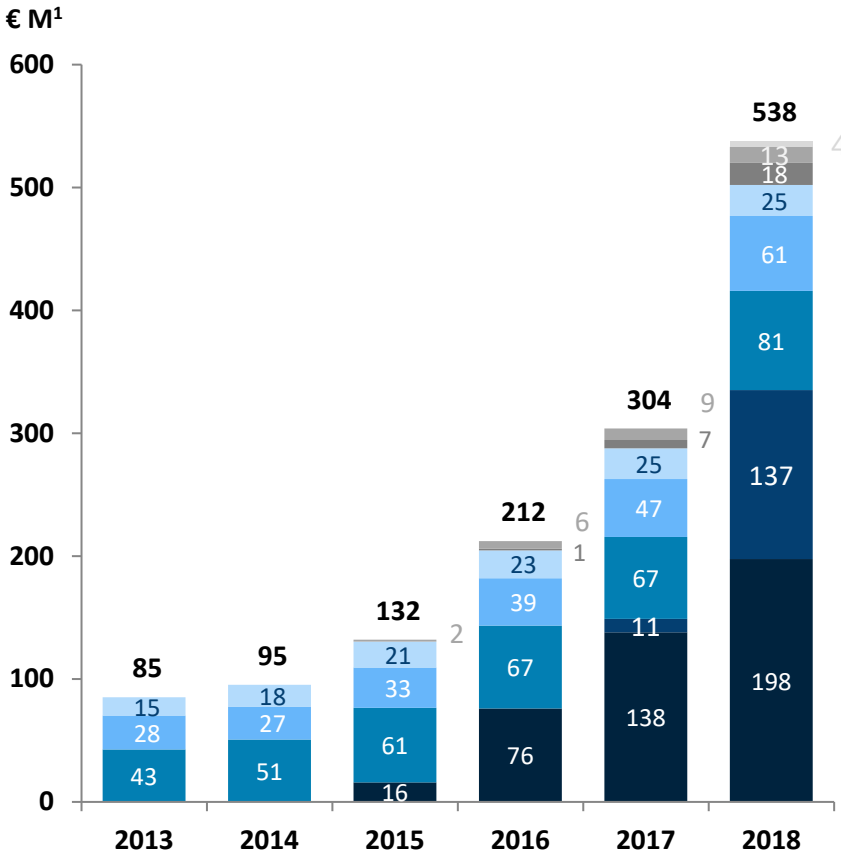
Note: In 2016, 2017 and 2018, the net prices were respectively 50%, 55% and 52% lower than the ex-factory prices excluding taxes and rebates (mainly through tenders) on the hospital market. The rebates granted in the retail market are considered as negligible

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	▪ Biogaran	▪ Sep. 2017	€ 104.8 M	€ 0.0 M	€ 104.8 M	82.2%
	▪ Rixathon	▪ Sandoz	▪ Jan. 2018	€ 18.1 M	€ 0.0 M	€ 18.1 M	
	2 products	2 companies		€ 122.8 M	€ 0.0. M	€ 122.8 M	
Trastuzumab (Herceptin, Roche)	▪ Herzuma	▪ Biogaran	▪ Jul. 2018	€ 10.7 M	€ 0.0 M	€ 10.7 M	62.3%
	▪ Ontruzant	▪ MSD	▪ Sep. 2018	€ 2.4 M	€ 0.0 M	€ 2.4 M	
	▪ Kanjinti	▪ Amgen	▪ Aug. 2018	€ 1.4 M	€ 0.0 M	€ 1.4 M	
	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)

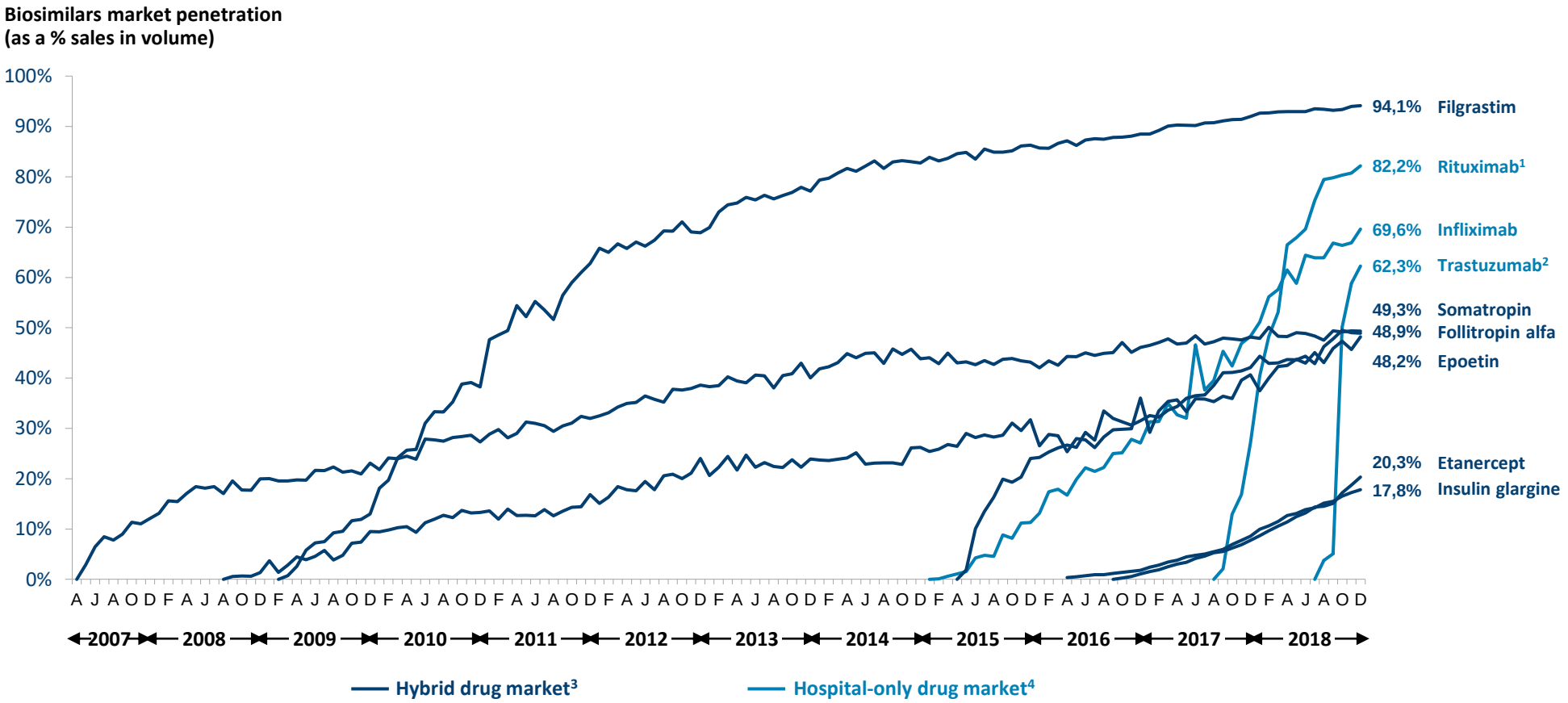
EPhMRA 4 therapeutic class	INN[1] (Originator)	Product name	Pharma company	Launch date	Hospital sales[2]	Retail sales[2]	Total sales[2]	Biosimilars penetration[3]
Erythropoiesis-stimulating agents	Epoetin (Eprex, Janssen)	▪ Binocrit ▪ Retacrit ▪ Eporatio[4]	▪ Sandoz ▪ Pfizer ▪ Teva	▪ Jul. 2008 ▪ Mar. 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



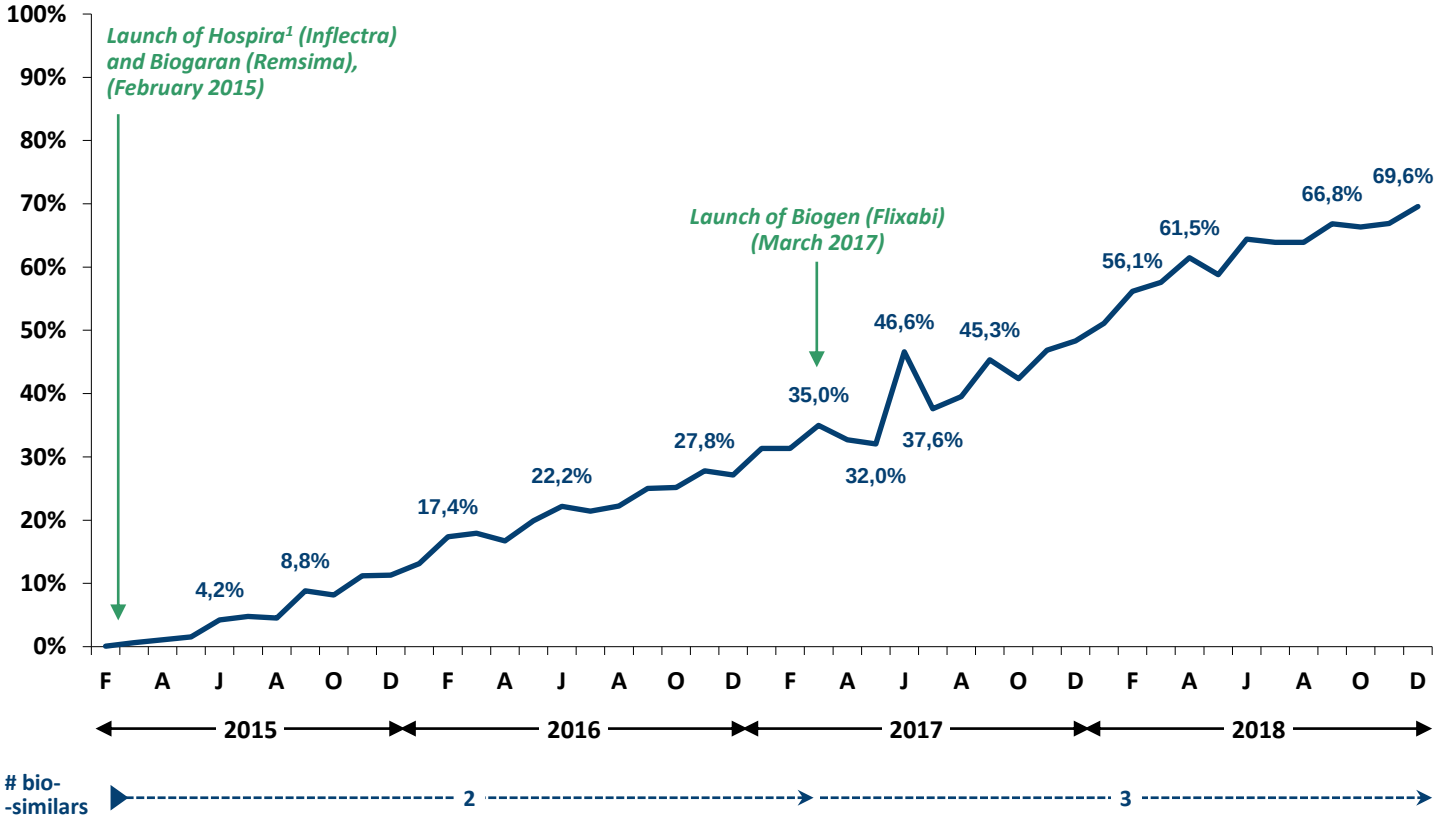
Sources: GERS – Smart Pharma Consulting analyses

[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

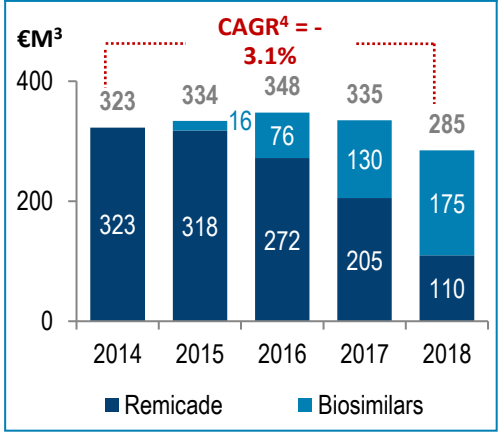
Penetration rate in volume – Infliximab case study

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

[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 October 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

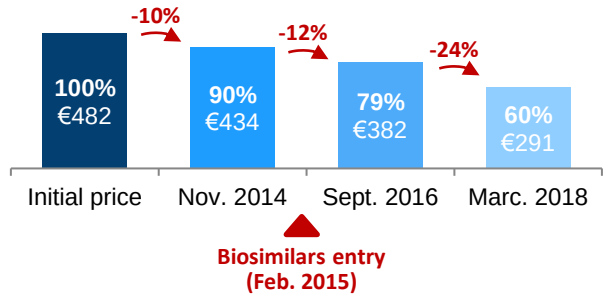
[1] CAQES: contract for healthcare quality and efficiency enhancement – [2] In December 2017, the government has set the global (hospital and retail markets) objective of 80% biosimilar penetration by 2022 – [3] Directorate of Health Care Supply – [4] Directorate of Social Security – [5] Directorate 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%

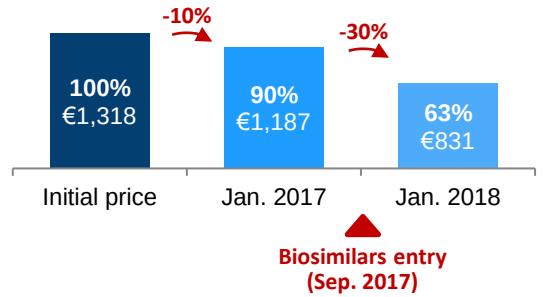
Historical imposed price cuts over time

Hospital-only products

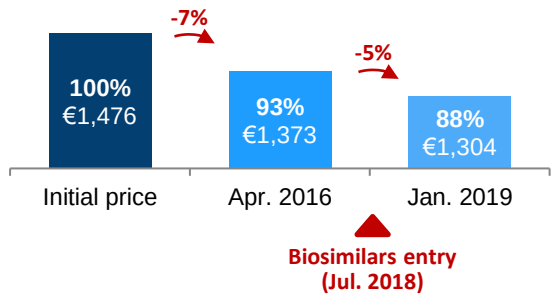
Infliximab (Remicade)



Rituximab (MabThera)

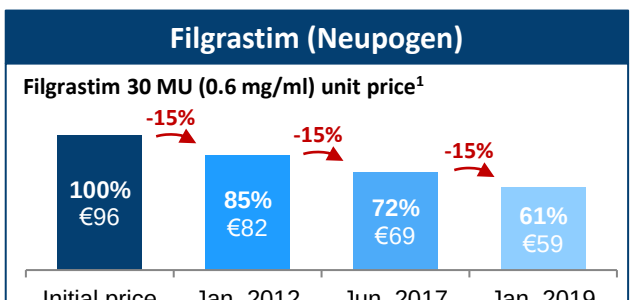


Trastuzumab (Herceptin)

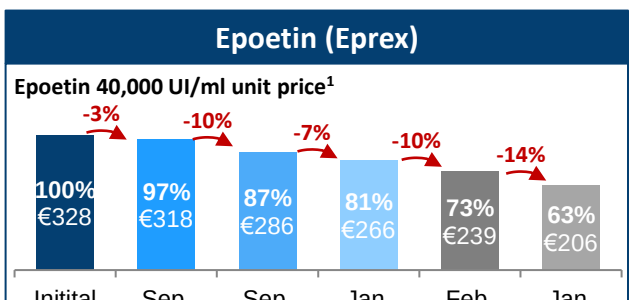


Hybrid products[2]

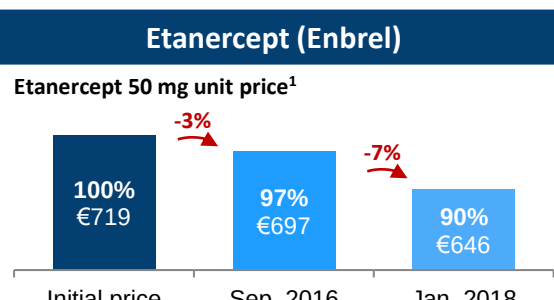
Filgrastim (Neupogen)



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 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

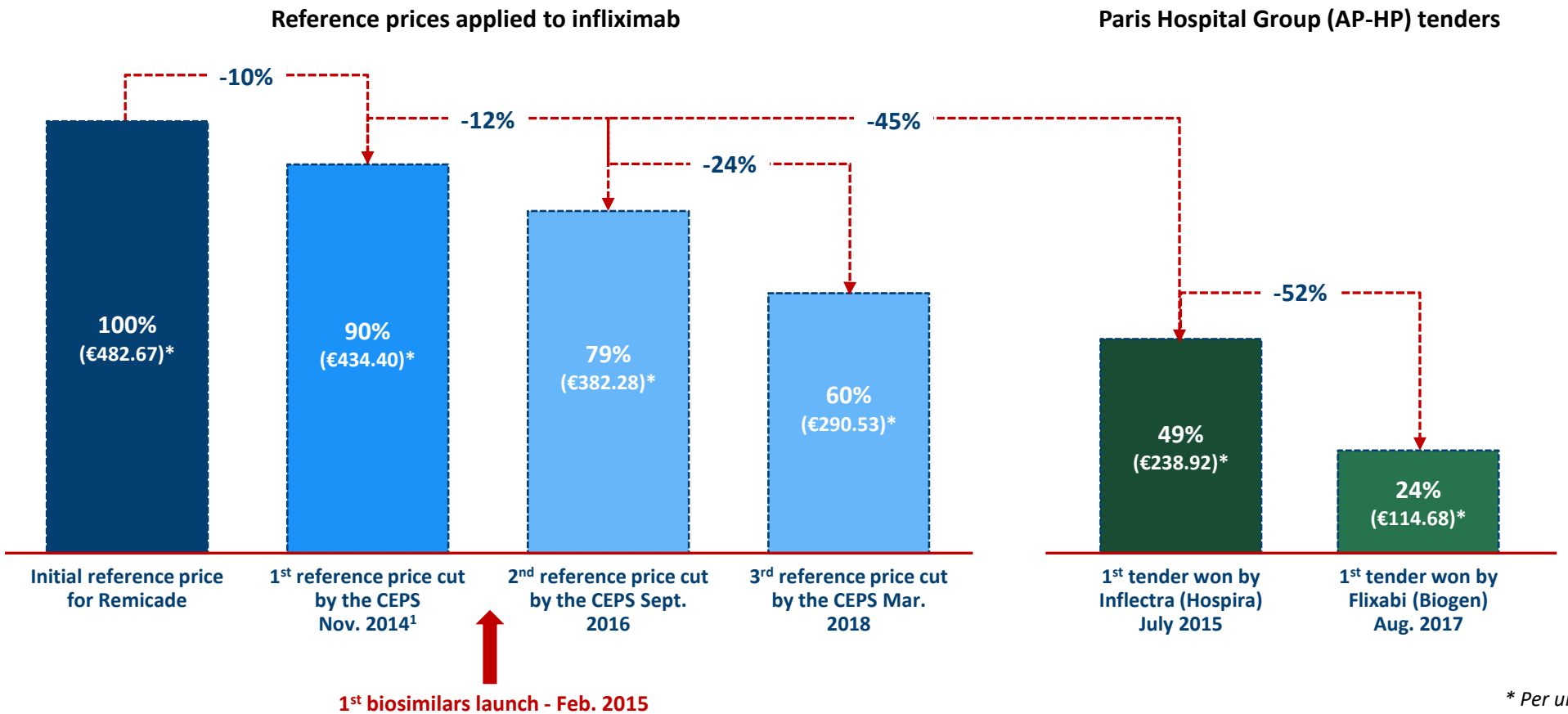
Prescription of biosimilars may help better control the cost evolution of drugs prescribed in hospital and dispensed in retail pharmacies

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*

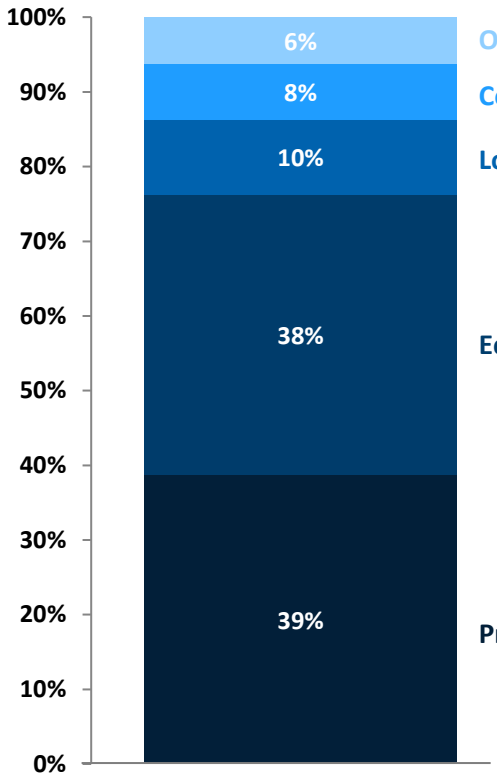
Sources: Desk research – APM News – Interviews – Smart Pharma Consulting analyses

[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

- *"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)*

Logistics aspects

- *"Are to be considered even when the volumes of drugs in hospitals remain low such as for G-CSF" (2)*

Economic aspects

- *"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

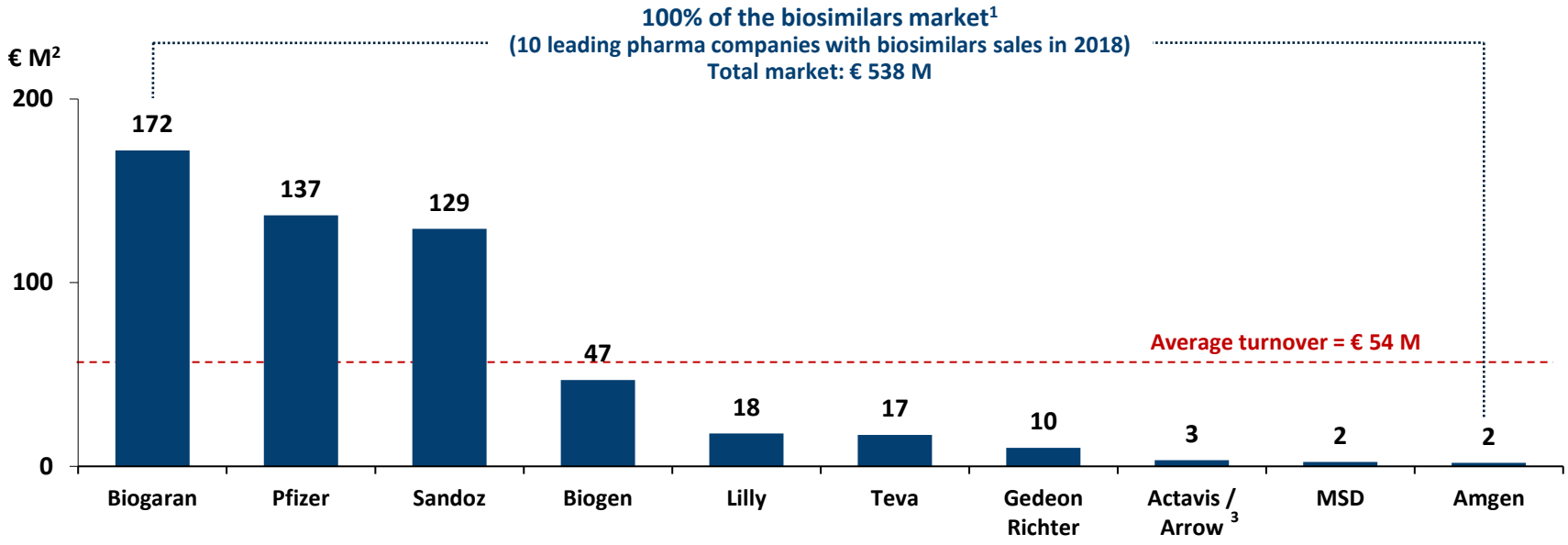
(X): Number of quotes

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)



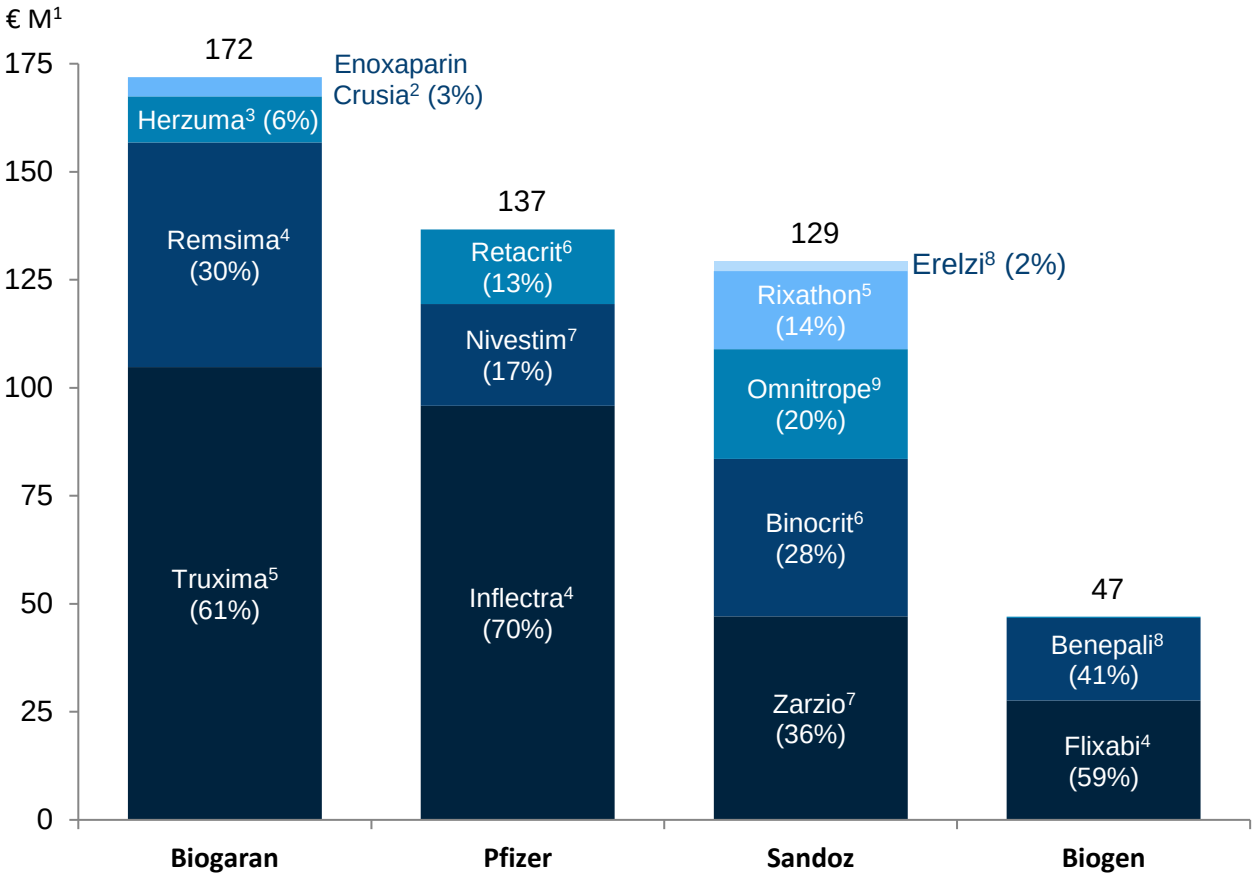
	Biogaran	Pfizer	Sandoz	Biogen	Lilly	Teva	Gedeon Richter	Actavis / Arrow [3]	MSD	Amgen
Market share	32.0%	25.4%	24.1%	8.7%	3.3%	3.2%	1.9%	0.6%	0.4%	0.4%
Biosimilars weight in the portfolio	14.2%	10.0%	19.2%	12.3%	5.0%	2.5%	66.9%	0.7%	0.2%	0.3%
2017-2018 evolution	+277.5%	+7.2%	+46.4%	+277.4%	+161.9%	+11.3%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

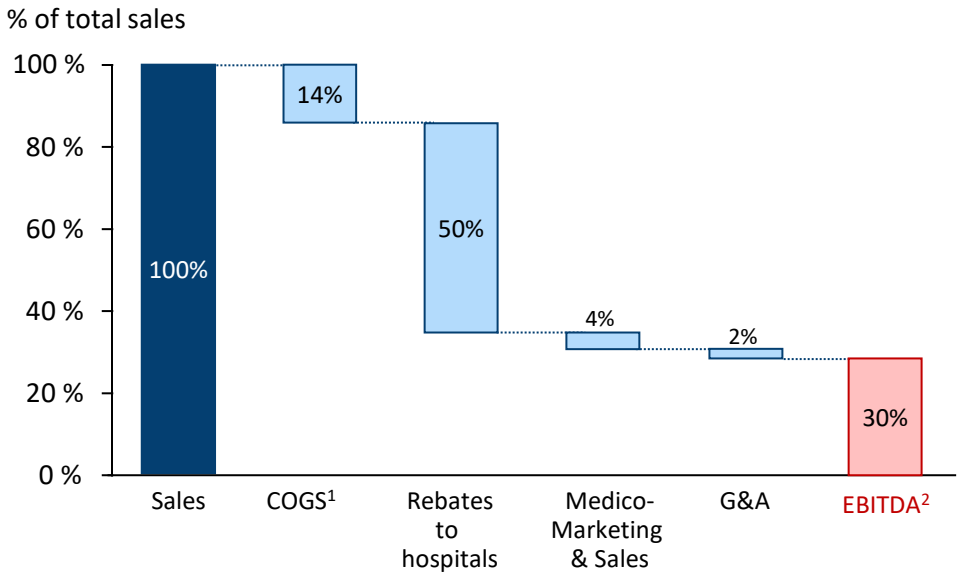
Sources: GERS – Smart Pharma Consulting analyses

[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

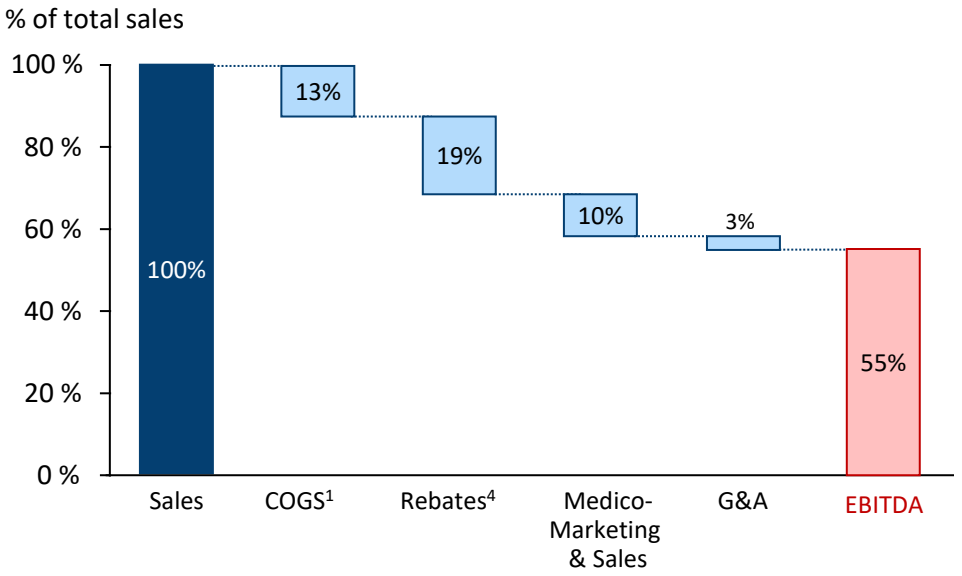
Estimated profitability of leading pharma companies on the biosimilars market (2018)

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. 83 to 86)
- 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

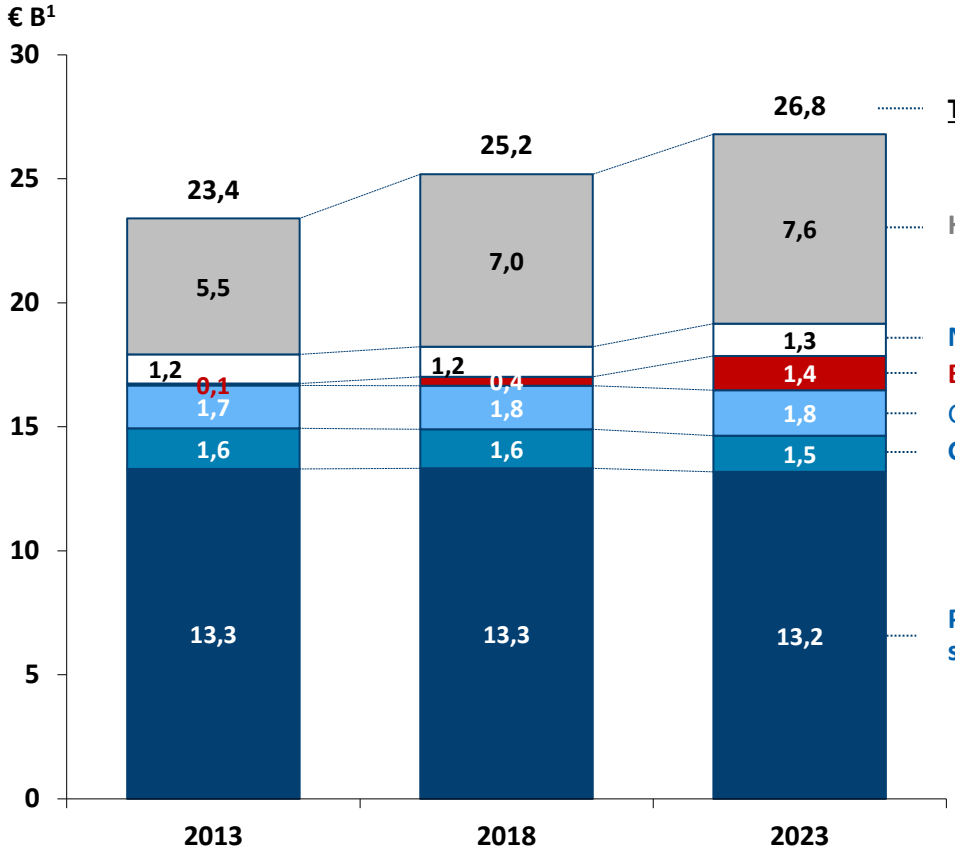
- There are possibilities to differentiate biosimilars amongst themselves and vs. the corresponding original biologic:
  - Amgevita (Amgen) and Hulio (Mylan) propose a citrate-free version of adalimumab, as Humira (AbbVie)[1] does since 2018, associated with less injection site-related pain[2]
  - Benepali (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

Executive summary

1. The market structure and dynamics

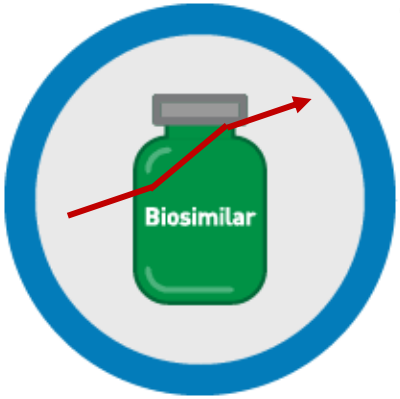
- Since 2014, the market has increased four-fold[1]
- The penetration of hospital-only biosimilars is must higher than the one of biosimilars which are also delivered on the retail market

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

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)



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

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

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

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

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in the complementary domains of strategy, management and organization

The Collection 2021

- The "Collection 2021" which includes Smart Pharma Consulting best position papers, is published on its 20th anniversary
- This e-book proposes effective and practical solutions to help pharma companies improve their performance
- Its content will be released in six parts, overt the 4th quarter 2021:

1. Market Insights
2. Strategy & Market Access
3. Medical Affairs & Marketing
4. Sales Force Effectiveness
5. Management
6. Training Programs

Part 1

Market Insights

Concepts – Methods – Tools

- This 1st part of Smart Pharma Consulting's best position papers, covers the following topics:
  - Pharma Market Insight Studies
  - French Pharma Market 2020 – 2025
  - Global Pharma Market & Covid-19 Impact
  - French Retail Pharmacies
  - French Biosimilars Market

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  - 10 position papers in the "Smart Tool Series"
  - 10 position papers in the "Smart Manager Series"
- Our research activities in pharma business management and our consulting activities have shown to be highly synergistic
- We hope that this new publication will be useful for you
- We remain at your disposal to carry out consulting projects or training seminars to help you improve your operations

Best regards

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