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Study of API supply vulnerabilities for the European pharmaceutical industry
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Final Report

July 2021

Executive summary (1/2)

- Global pharmaceutical demand is expected to grow by **4% per year by 2025**, driven mainly by 7 major therapeutic areas
- To ensure this growing demand is met in a heavily regulated environment, a **complex globalized and fragmented chain** of sub-components has emerged throughout time
- Against the constant pressure on price and production constraints in Europe, part of the API production has **progressively moved to Asia** where manufacturers are specialized in high volume and low margin production - Investment and operating costs for active ingredients are indeed **20-40% lower in Asia**, favoring the relocation of production capacities there
- This competition impacts European players, their **VA deteriorating** due to a potential **mature product portfolio or stronger negotiating power of suppliers –** this results in **a deteriorating competitiveness**, increasing reports of **tensions**, and **sovereignty undermined** by major sanitary crises
- The analysis of the value chain and the health stake of APIs allows us to identify **5 main segments with differentiated vulnerabilities**:
  - APIs facing **fragile input supplies**
  - APIs with **complex production** chains that are difficult to control
  - APIs relying on **production including pollutants to treat**, whose production cost to meet European standards would be prohibitive
  - APIs facing **low price levels** that do not allow for a sustainable economic positioning
  - APIs with **unstable demand** that does not provide the necessary visibility to manufacturers

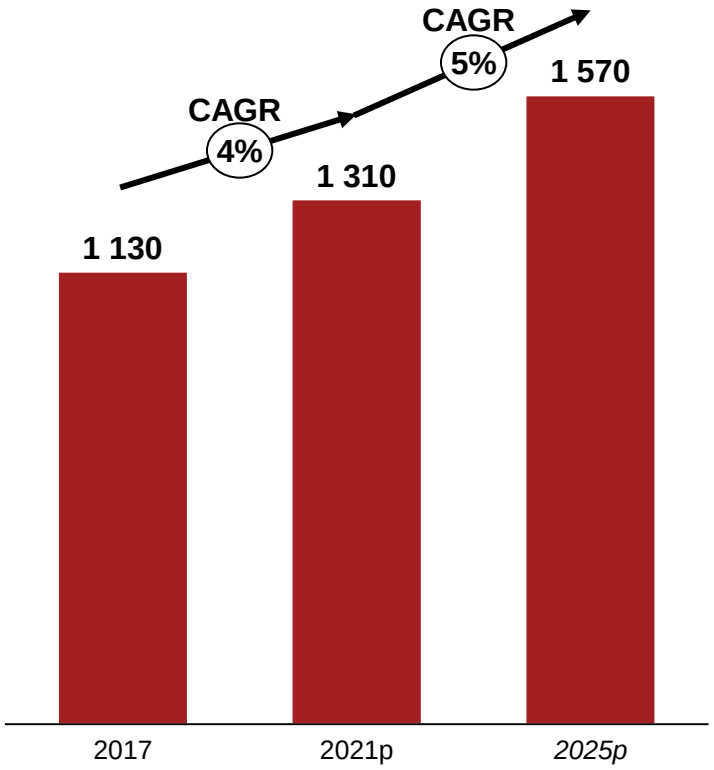
Executive summary (2/2)

- The proposed measures address all the vulnerabilities identified in the API value chain:
  - Measures are in place to better manage a crisis when it arrives by limiting **shortages** thanks to the strengthening of the **security of supply in the short-term and information sharing at European level**
  - Other measures contribute towards **the valorisation of additional criteria other than the only price criteria** in tenders and developing **funding policies for medicines**
  - Measures to build a **sustainable, safe and environmentally friendly production** in Europe
- Innovation including on mature APIs is also an amazing lever to durably improve the offer - support to innovation must allow to limit the **impact on the production costs and create sustainable value in Europe**
- This support to innovation should also facilitate the emergence of **disruptive innovations** that respond to **identified market failures and restore the leadership position of Europe in the Health industry**
- In order to help finance them, the **Health IPCEI** would make it possible to **support and accelerate these innovations** up to the FID
- IPCEI raises European funds to finance **disruptive technologies** that enhance EU sovereignty and the innovations identified **meet the criteria of the Health IPCEI** and could provide significant and lasting added value for Europe in the framework of its pharmaceutical strategy

Global pharmaceutical demand is expected to grow by 4% per year by 2025, driven mainly by 7 major therapeutic areas

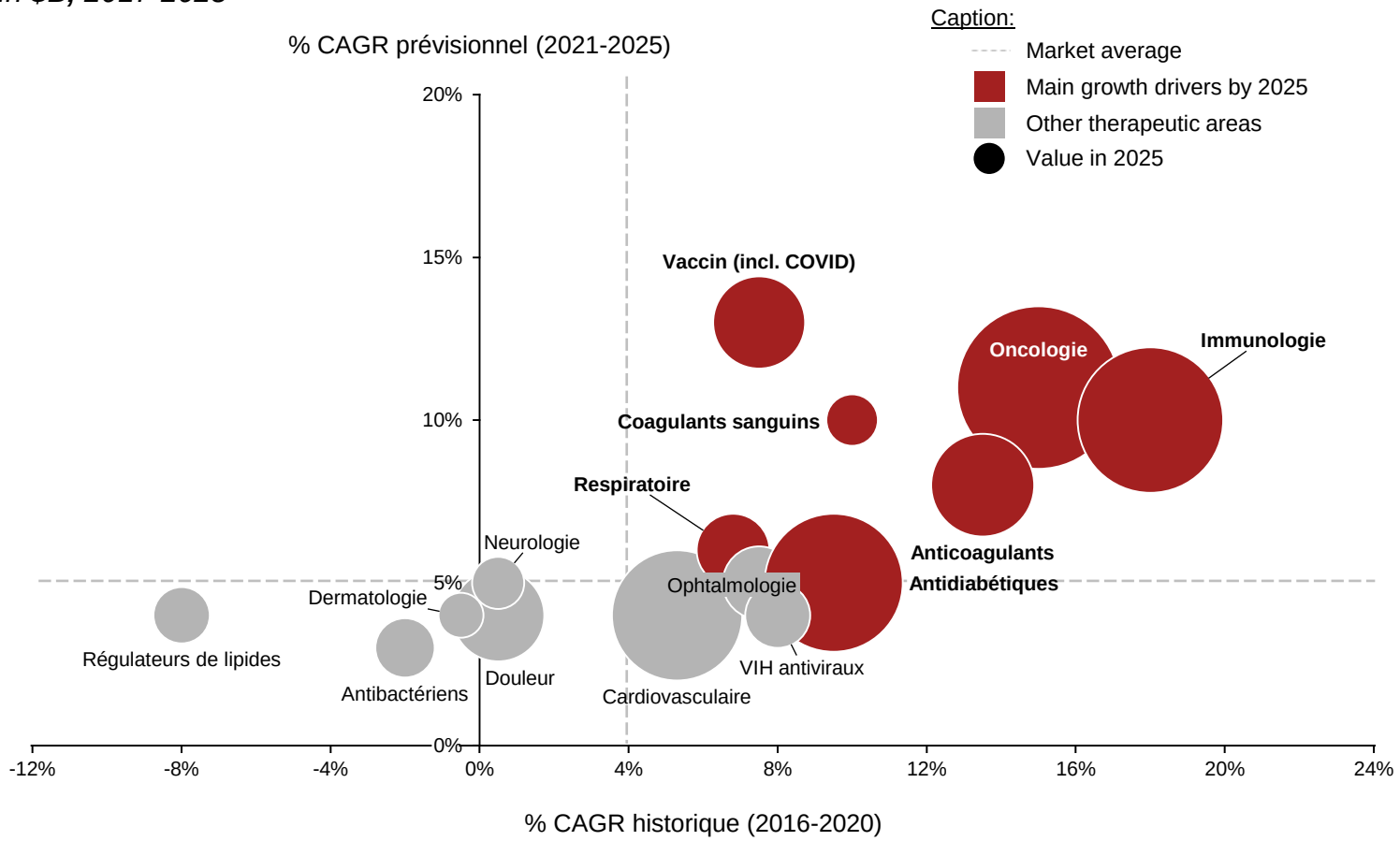
Global Pharmaceutical Expenses

In $B, 2017-2025



Growth in expenses by therapeutic area

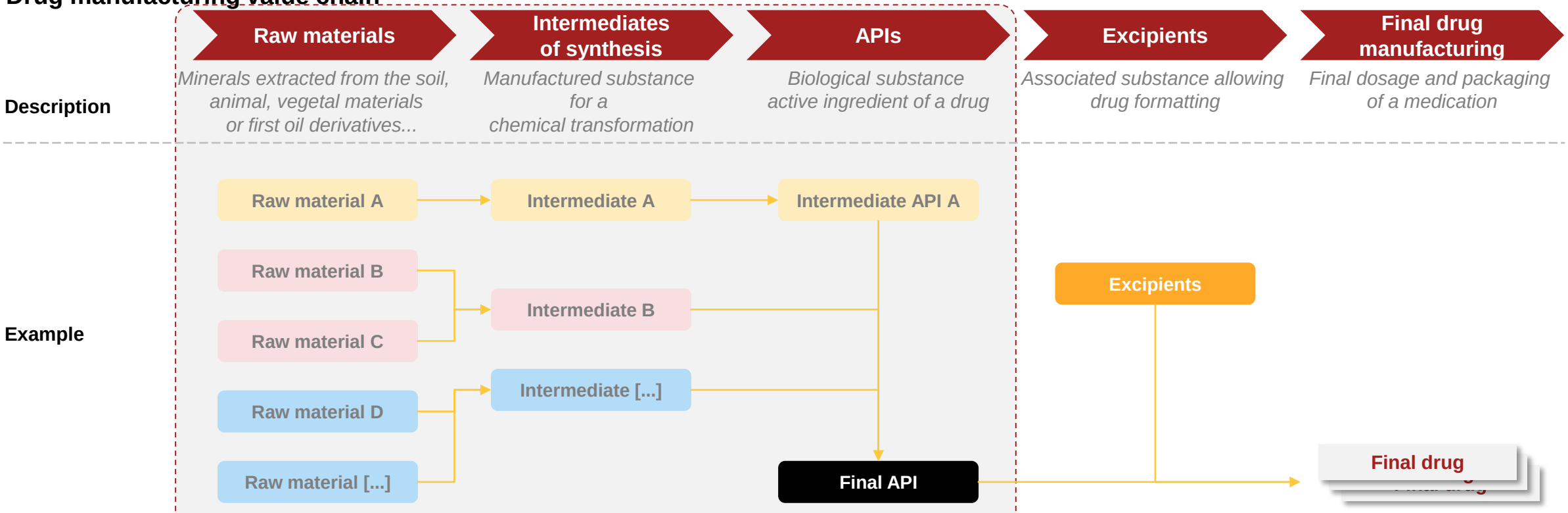
In $B, 2017-2025



Sources: IQVIA, Strategy Analyses&

To ensure this growing demand is met in a heavily regulated environment, a complex globalized and fragmented chain of sub-components has emerged throughout time

Drug manufacturing value chain

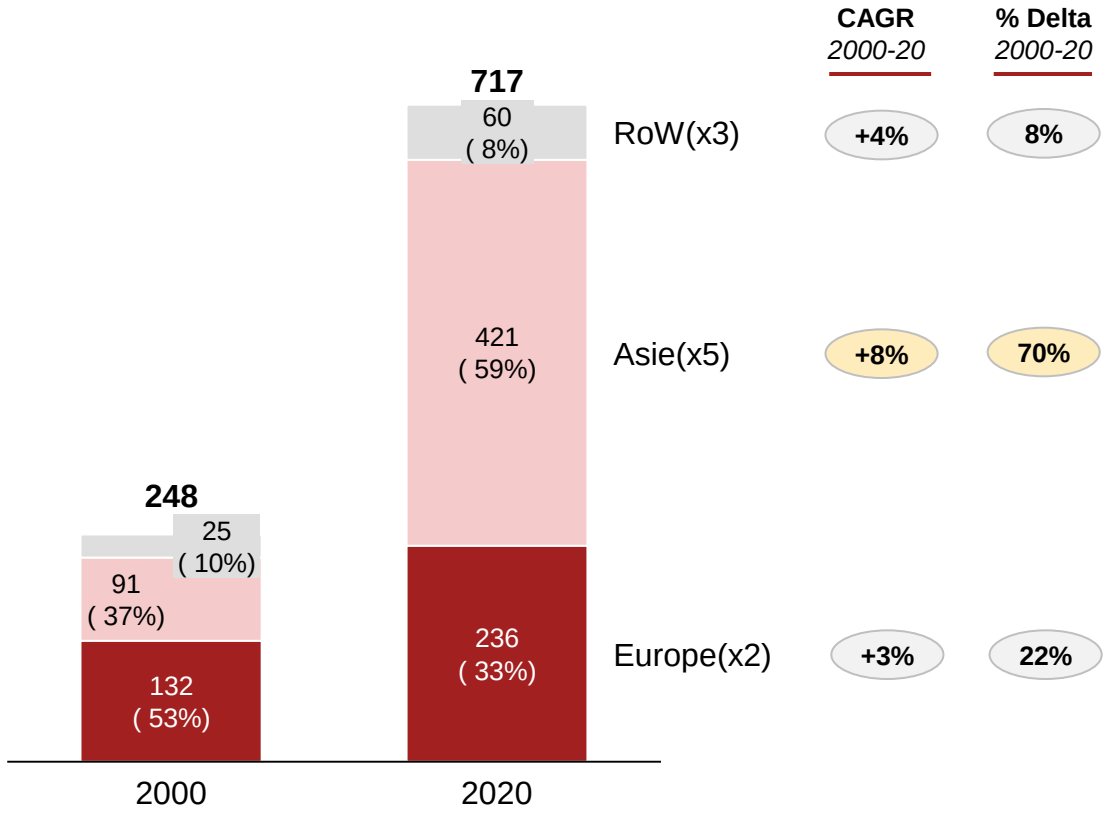


Sources: EFCG, SICOS, LEEM, G5 Santé, Analyses Strategy&

Part of the API production has progressively moved to Asia where manufacturers are specialized in high volume and low margin production

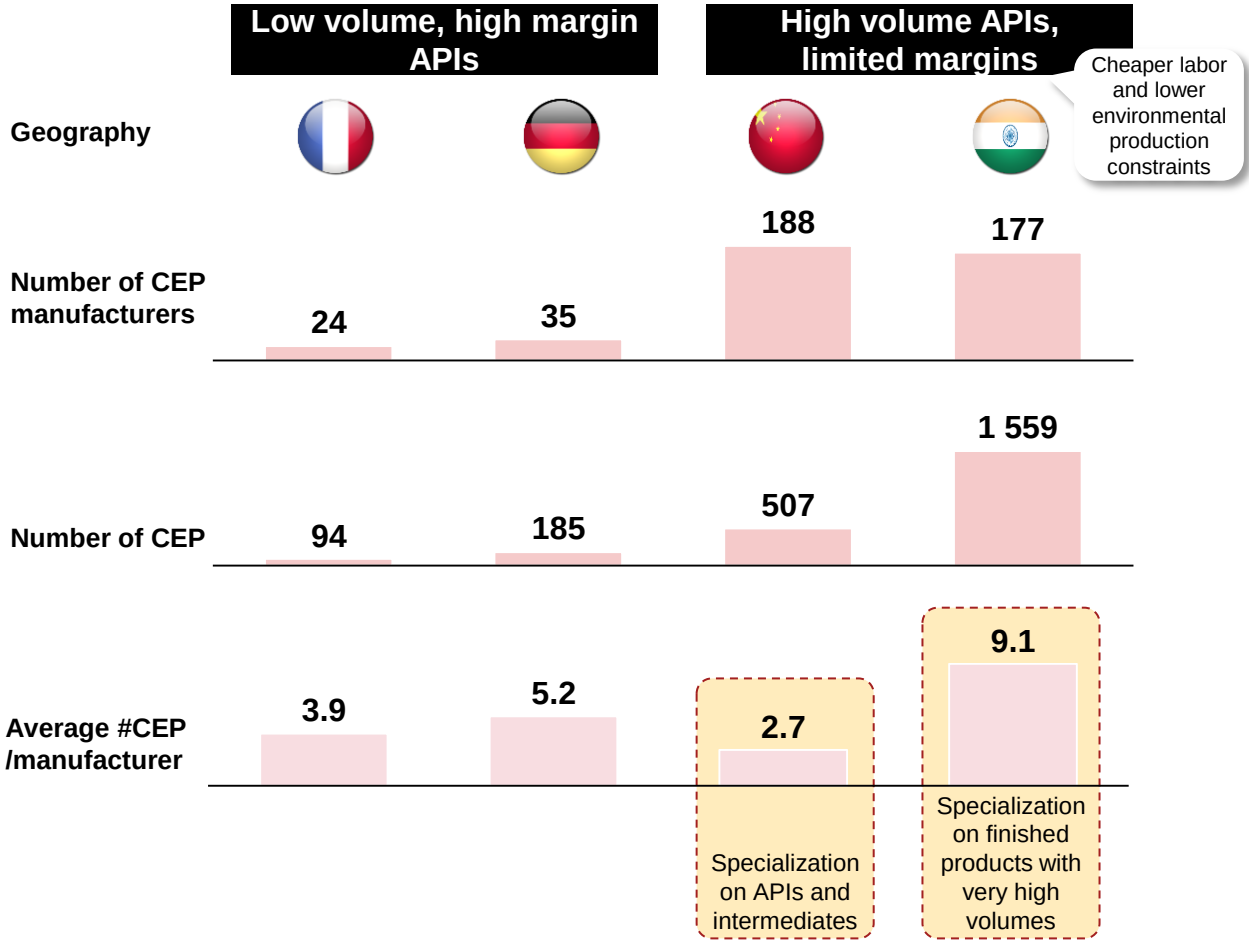
Distribution of CEP manufacturers in the world

In #Manufacturers, 2000-2020



Benchmark and CEP manufacturers by region

2020

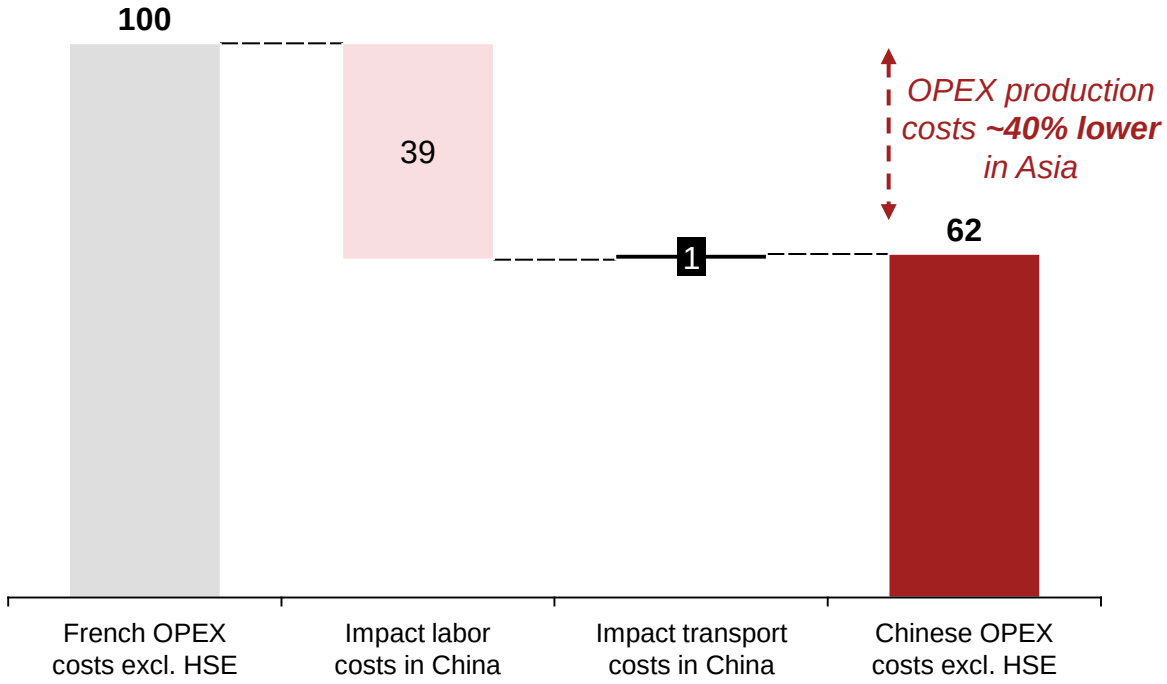


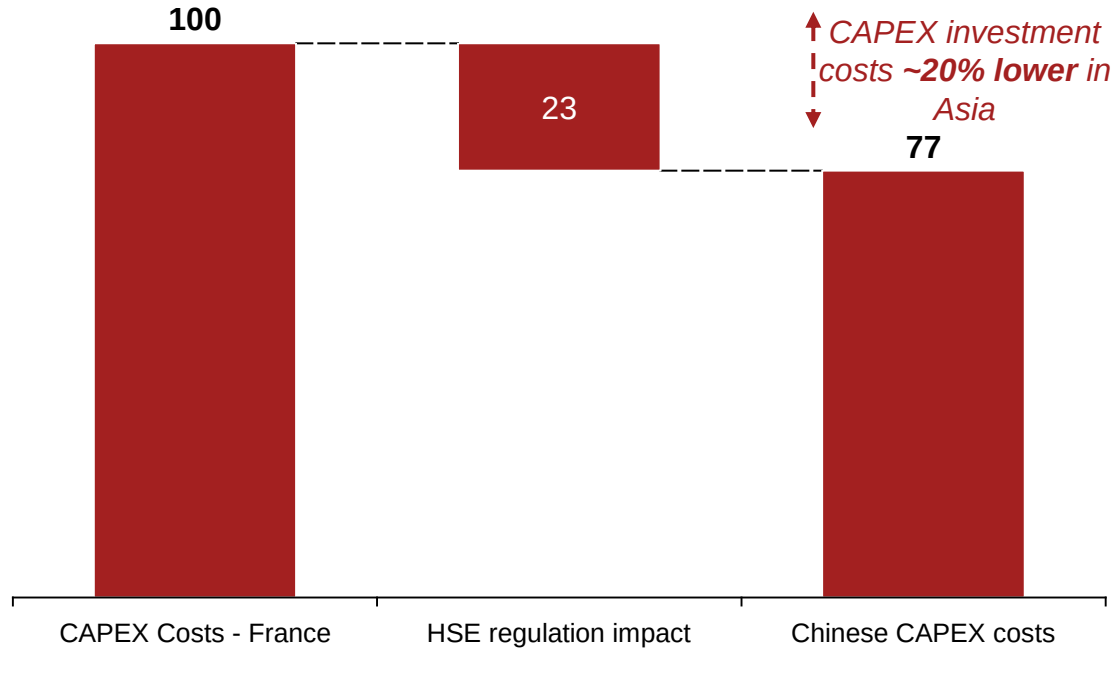
Sources: ProGenerika, Strategy Analyses&

Investment and operating costs for active ingredients are 20-40% lower in Asia, favoring the relocation of production capacities there

Business case of a pharmaceutical API production in France vs. China *(proxy for Asia)*

Base 100 = French costs, 2020





Hypothesis:
- **Equal productivity** between French and Chinese workers
- Cost structure: **50% labor cost** and 10% transportation cost
- **Salaries 4.5x higher** in France than in China
- **5x less** distance traveled

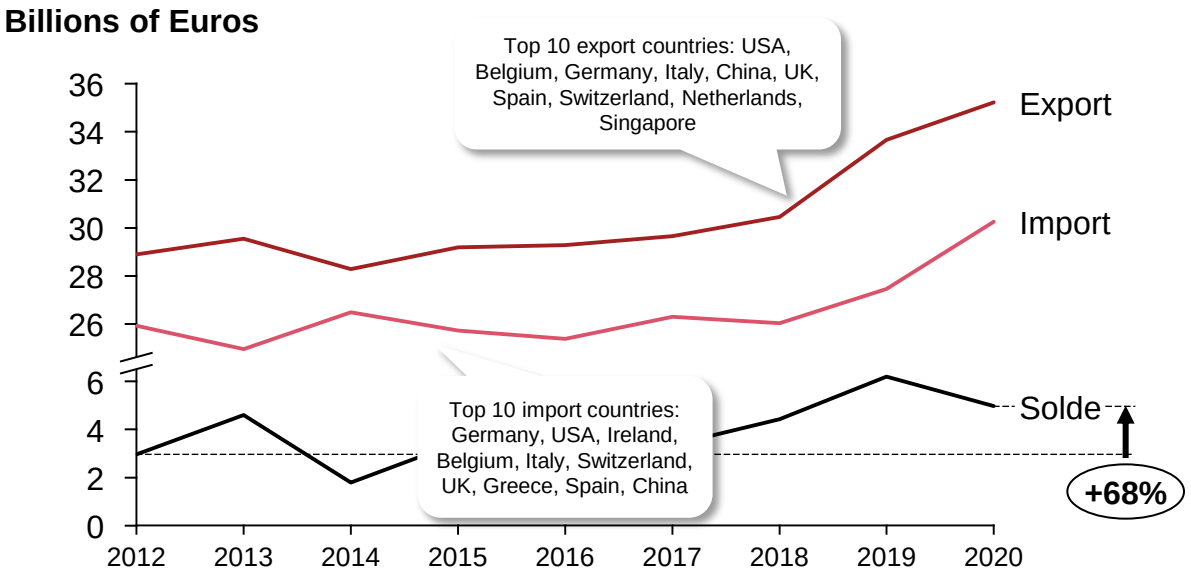
Hypothesis:
- **Size of** production **tools similar** between France and China
- **Similar** production **technologies** between France and China
- **20-30% additional HSE and Opex costs** (treatment costs, WWTP...) due to European environmental regulations

Sources: G5 Health, Strategy Analysis&.

This competition impacts French players, their VA deteriorating due to a potential mature product portfolio or stronger negotiating power of suppliers

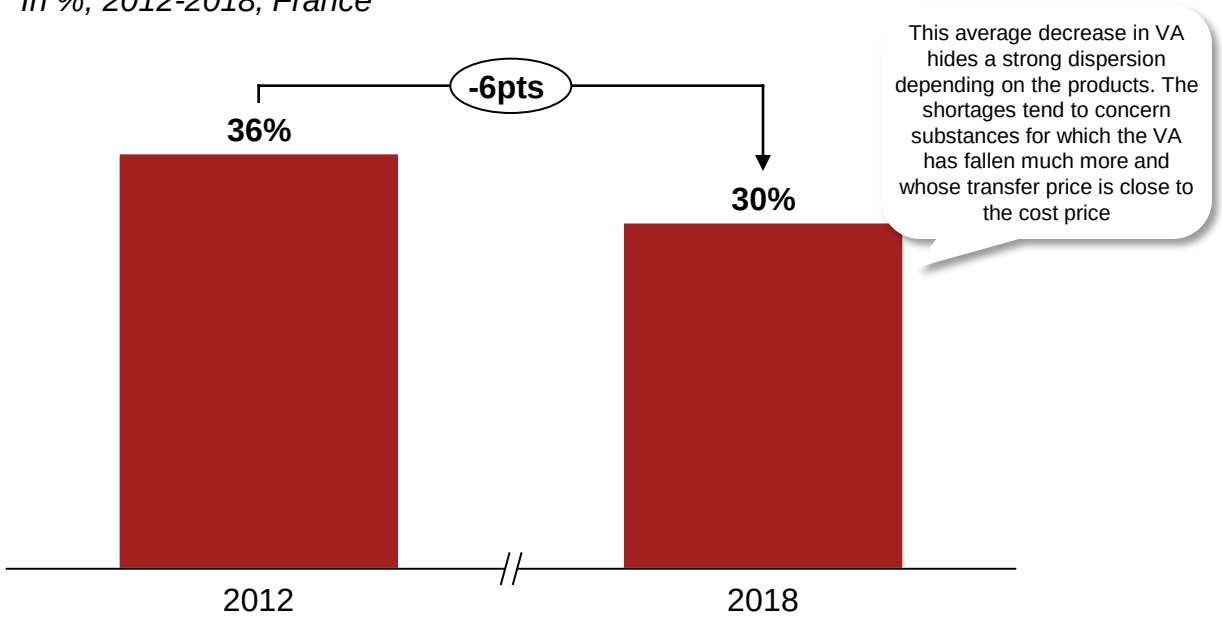
Trade balance of the pharmaceutical industry

In billions of euros, 2012-2020, France



Share of Added-Value (VA) in pharma. industry production

In %, 2012-2018, France



French pharmaceutical added value is deteriorating, reflecting possible difficulties in positioning and supply:

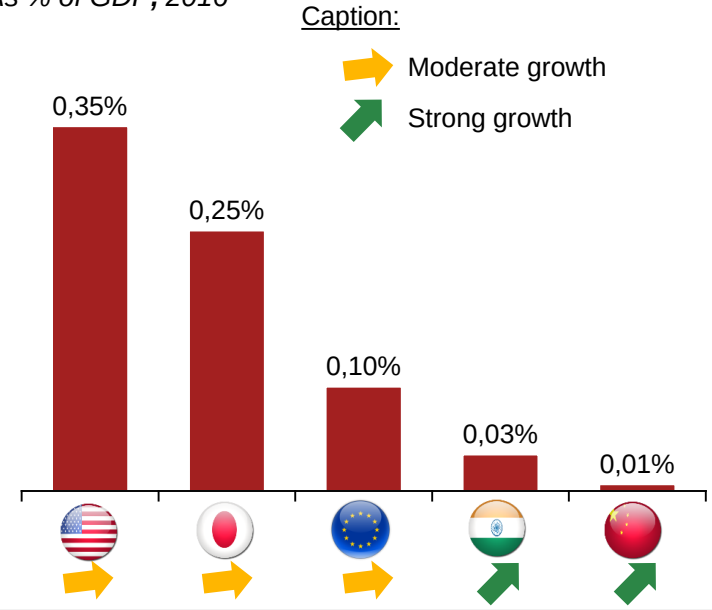
- French laboratories **are more competitive internationally, as** shown by the increase in exports and the trade balance since 2012
- **Pharmaceutical added value is deteriorating**, resulting either from **downward pressure on international prices** or from an **increase in intermediate consumption**
- The **downward pressure on prices** can be explained by a **large portfolio of drugs being commoditized** and by **the entry into the market of** high-volume **Asian producers** benefiting from significant scale effects, leading to a **gradual shift in volumes towards Asia**
- The shift to Asia is **accentuated by cheaper labor** and **lower production constraints** (notably safety/environmental)
- The increase in intermediate consumption can be explained by the **greater bargaining power of suppliers of intermediate products and APIs**

Sources: Eurostat, French Customs, Strategy Analyses&.

The result is a deteriorating competitiveness, increasing reports of tensions, and sovereignty undermined by crises

European competitiveness is being challenged by the US, Japan, India and China

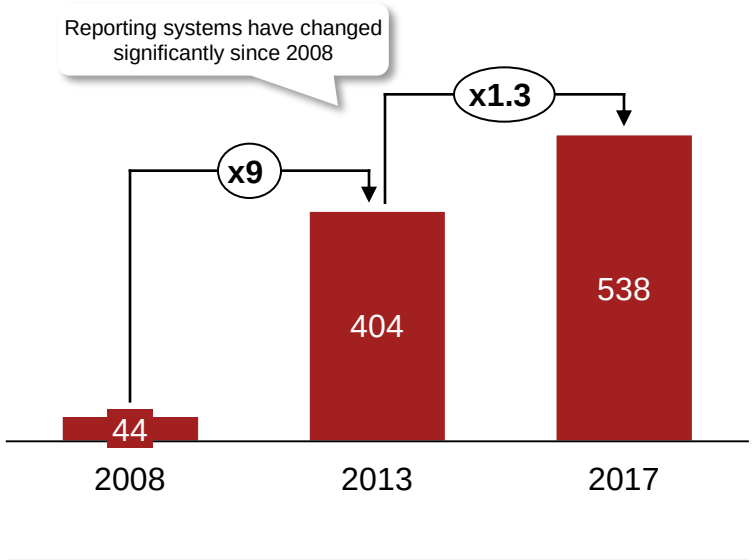
Pharmaceutical R&D expenditure - private sector
As % of GDP, 2016



Europe is caught between :
- **Developed countries** investing up to **3x more** in R&D, widening **the competitiveness gap**
- **Developing countries** with an **accelerated pace of innovation**, **reducing their** competitiveness **gap**

Reports of shortage have increased 12-fold since 2008, mainly for injectables

Reports of shortages and/or tensions on MiTM
In #reports, France, 2008-2017



- Shortage reports are **x12 in 10 years**
- **Hospital injectables** are the most affected by these vulnerabilities
- **Flexibility, production capacity**, and **unforeseen fluctuations pbs. explain** 48% of ruptures in 2017 vs. 34% in 2013

These vulnerabilities cause a lack of sovereignty revealed in times of crisis

Less bargaining power vs. laboratories

In the absence of sufficient local production capacity, **the European Union must turn to foreign laboratories to meet its needs in times of crisis**, which exposes it to the vagaries of market laws

e.g. AstraZeneca supplying the UK before the EU during the Covid-19 crisis because of a preferential clause in a contract

Less bargaining power vs. states

In the event of a crisis, countries with a strong local pharmaceutical industry tend to concentrate the production of their national players on the domestic market, **relegating foreign demand such as that of the European Union to the background**

e.g., China and the United States during the Covid-19 crisis were able to rely on their national laboratories to meet their entire domestic demand before they began exporting doses

Sources: LEEM, OECD, China Statistical Yearbook, Strategy Analyses&.

The analysis of the value chain and the health stake of APIs allows us to identify segments with differentiated vulnerabilities

Segmentation approach followed

2 main axes retained for the segmentation

Axis	Objective	Selected segments					
Health stake	• **Characterize the Health stake** posed by the molecule	**MiTM without therapeutic alternatives**	**MiTM with alternatives**				
		Strategic molecules, recognized as being of major therapeutic interest by the ANSM, and presenting a significant loss of chance for patients in the event of unavailability, having no possible substitute	*Strategic molecules recognized as being of major therapeutic interest by the ANSM, and presenting a significant loss of chance for patients in the event of unavailability, with possible substitutes*				
Value chain	• **Identify** the **link in the value chain** that constitutes a **vulnerability**	**Fragile supply of inputs**	**Complex production**	**Production including pollutants to treat**	**Low price of the API**	**Unstable demand**	
		Molecules based on raw materials, reagents and intermediates purchased from a limited number of players and/or outside Europe	*Unstable manufacturing processes, large number of steps or specific technology*	*Molecules manufactured using old technologies with toxic emissions to treat and with limited regulation outside the EU*	*Low economic attractiveness due to the low added value of the molecule*	*Molecules whose unstable end demand makes it difficult to plan production*	

5 key segments highlight the major market failures impacting the resilience of the APIs value chain

Segmentation of molecules

NON-EXHAUSTIVE LIST of APIs

Main problem encountered on the cdv: Upstream → Value chain → Downstream

Health stake	Fragile supply of inputs	Complex production	Production including pollutants to treat	Low price of the API	Unstable demand
	Molecules based on reagents and inter. made by limited actors / outside Europe	*Unstable processes, #important manufacturing steps or specific technology*	*Molecules manufactured using old technologies with toxic emissions to treat and with limited regulation outside the EU*	*Low economic attractiveness due to the low VA of the molecule*	*Molecules whose unstable end demand makes it difficult to plan production*
MiTM without therapeutic alternative	Docetaxel / Paclitaxel Corticosteroids *(ex: Prednisolone)* Macrolides *(ex: Azithromycin)* Ramipril	Insulin Fludarabine Oxytocin Ibuprofen	5-FU Azathioprine Estrogen Formoterol Amoxicillin	Metamizole Metformin	Codeine Morphine
MiTM with alternative	Heparin Methotrexate Gliclazide	Sartans *(ex: Candesartan, Losartan...)* Salbutamol	Metronidazole Piperacillin + Tazobactam Bisoprolol Doxycycline Levofloxacin PPI *(e.g. Omeprazole)* Midazolam	Paracetamol Metoprolol Statins *(ex: Simvastatin, Atorvastatin)*	Propofol

Notes:
- APIs selected on the basis of redundancy between 5 separate studies identifying ~230 strategic APIs (see appendix slide 42 for details)
- Ibuprofen: molecule also concerned by the "low API price" segment

Sources: Interviews, Studies, Strategy Analyses&.

APIs face fragile input supplies or complex production chains that are difficult to control

Summary by segment

Segment	Examples of critical molecules	Issues identified in the value chain	Consequences
Fragile input supply	**Docetaxel / Paclitaxel** **Heparin** **Macrolides** *(ex: Azithromycin)* **Corticosteroids** *(ex: Prednisolone)*	• Segment grouping molecules with a **tight** supply of **raw materials, Registered Starting Materials** *(chemical reagents, natural materials, etc.)* **and synthesis intermediates** • **Some inputs** (e.g., antecedents of corticosteroids) serve as precursors to **several critical molecules** • **These key inputs** are **manufactured almost exclusively outside Europe,** whether they are **natural** (e.g. yew leaf) **or synthetic** (e.g. erythromycin)	• **The production of APIs** derived from these inputs **is vulnerable** and puts **the related finished products at risk of rupture** (e.g. Taxotere®, Zithromax®...) • Because of **the importance of these inputs** in the manufacture of API, producing these molecules in **Europe would** first **require** the **manufacture of key inputs** to avoid tensions and make the **equation economically sustainable**
Complex production	**Ibuprofen** **Insulin** **Fludarabine** **Sartans** *(e.g. Losartan)*	• Segment regrouping molecules with **processes :** – **Unstable**, due to **synthesis routes** creating **API impurities** or **low yields** – **Complex**, with an **important number of manufacturing steps** (ex: >30 steps) – **Highly regulated** with **important manufacturing standards** to be respected • The complexity **generates high production costs** in Europe (expensive labor, important production constraints), **preventing European players from positioning themselves** competitively and meeting local needs	• The **production capacity of** these molecules is **limited in Europe**, **reducing** the capacity to **respond to local demand** during crises • **The production chain is rigid,** making it difficult to **respond to fluctuations in demand,** particularly in the event of a health crisis • When these **productions are delocalized,** they are difficult to relocate (loss of expertise)

Sources: Interviews, Studies, Strategy Analyses&.

Other APIs rely on production including pollutants to treat, whose production cost to meet European standards would be prohibitive

Summary by segment

Segment	Examples of critical molecules	Issues identified in the value chain	Consequences
Production including pollutants to treat	**5-FU** **Azathioprine** **Estrogen** **Metronidazole** **Doxycycline**	• Segment including molecules whose manufacturing processes may **generate a high level of toxic or odorous waste** or whose **chemical reactions are dangerous** • The application of **European regulations** in terms of safety and respect for the environment **generate very significant additional costs** compared to competitors **outside Europe who are not generally subject to the same production standards** • **Although European regulations are essential** for safe and environmentally friendly production in Europe, they do **not regulate production outside Europe** and **therefore have a strong impact on the competitiveness** of European producers and can make relocation difficult. • Finally, **these productions outside Europe** are **generally unsustainable**, posing a **long-term structural risk** to supply (e.g. risk of API manufacturing site closure due to the necessary integration of environmental norms – Blue sky in China)	• The environmental upgrade **generates additional production costs of ~30%** on CAPEX and OPEX for **European molecules** • **European production** is gradually **moving to countries with the least restrictive environmental and social regulations,** without altering the quality of molecules • Europe **thus loses the capacity to produce these essential molecules** and its **sovereignty** during **health crises** is exposed to the **risk of being supplied** by unsustainable producers - which is not sustainable, cf. the **trend** towards **stricter regulations in Asia** (e.g. Blue Sky in China) • **Europe loses sovereignty,** especially during **health crises**

Sources: Interviews, Studies, Strategy Analyses&.

Finally, some APIs are facing low price levels that do not allow for a sustainable economic positioning, or unstable demand that does not provide the necessary visibility to manufacturers

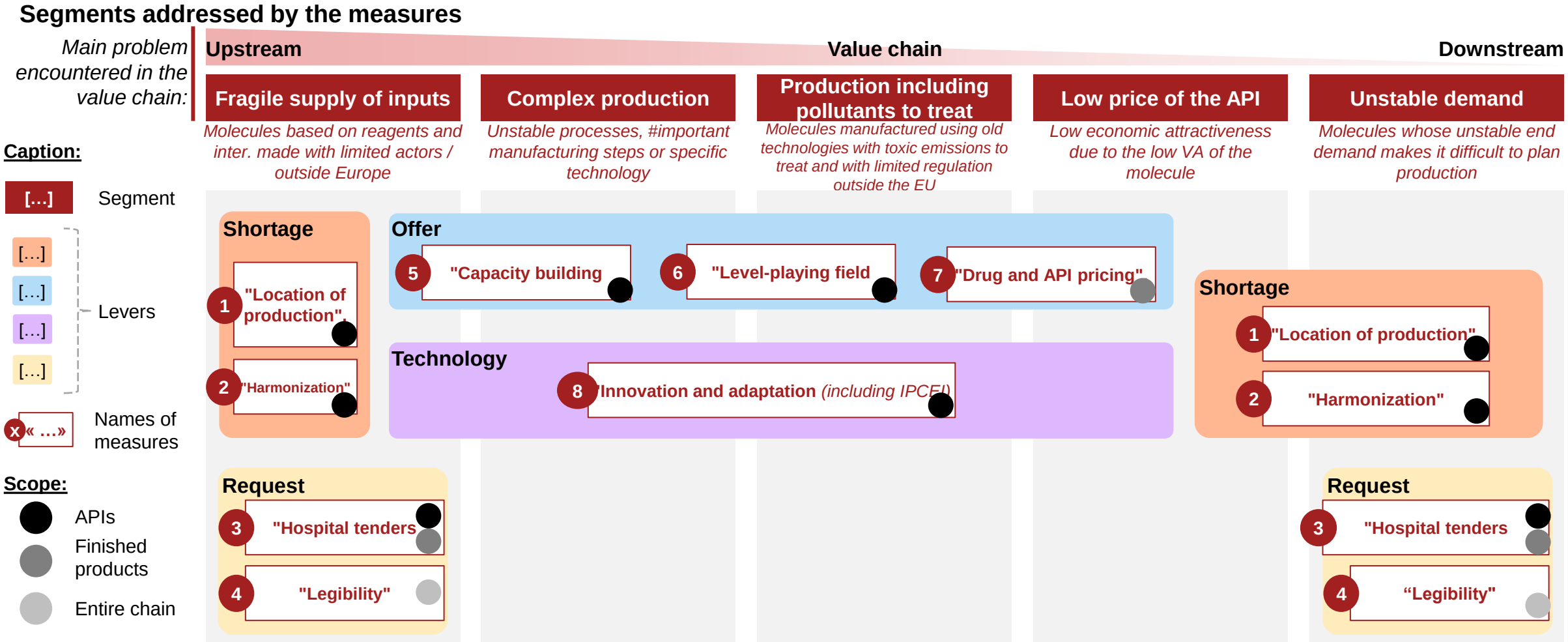
Summary by segment

Segment	Examples of critical molecules	Issues identified in the value chain	Consequences
Low price of the API	**Paracetamol** **Metamizole** **Metformin** **Statins**	• Segment with **very low priced APIs (<10€/kg)** and/or high **volumes consumed in** Europe (5-40k **tons/year)** • Production is carried out in **countries with low cost structures** allowing for **critical size** and **significant economies of scale**, or with **privileged access to critical inputs** • **EU** production **is carried out at marginal cost** with **depreciated assets and no leeway to invest** or sustain the activity • **During health crises**, **tensions may arise** when borders are closed	• The **production of these molecules is mainly carried out in Asian countries throughout the value chain** (with the exception of Paracetamol, which is also produced in the USA - but the recent switch of Mallinckrodt to Chapter 11 shows the low level of margin for these molecules). When final drug manufacturing is maintained in Europe, the equilibrium is very fragile • Current manufacturing **technologies and processes** do **not allow European players to position themselves without innovation**
Unstable demand	**Propofol** **Morphine** **Codeine**	• Segment including **key molecules in the hospital environment** for the treatment of **patients in intensive care** • The **consumption of these molecules varies** according to **health needs** and does **not allow actors to** have a **clear visibility** on the **volumes to be produced** • The **inputs of** these molecules are regulated and **produced mainly in India** (e.g. poppies), making their **supply sometimes difficult**	• European **units** are **less competitive** due to their **lack of volume/economies of scale** and **some are closing** due to the **lack of clarity of outlets** • The **time required to reopen** production lines **is long and costly**, making it **difficult to react to fluctuations in demand** (e.g. propofol)

Sources: Interviews, Studies, Strategy Analyses&.

The proposed measures address all the vulnerabilities identified in the API value chain

Segments addressed by the measures



Measures are in place to manage the crisis when it arrives by managing shortages and ensuring security of supply in the short-term

List of proposed measures

Scope: APIs; Finished products; Entire chain

Name	Description of the measure	Segment covered
1 "Location of production"	• Guarantee the **security of supply** of **critical molecules** by promoting **supply criteria** (diversity of supply, bonus for reliable and sustainable production in Europe, etc.) as well as (possibly European) **back-up production** (diversity of supply): • Supporting companies to **accelerate investment** in the **modernization** and **development of** the existing **European industrial fabric**	Fragile supply of inputs Low price of the API Unstable demand
2 Harmonization"	• Implement **shortage prevention plans** for **suppliers of inputs, intermediates or active ingredients** • **Improving** demand **predictability** and limiting shortages through **Cooperation between MS** • **Establish** a **coordinated stock management strategy** at the European level • **Establish** a **centralized definition and monitoring** of shortages at European level • Increase **flexibility for emergency imports in the** event of critical shortages	Fragile supply of inputs Low price of the API Unstable demand

Request

Other measures allow to value additional criteria to the price in the AO and to share information at the European level

List of proposed measures

Scope: APIs, Finished products, Entire chain

	Name	Description of the measure	Segment covered
3	"Calls hospital supply "	• Review the **terms and conditions** of **public procurement practices** (volumes, award criteria, award deadlines, etc.) • Set up **multi-tender calls** with **volume commitments** for each of the tenderers in order to **perpetuate the number of players and their production and ensure redundancy in case of crisis** • **Enhance the value of environmental and societal criteria** in calls for tender; in fact, the purchasing strategies of hospitals are mainly based on price criteria • **Valuing security of** supply **criteria** in the value chain	**Fragile supply of inputs** **Unstable demand**
4	"Legibility"	• **Share information** on tensions with **authorities**, • Sharing **information between EU states** for enhanced European coordination • **Extend the information obligations** of the European databases to manufacturers of active substances outside the European Union who supply the EU. • **Know the value chain** • **Create a "Made in Europe" label** on the boxes of medicines to promote the production origin of APIs, intermediates and raw materials	**Fragile supply of inputs** **Unstable demand**

Offer

Measures to build a sustainable, safe and environmentally friendly production in Europe

List of proposed measures

Scope: APIs; Finished products; Entire chain

Name	Description of the measure	Segment covered
5 "Capacity Building	• **Support the construction or modernization** of facilities for the production of **critical molecules** in Europe • **To maintain and develop the production capacity** in Europe of **essential active ingredients and intermediates at an acceptable cost** and in compliance with the strictest safety and environmental standards	Fragile supply of inputs Complex production Production including pollutants to treat Low price of the API
6 "Level-playing field	• To take into account, in addition to quality requirements and in addition to price alone, **minimum criteria of respect for the environment, health and safety rules and quality for suppliers of** medicines, APIs or raw materials • In the same way as quality, the **failure to respect a sufficient level of employee safety** and **respect for the environment** must lead to the possibility of sanctioning (tax, customs duty, import ban, etc.) any supplier who does not meet European standards and therefore is not sustainable	Fragile supply of inputs Complex production Production including pollutants to treat Low price of the API
7 "Drug prices and APIs "	• **Recognize that the pressure on the price of mature molecules and the successive price cuts have their limit**. Illustration: in 2019, the median price of generic drugs was 11 cts/cp. • The **pricing doctrine** for mature drugs **must be adapted** by taking into account **the industrial, environmental and social footprint** at the European level or the **security of supply** • **Introduce a threshold price for mature drugs**	Fragile supply of inputs Complex production Production including pollutants to treat Low price of the API

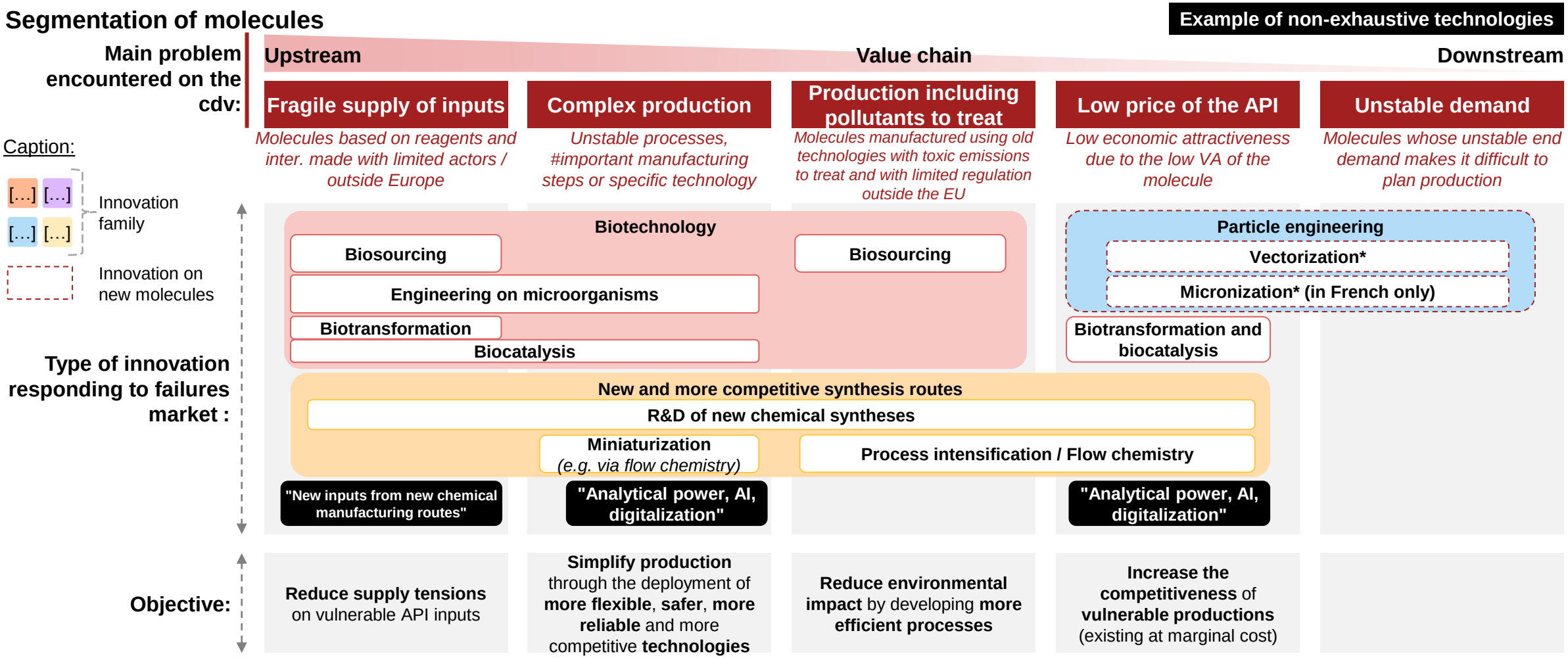
Innovation is also an amazing lever to durably improve the offer - support must allow to limit the impact on the production costs and create value

List of proposed measures

Scope: APIs, Finished products, Entire chain

Name	Description of the measure	Segment covered
8 "Innovation and adaptation	• **To support innovation in new manufacturing process technologies** (inputs and APIs) combining competitiveness, reliability, durability, safety, quality and respect for the environment. • **Accelerate the transformation of industrial processes** to relocate or strengthen the value chain for molecules of major therapeutic interest that are highly vulnerable in Europe • Promote **technology transfer** between academia and industry on the one hand, and within industry on the other (intra-disciplinary cross-fertilization) • Support **the evolution of employee skills** in the appropriation of these new technologies • Encourage all organizational and regulatory innovations through **digital transformation and artificial intelligence** • **Use Health IPCEI as a vehicle to support** R&D **funding for** disruptive technologies at IDF	**Fragile supply of inputs** **Complex production** **Production including pollutants to treat** **Low price of the API**

This support to innovation should also facilitate the emergence of disruptive innovations that respond to identified market failures



Notes:
Unstable or complex/specialized demand or value creation levers for European production or future disruptive innovations

Techno.

In order to help finance them, the Health IPCEI would make it possible to support and accelerate these innovations up to the FID

Financing vehicles

Innovations requiring more modest financing needs and **not involving many actors** can be **handled in the short term** via local vehicles (e.g. PCR test in France)

				Horizon Europe					*European sectoral programs*	
		IPCEI	**EIB**	**EIC**	**Eurostars**	**PAA Pillar 2 & PPP**	**EIT Health**	**FESI**	**EU4Health**	**Digital Europe**
Type of support	Grant	✓		✓	✓	✓	✓	✓	✓	
	Other		Loans/equity contributions	Equity up to 15m€.			Investment			Co-financing
Perimeter	Basic research	✓	✓	✓	*(only from TRL 5)*	✓		✓	*n.a.*	Variable
	PoC	✓	✓	✓		✓				
	FiD	✓	✓	✓						
	Other		Various	Various			Training, start-ups, GtM			
Amount of funding	Capped		60 billion/year for the EU	2.5M dilutive, 15M dilutive	Up to 30/40%.	Up to 70% off	*n.a.*	Decision of the region	5.3 billion following Covid-19	*n.a.*
	Uncapped	✓								
Sectors concerned	Sectors concerned	All sectors combined	All sectors combined	All sectors combined	All sectors combined	Health	Health	All sectors combined	Covers the 4 axes of the IPCEI	Digital health infrastructure
Easy access	Competitive	No	No	Yes	Little	Yes	Very few	Easily mobilized by the region	No	*n.a.*
	Time constraint	No	No	Yes	Yes	Yes	*n.a.*		Yes	*n.a.*

Sources: Strategy Analyses&

IPCEI raises European funds to finance disruptive technologies that enhance EU sovereignty

Presentation of the IPCEI

Description

A **IPCEI** (Important Project of Common European Interest) is a **legal framework** allowing MS to **invest in a concerted way** to support private actors in the **R&D and/or the first industrial deployment of** a **disruptive and ambitious technology, beyond what is** allowed by the **current EU regulation**

Interest

- A **higher level of public funding**
- A **broader scope** (including industrial deployment)
- A **European approach**

Eligibility Criteria

***General criteria** (all projects)*

1. **Quantitative or qualitative importance** in size and/or level of technological or financial risk
2. Impact on **EU competitiveness and sustainable growth**
3. Alignment with **EU objectives**
4. Involvement and benefits spread over **more than one MS**
5. **Positive impact** on the European economy and society
6. **Co-financing** by the recipient
7. **Respect for the environment**

Specific criteria

1. **For R&D projects: major innovative character or significant VA contribution in** terms of R&D
2. **For industrial deployments:** development of an **R&D-intensive** product and/or an **innovative production process**

Favorable indicators

1. **Participation of all MS**
2. Involvement of the **European Commission** in the **design of** the project
3. Involvement of the **European Commission** in the **selection of** the project
4. Involvement of the **European Commission** and **several MS** in the **governance of** the project
5. **Strong collaborative dimension** (number, size and diversity of partners)
6. **Co-financing by an EU fund**

Compatibility criteria

- **Necessity of the assistance** (without CEIIP assistance the project would not be possible or the benefits would be significantly reduced)
- **Proportionality of aid** (the level of aid is determined by the difference between private funding and eligible costs)

Examples of IPCEIs

- **R&D in microelectronics (2018):** €1**.75** billion of public funding for €6 billion of private funding, involvement of 4 MS (France, Germany, Italy, UK), 29 direct participants (industry and research organizations)
- **R&D on the battery value chain (2019):** €3**.2** billion of public funding for €5 billion of private funding, involvement of 7 MS (Belgium, Sweden, France, Germany, Italy, Poland, Finland), 17 direct participants *2nd battery IPCEI validated in 2021*

Sources: European Commission, Strategy Analyses&.

The innovations identified meet the criteria of the Health IPCEI and could provide significant and lasting added value for Europe

Segmentation of molecules

		Alignment with EU objectives			Scale / impact on the European economy		
Type of inno.	**Description**	**Sovereignty**	**Sustainability**	**Scale / Impact**	**Techno disruption.**	**Need for financing**	**Value creation**
Biosourcing	Allows the **replacement** of non-renewable **mineral** or fossil-based **inputs** by biological and/or renewable materials *(e.g. plant extraction, synthetic biology production and biomass cracking and recombination)*	Depends on the product	Yes	Medium	• Depends on the technology developed	• OPEX financing • CAPEX financing for biomass cracking and recombination	• Possible spill-over to other sectors
Engineering on microorganisms	Development of **biochemical fermentation techniques** to **program natural strains or materials** in **an industrial way.** Techno. brick Essential for the production of ingredients by fermentation and synthetic biology	Yes	Yes	Fort	• Very disruptive, at the R&D stage	• Development cost (Gen. Handling time)	• Fort
Bio Transformation	Development of **mixed processes** associating a fermentation with **a** chemical synthesis allowed by **DNA engineering of stem molecules.**	Yes	Yes	Fort	• Important R&D field for the development of new synthesis routes	• R&D CAPEX	• Strong (improvement via catalysts)
Biocatalysis	**Development** of new **synthesis routes using enzymatic catalysis**, alone or in **combination with other innovative catalytic systems** (multicatalysis)						
Particle engineering - vectorization	Technology to optimize **particle size, distribution and surface area** for **effective dosing and** treatment of patients with **APIs** **Material** consumption **is reduced, therapies are targeted**	Yes (sovereignty of the future)	Yes on the whole chain	Fort	• Very strong	• Important development cost	• Very strong • Enables the improvement of bioavailability of current and future drugs
Particle engineering - micronization						• Important development cost • CAPEX	

The innovations identified meet the criteria of the Health IPCEI and could provide significant and lasting added value for Europe

Segmentation of molecules

Type of inno.	Description	Alignment with EU objectives			Scale / impact on the European economy		
		Sovereignty	Sustainability	Scale / Impact	Techno disruption.	Need for financing	Value creation
R&D of new chemical syntheses **Miniaturization (e.g. via flow chemistry)** **Process intensification / Flow chemistry**	**Simplification of processes** by **researching new metabolic pathways** to **gain in competitiveness, flexibility, reliability and safety.** **Innovative**, **flexible, reliable, safe, competitive and** (environmentally) **efficient** manufacturing processes**,** based on the design of new synthesis routes via catalytic combinations (multicatalysis, e.g. biocatalysis + photocatalysis, etc.), and/or **continuous production** from raw material to final API, using **less inputs, solvents and energy and more automated**	Yes	Yes	Fort	• Yes on some synthesis routes even if first industrial units are emerging	• Funding of preliminary studies and regulatory costs	• Very strong
"Analytical power, AI, digitalization"	Data **analysis techniques** via **digitalization** and **specific equipment**. **Vector of all innovations**	Yes	Yes	Medium	• Application to pharmaceutical synthesis of existing technologies in other sectors		• Accelerates the deployment of disruptive process innovations

Contents

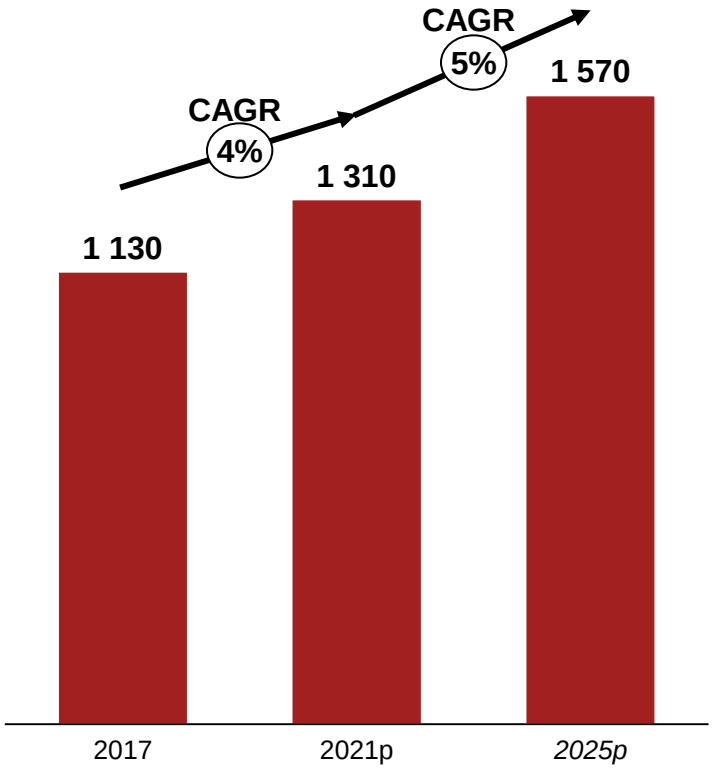
All of the studies analyzed reveal the same findings, causes and proposals to make the European pharmaceutical industry more resilient

Category	Description
1 Findings	• The global **pharmaceutical market is** expected to grow **at a steady pace**, driven geographically by the **US and China**, **therapeutically** by **oncology/pneumonics** and **technologically** by **biomedicines** • **Since 2000, part of the production of molecules has moved to Asia, where players historically specialized in large-volume older molecules have become competitors of European production for new molecules** • This situation **threatens European 'sanitary' sovereignty,** as we saw during the COVID crisis
2 Causes	• The **difference in investment and operating costs** between Europe and Asia is **difficult to pass on in prices** under the current **framework** procedures • Furthermore, **the European commitment to the environment, health and safety** implies the application of **complex and costly standards to molecules produced in Europe,** which are **not applied to those produced outside Europe** • **Because of** the cost differential, **the production of older molecules is progressively destined to be moved to low-cost countries**, regardless of their therapeutic or strategic nature • The **specialization of subcontractors** on a single stage of synthesis or pharmaceutical formatting increases the risk of shortage
3 Proposals	• **Transparency of the value chain** could be **improved** to better **identify vulnerabilities** and increase **cooperation of actors** • The **economic sustainability** of production in Europe **could be strengthened**. This could be achieved through measures related to tenders**, prices and taxation** • **HSE constraints**, which are important for long-term industrial sustainability, could **be harmonized for all products**, regardless of **their origin,** through **regulatory or fiscal** means • **Innovation is necessary** to **make** European **production sustainable** in the long term

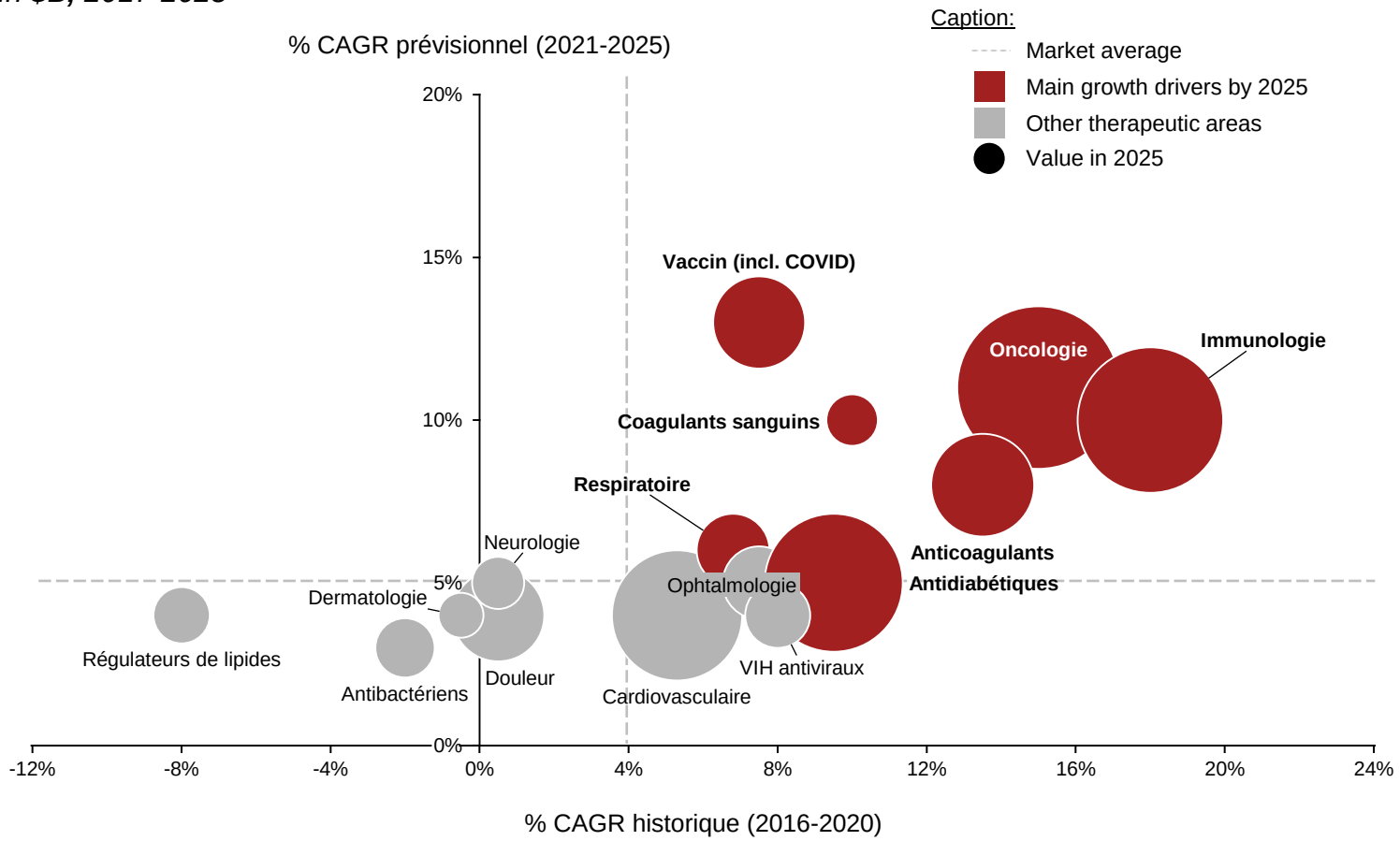
Contents

Global pharmaceutical demand is expected to grow by 4% per year by 2025, driven mainly by 7 major therapeutic areas

Global Pharmaceutical Expenses
In $B, 2017-2025



Growth in expenses by therapeutic area
In $B, 2017-2025

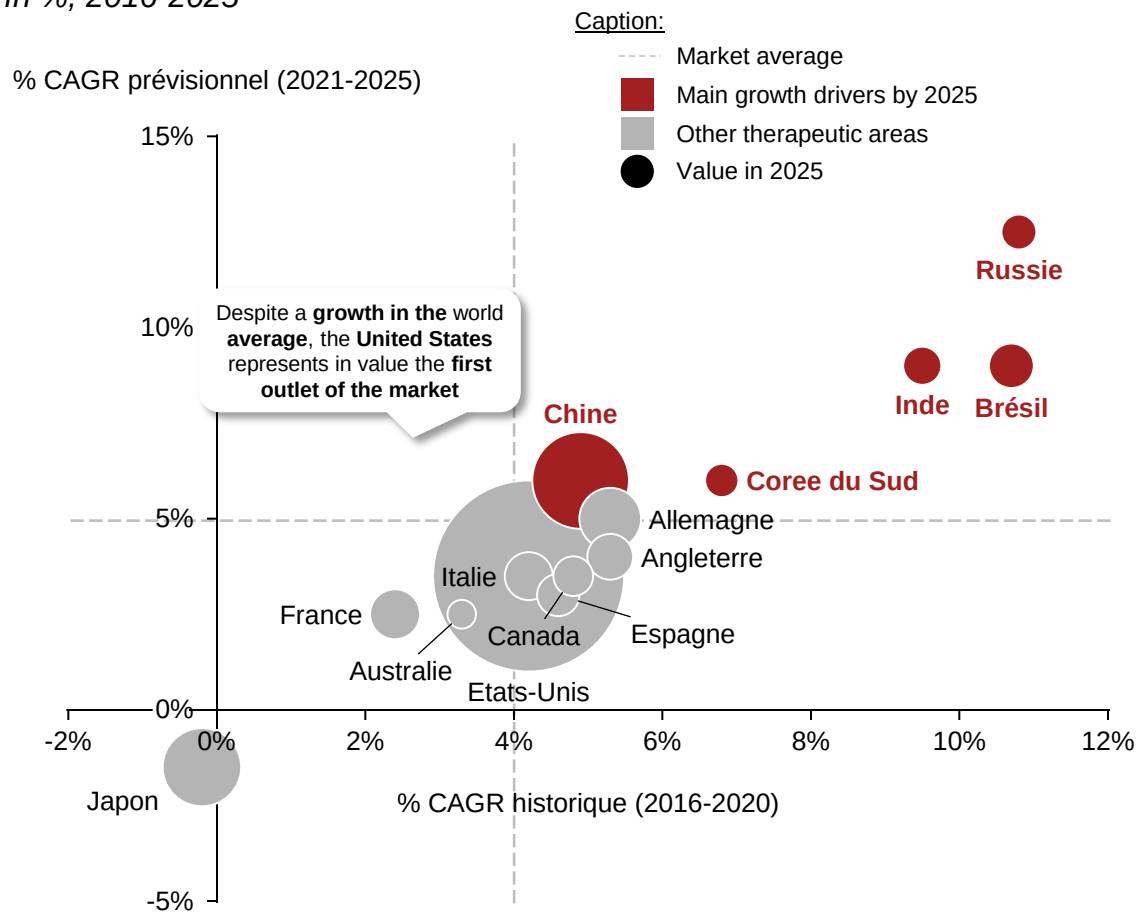


Sources: IQVIA, Strategy Analyses&

The United States and China should be the main markets for pharmaceutical companies

Pharmaceutical Expenditures by Geography

In %, 2016-2025



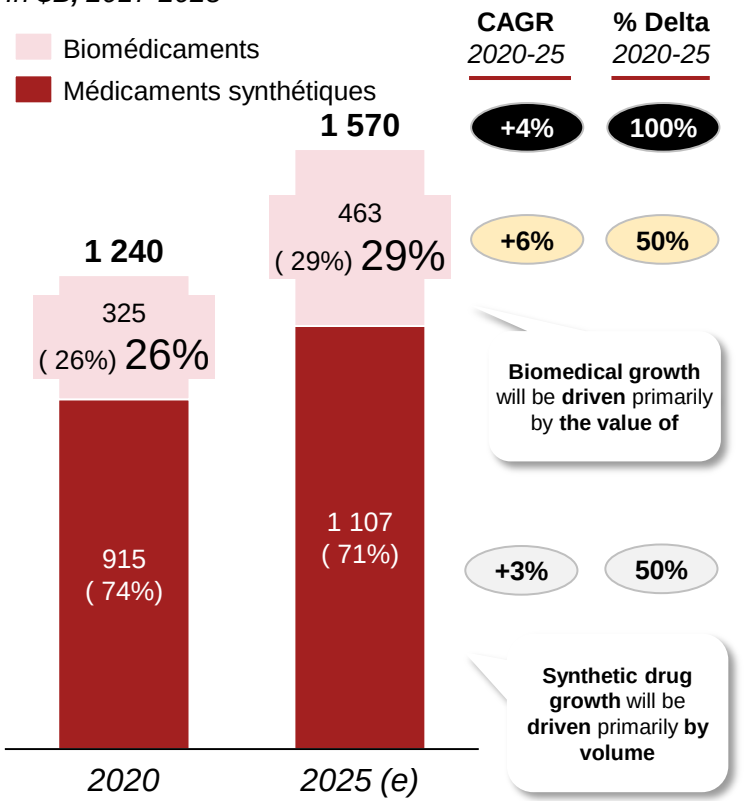
Geography	Dynamics	Drivers
	Strong growth	+ Strong growth in original brands and generics + More frequent updates of the national list of reimbursed drugs + Growing volume of aging patients
	Negative growth	- National pricing system with a mandatory price reduction every two years - Total population down
	Moderate growth	+ Adoption of new products with unregulated prices - Loss of exclusivity and competition from biosimilars resulting in lower margins
	Moderate growth	+ Entry of new players and new brands on the market - Pandemic slows the pace of innovation

Sources: IQVIA 2021, Strategy Analysis&.

Biomedicines will account for 50% of this growth, particularly in terms of value and in developed countries, hence the need for positioning

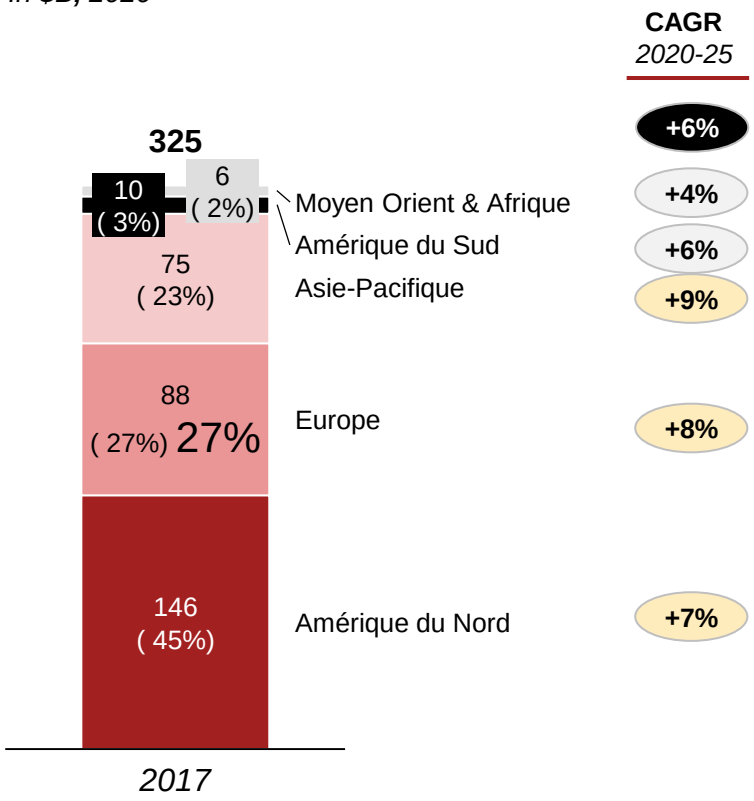
Biomedicines are expected to account for 50% of market growth by 2025

Global pharmaceutical expenditure
In $B, 2017-2025



Developed countries are expected to contribute strongly to market growth

Biomedical Expenditures by Geography
In $B, 2020



The therapeutic interest of biomedicines drives R&D and new molecules

Therapeutic drivers

The use of biomedicines is expected to increase because:

- They allow us to find **treatments for incurable diseases** (e.g. autoimmune diseases)
- They have **limited side effects** compared to chemical drugs or other invasive treatments

In particular, **oncology applications (21% of the market) should continue to drive growth** by 2025

Volumetric drivers

The number of **new biomedicines discovered and approved for the** market is expected to **increase and drive growth**:

- **~40% of** pharmaceutical companies' **R&D budgets** should be **devoted to biomedicines** on average **(vs.** 15% in early 2000)
- ~35 new biomedical products are approved by the FDA on average over the last 5 years vs. ~20 over the previous period. This trend should continue over the next 5 years

The number of approved **biosimilars** should drive **growth, mainly in Europe** (more permissive regulations)

Sources: IQVIA 2021, Mordor 2020, Strategy Analyses&

To ensure that this growing demand is met, a complex globalized and fragmented chain of sub-components is required for the production of medicines

Drug manufacturing value chain

	Raw materials	Intermediates of synthesis	APIs	Excipients	Final drug manufacturing
Description	*Minerals extracted from the soil, animal, vegetal materials or first oil derivatives...*	*Manufactured substance for a chemical transformation*	*Biological substance active ingredient of a drug*	*Associated substance allowing drug formatting*	*Final dosage and packaging of a medication*
Example	Raw material A Raw material B Raw material C Raw material D Raw material [...]	Intermediate A Intermediate B Intermediate [...]	Intermediate API A Final API	Excipients	Final drug
Main issues identified	• A **significant number of APIs and/or synthetic intermediates** are no **longer/almost not produced in EU** • The **lack of control** over these APIs and/or their intermediaries can **put stress on** the supply chain and **lead to disruptions downstream of the chain**			• **Injectable forms**, used in hospitals, are **the most affected** by reports of tension/shortage • The **market has** a **global shortage of production capacity for these dosage forms**	

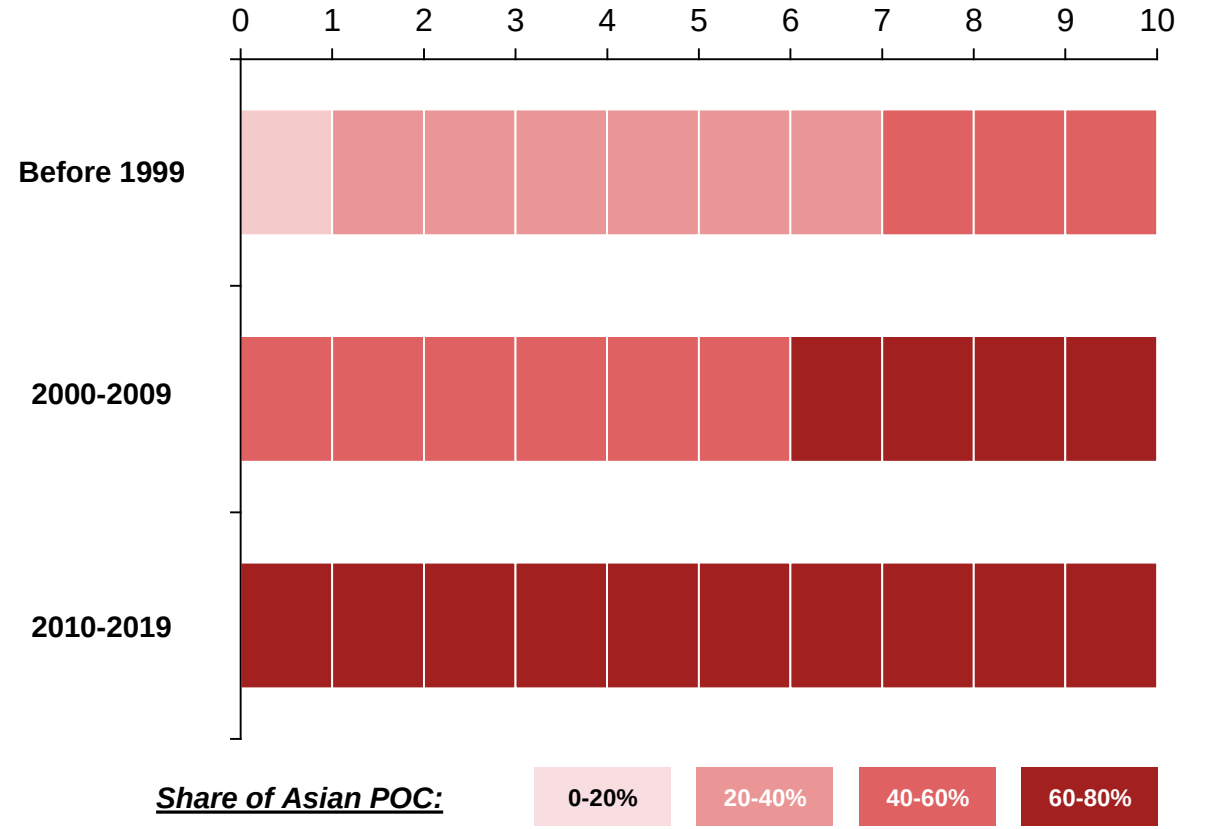
Scope of the study

Sources: EFCG, SICOS, LEEM, G5 Santé, Analyses Strategy&

However, the European production is challenged on all this chain, more and more on contemporary products

Proportion of Asian manufacturers with APIs in the CEP process

Type of molecules	Description	Example	Margin Level
Commoditized molecules or drugs	• **Old molecules** with **large volumes** • **Manufacturing processes** for certain **pollutants** with a **limited number of steps** • **Gradual shift to Asia** where large volume producers with significant scale effects are located	• **Metformin** • **Metamizole** (first a volume effect)	1
		• **Azithromycin** • **Ramipril**	2
Molecules or drugs under commoditisation	• **Lower volume molecules** • **Complex manufacturing processes** with a **greater number of steps**	• **Candesartan**	3

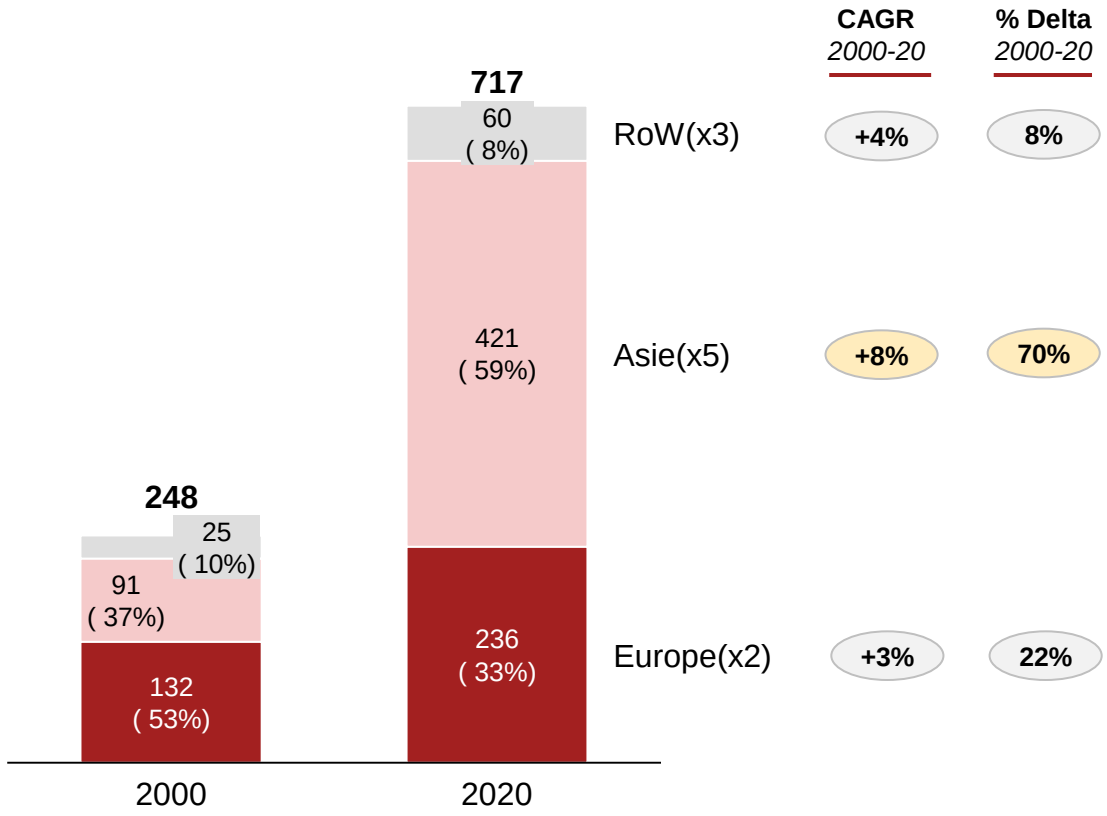


Sources: ProGenerika, Strategy Analyses&

Part of the API production has progressively moved to Asia where manufacturers are specialized in high volume and low margin production

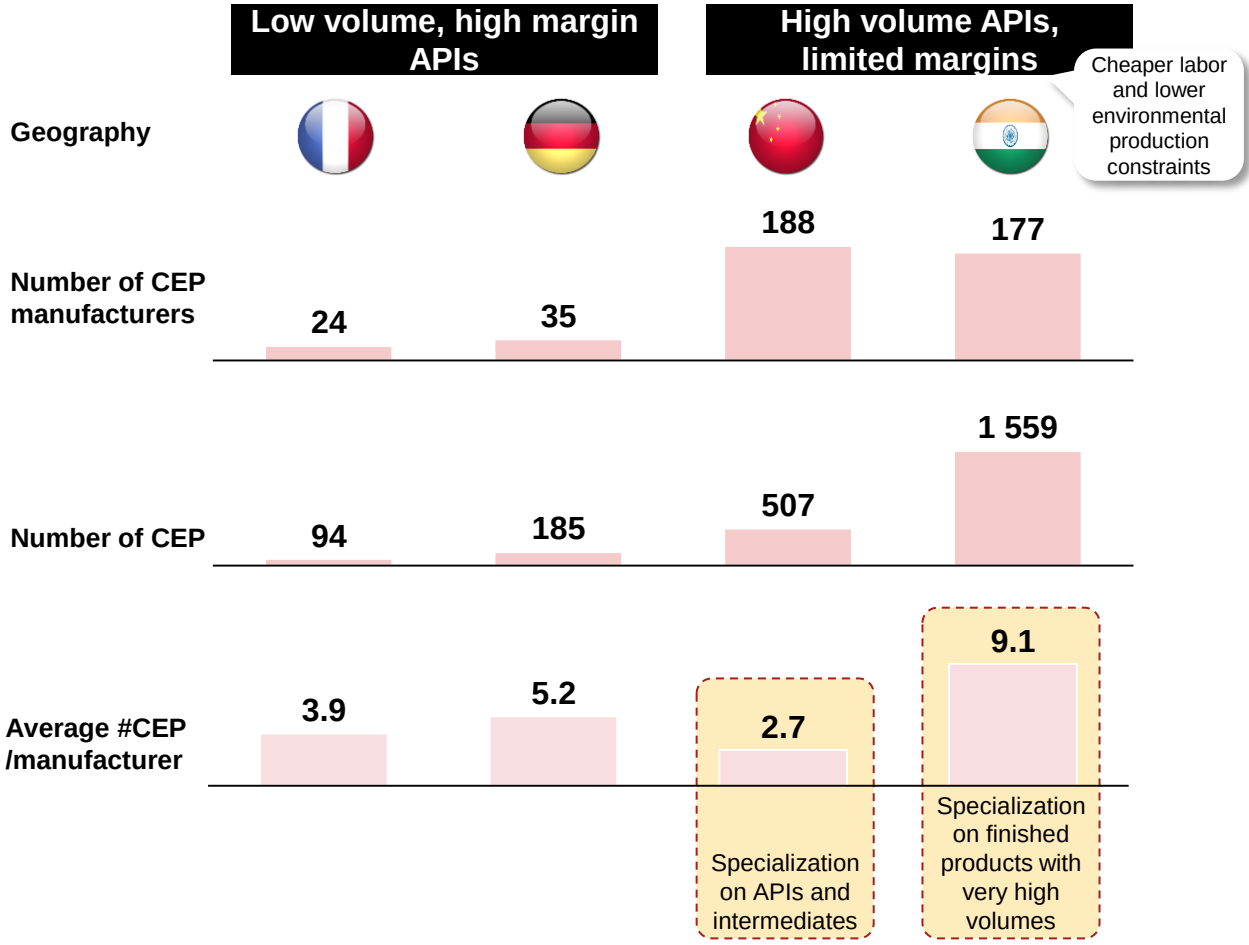
Distribution of CEP manufacturers in the world

In #Manufacturers, 2000-2020



Benchmark and CEP manufacturers by region

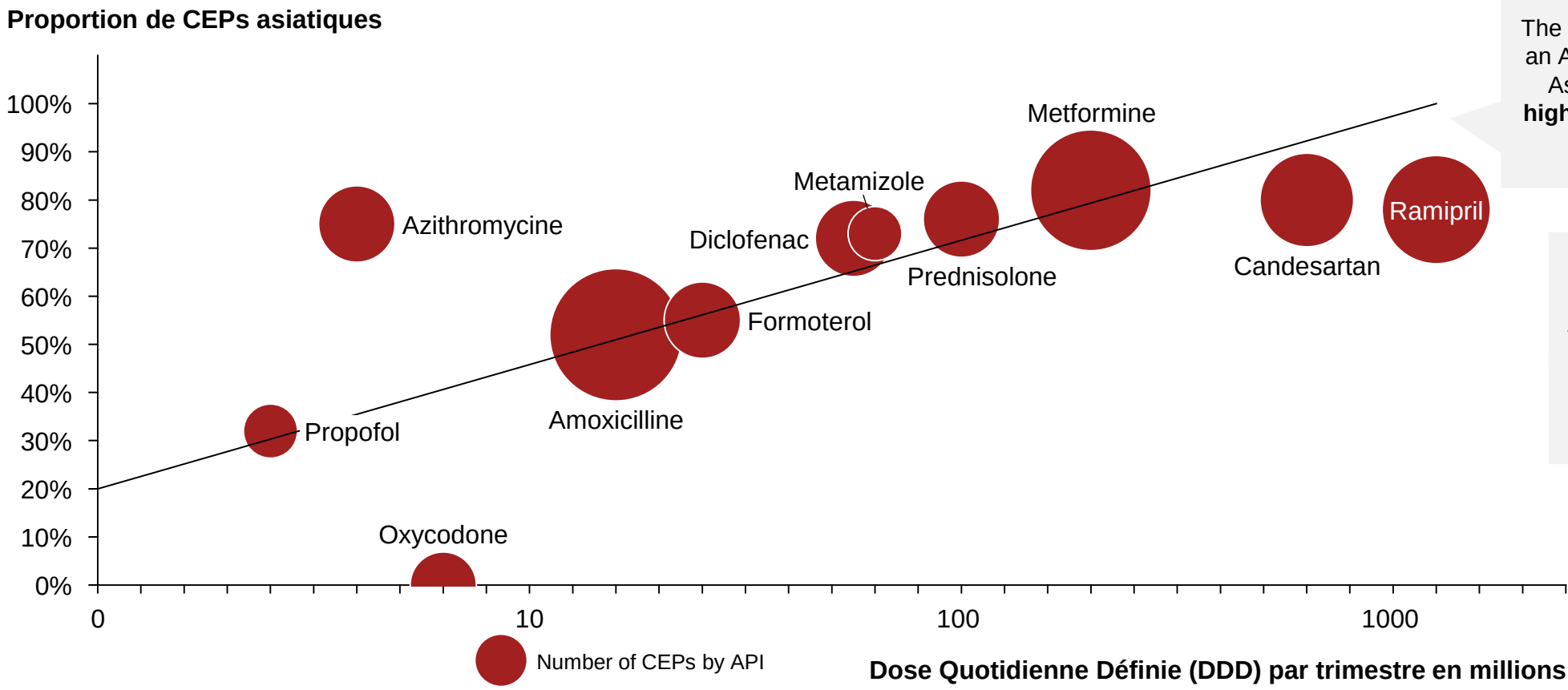
2020



Sources: ProGenerika, Strategy Analyses&

The share of Asian CEPs tends to increase as the defined daily doses of the molecules are increased

Daily doses defined in relation to the proportion of Asian CEPs on a selection of APIs
2020



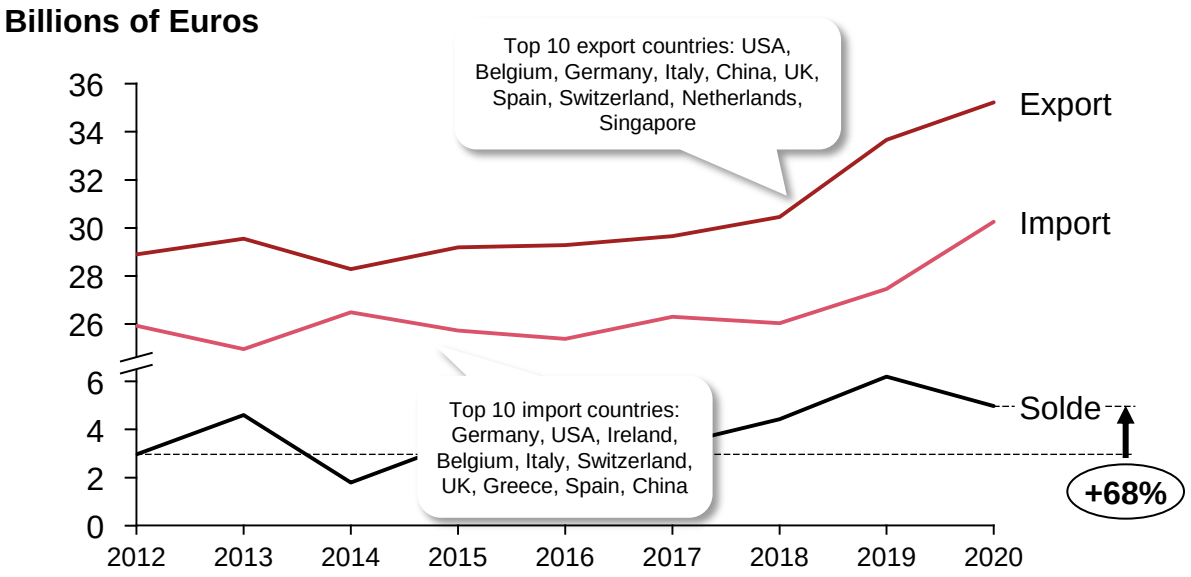
The higher the defined daily dose of an API, the higher the proportion of Asian CEPs for that same API: **higher volume APIs are therefore produced more in Asia**

Within Asia, we observe the same correlation between high volumes and CEPs produced in India: **India is thus the main Asian producer of high-volume APIs**

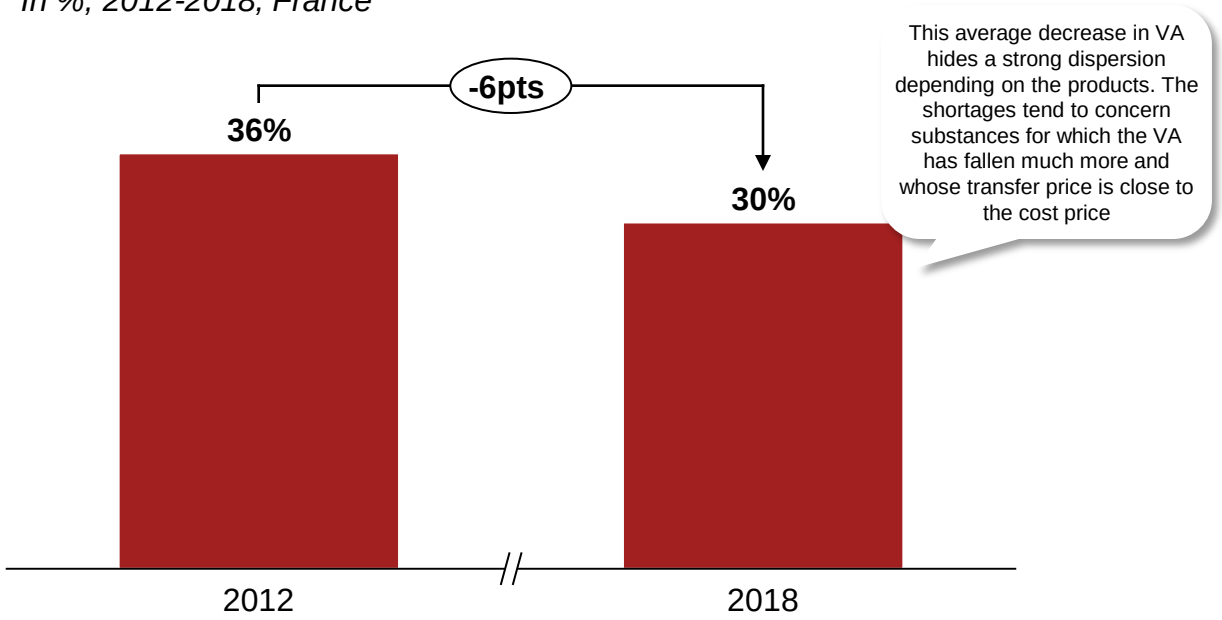
Sources: ProGenerika, Strategy Analyses&

This competition impacts French players, their VA deteriorating due to a potential mature product portfolio or stronger negotiating power of suppliers

Trade balance of the pharmaceutical industry
In billions of euros, 2012-2020, France



Share of Added-Value (VA) in pharma. industry production
In %, 2012-2018, France



French pharmaceutical added value is deteriorating, reflecting possible difficulties in positioning and supply:

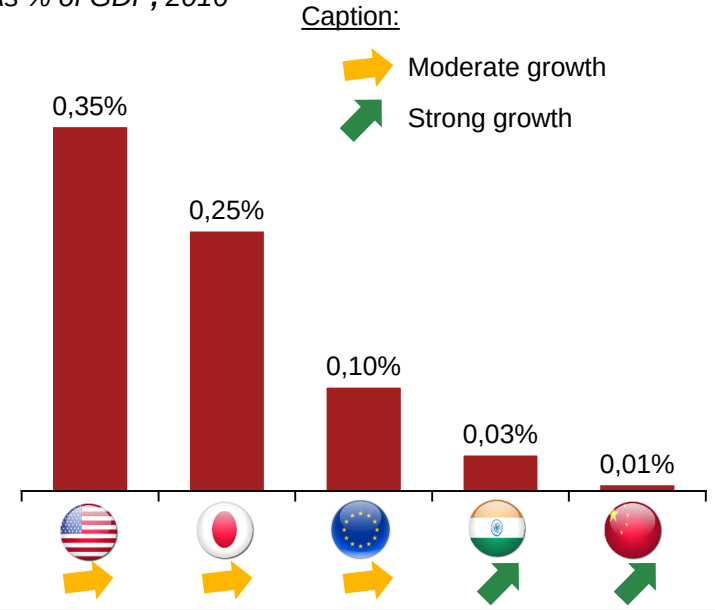
- French laboratories **are more competitive internationally, as** shown by the increase in exports and the trade balance since 2012
- **Pharmaceutical added value is deteriorating**, resulting either from **downward pressure on international prices** or from an **increase in intermediate consumption**
- The **downward pressure on prices** can be explained by a **large portfolio of drugs being commoditized** and by **the entry into the market of** high-volume **Asian producers** benefiting from significant scale effects, leading to a **gradual shift in volumes towards Asia**
- The shift to Asia is **accentuated by cheaper labor** and **lower production constraints** (notably safety/environmental)
- The increase in intermediate consumption can be explained by the **greater bargaining power of suppliers of intermediate products and APIs**

Sources: Eurostat, French Customs, Strategy Analyses&.

The result is a deteriorating competitiveness, increasing reports of tensions, and sovereignty undermined by crises

European competitiveness is being challenged by the US, Japan, India and China

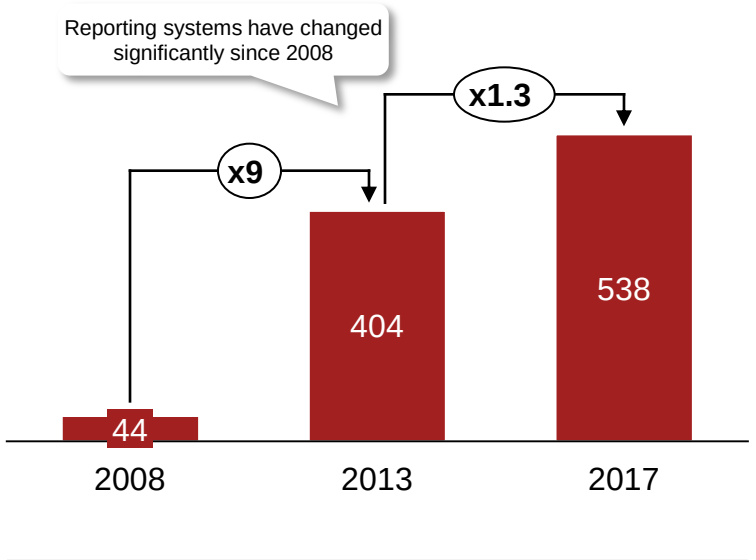
Pharmaceutical R&D expenditure - private sector
As % of GDP, 2016



Europe is caught between :
- **Developed countries** investing up to **3x more** in R&D, widening **the competitiveness gap**
- **Developing countries** with an **accelerated pace of innovation**, **reducing their** competitiveness **gap**

Reports of shortage have increased 12-fold since 2008, mainly for injectables

Reports of shortages and/or tensions on MiTM
In #reports, France, 2008-2017



- Shortage reports are **x12 in 10 years**
- **Hospital injectables** are the most affected by these vulnerabilities
- **Flexibility, production capacity**, and **unforeseen fluctuations pbs. explain** 48% of ruptures in 2017 vs. 34% in 2013

These vulnerabilities cause a lack of sovereignty revealed in times of crisis

Less bargaining power vs. laboratories

In the absence of sufficient local production capacity, **the European Union must turn to foreign laboratories to meet its needs in times of crisis**, which exposes it to the vagaries of market laws

e.g. AstraZeneca supplying the UK before the EU during the Covid-19 crisis because of a preferential clause in a contract

Less bargaining power vs. states

In the event of a crisis, countries with a strong local pharmaceutical industry tend to concentrate the production of their national players on the domestic market, **relegating foreign demand such as that of the European Union to the background**

e.g., China and the United States during the Covid-19 crisis were able to rely on their national laboratories to meet their entire domestic demand before they began exporting doses

Sources: LEEM, OECD, China Statistical Yearbook, Strategy Analyses&.

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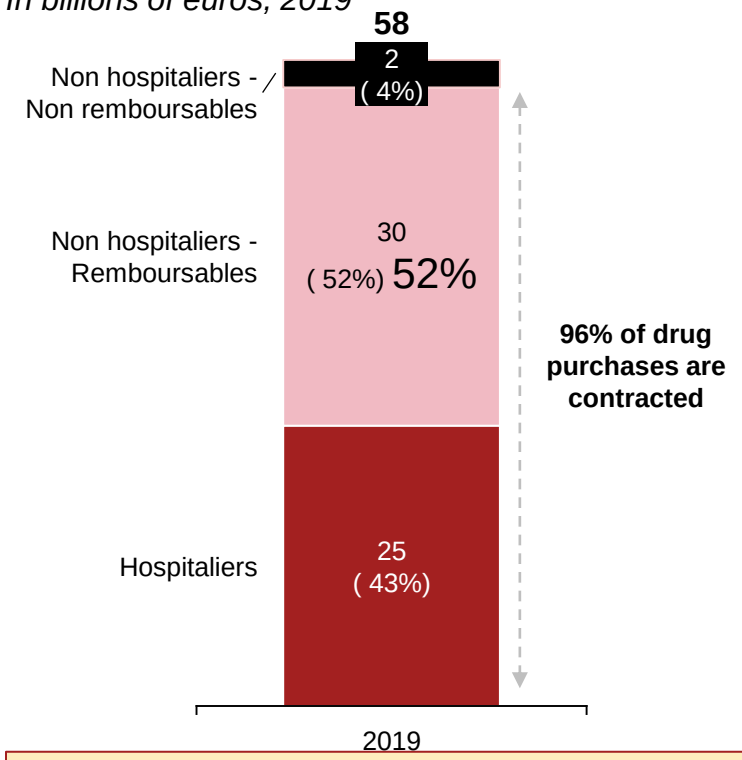
A combination of many factors explains this situation

Category	Description
Demand Dynamics	• **Price is often the main** selection **criterion** for calls for tenders (unless a TCO concept is taken into account, taking into account security, innovation and environmental criteria). This tends to **favor suppliers producing or subcontracting in low-cost countries** • **Hospital demand planning is sometimes "unstable",** making **industrial planning complex** (especially in view of the significant lead times in industry), which has the impact of bringing **certain production lines to a standstill**
Production cost	• The **operating costs of** a factory in Europe can be **up to 40% higher than in Asia**, making **the economic equation more tense** for the laboratories in place, especially in view of the **programmed fall in prices** • **The European environmental and social commitment** implies additional costs for molecules produced in Europe, which can reach **30% of the** total **CAPEX of** a plant, which is not the case for some **non-European players**
Dynamics of the offer	• **Vertically integrated European laboratories are** therefore pushing the **production of their competing APIs**, especially the less profitable ones (often generic APIs or APIs in the process of commoditization), **to subcontractors** • The **subcontractors, having themselves difficulty in remaining competitive**, are pushing for the relocation of **these productions to European soil**
Regulations	• **Certification processes** are often **long and inflexible** • **Binding HSE standards** apply to **products manufactured in Europe** but not to those sold on European soil, creating a **disadvantage for local production of molecules**
Industrial strategy	• Unlike other countries/regions in the world, **the European Union has only had a global pharmaceutical strategy since 2021** • A **global direction specifying the therapeutic areas** (in particular biomedicines, oncology...) and **technologies is necessary** to give a **clear framework to the market players**

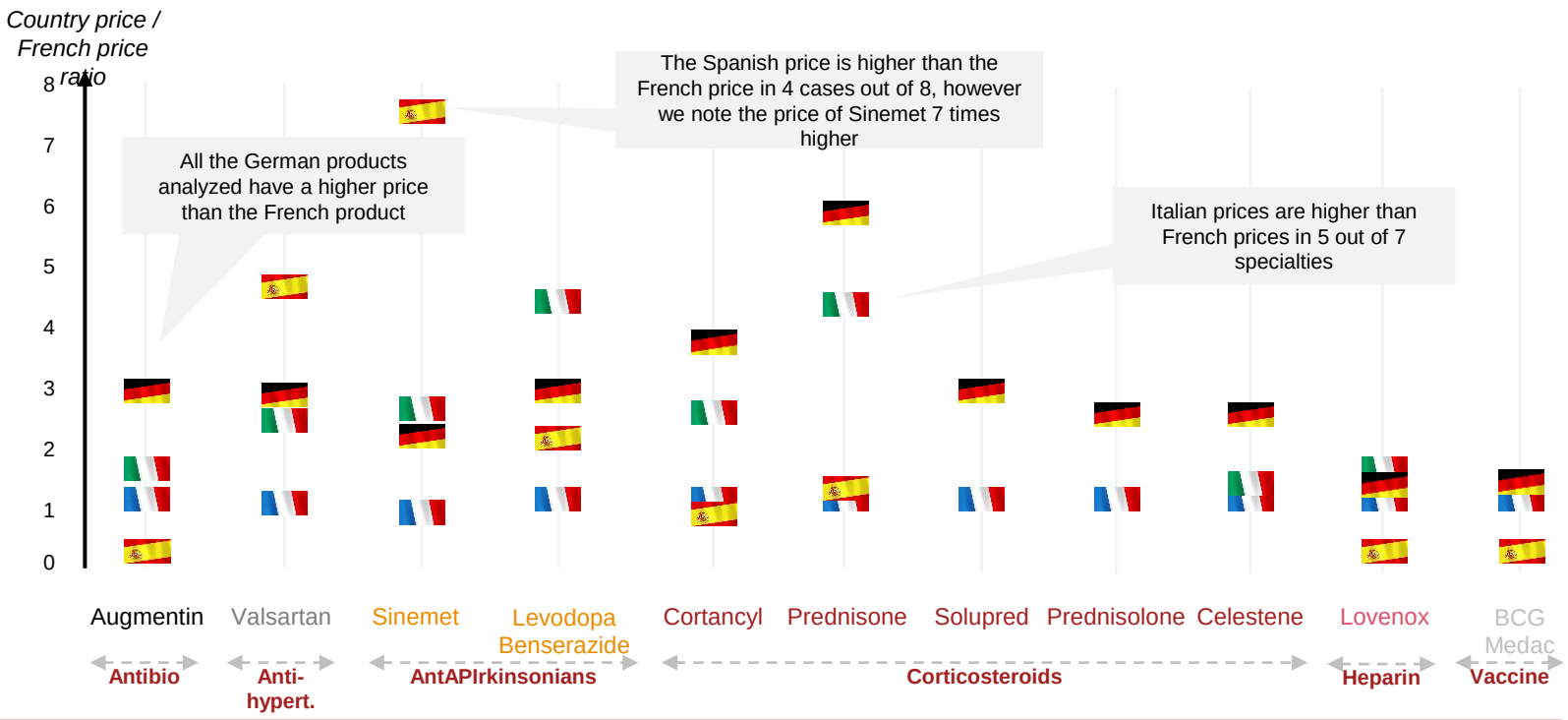
96% of drugs in France are under contract and are on average 2x cheaper than in Europe, promoting commoditization

Drug expenditures - France

In billions of euros, 2019



Drug price comparison on out-of-stock products - 2019



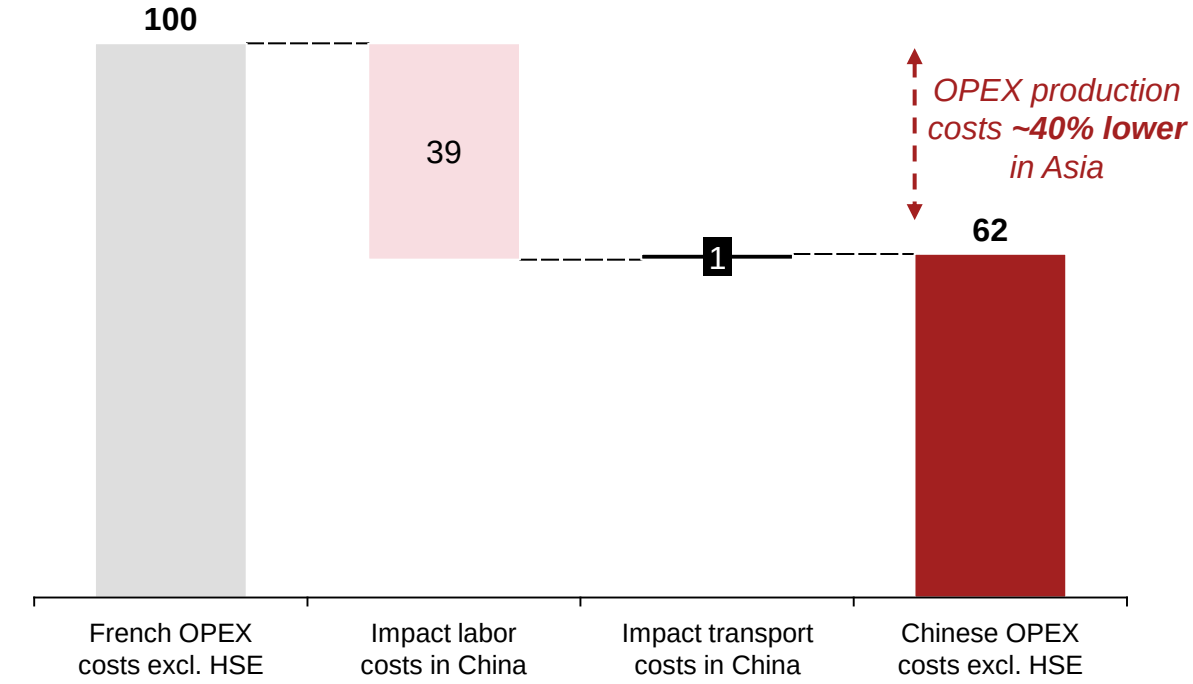
The low prices of French drugs:

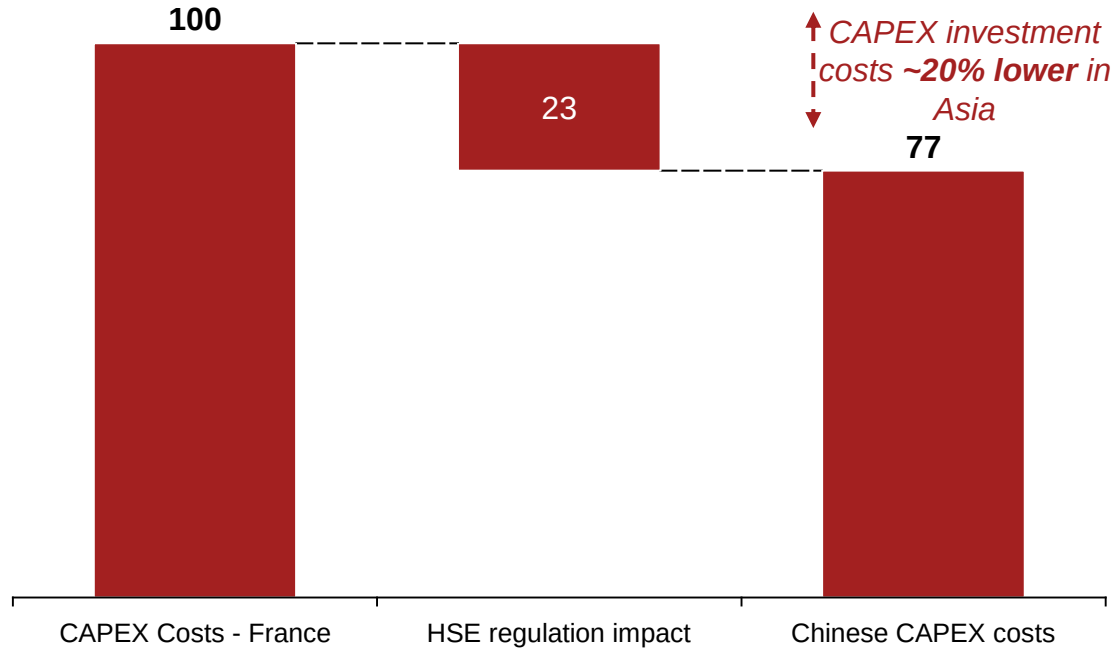
- **Favors high-volume API producers, many of whom are located in Asia** (especially India), with lower labor costs and less stringent environmental standards
- **Weigh on the margins of the** French **pharmaceutical sector**, **making the activity of current companies unsustainable** and dissuading new entrants
- **Complicates the costly integration of HSE standards**, favoring non-EU producers who tend to be less compliant

Investment and operating costs for active ingredients are 20-40% lower in Asia, favoring the relocation of production capacities there

Business case of a pharmaceutical API production in France vs. China *(proxy for Asia)*

Base 100 = French costs, 2020



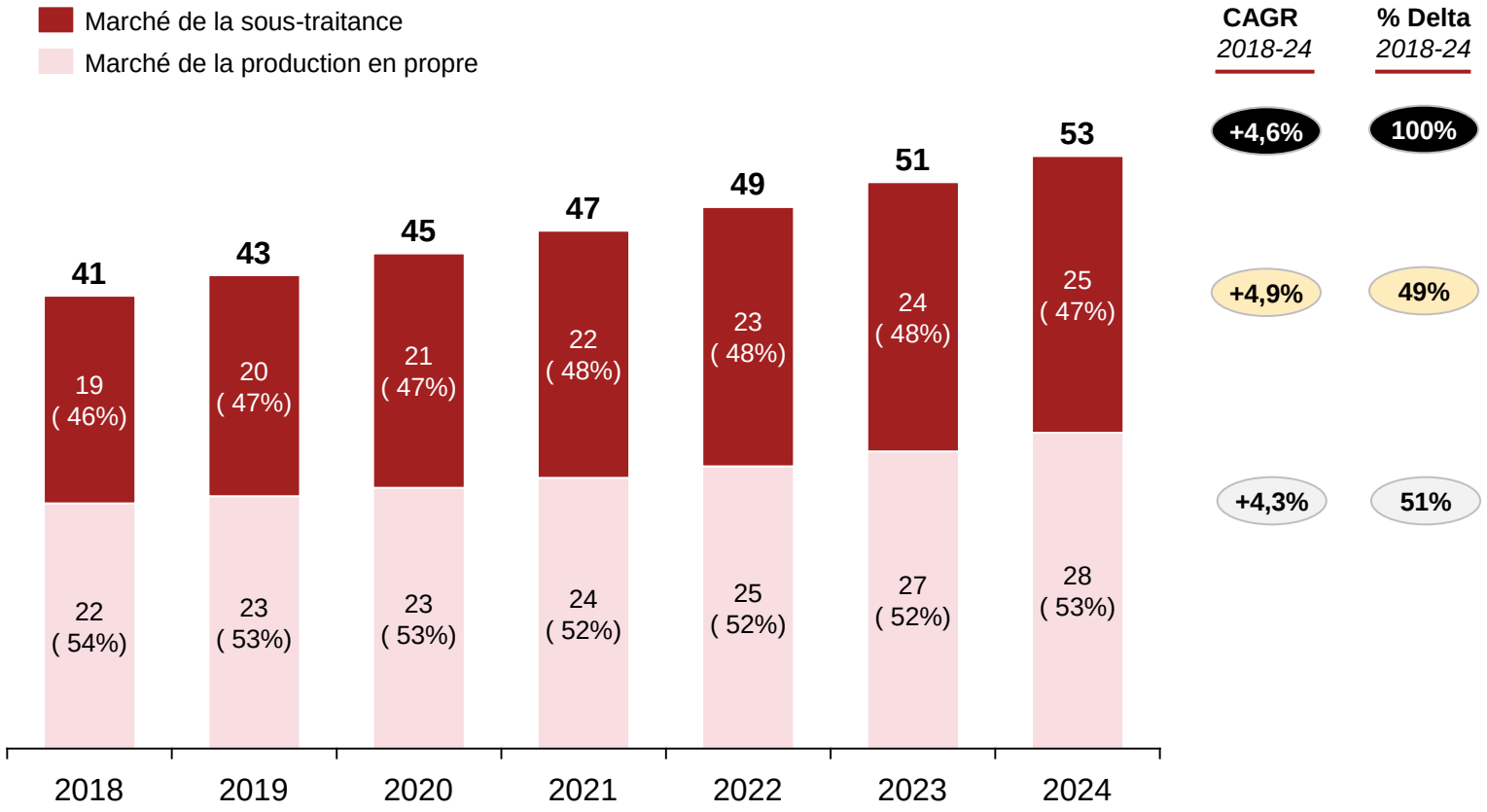


Hypothesis:
- **Equal productivity** between French and Chinese workers
- Cost structure: **50% labor cost** and 10% transportation cost
- **Salaries 4.5x higher** in France than in China
- **5x less** distance traveled

Hypothesis:
- **Size of** production **tools similar** between France and China
- **Similar** production **technologies** between France and China
- **20-30% additional HSE and Opex costs** (treatment costs, WWTP...) due to European environmental regulations

Increasing use of API outsourcing is precipitating the movement of producers to other geographies to gain competitiveness

European market for active ingredients
In $Billions, 2018-2024



CAGR 2018-24	% Delta 2018-24
+4,6%	100%
+4,9%	49%
+4,3%	51%

Low prices, cost and complexity of the production chain fuel the use of subcontractors

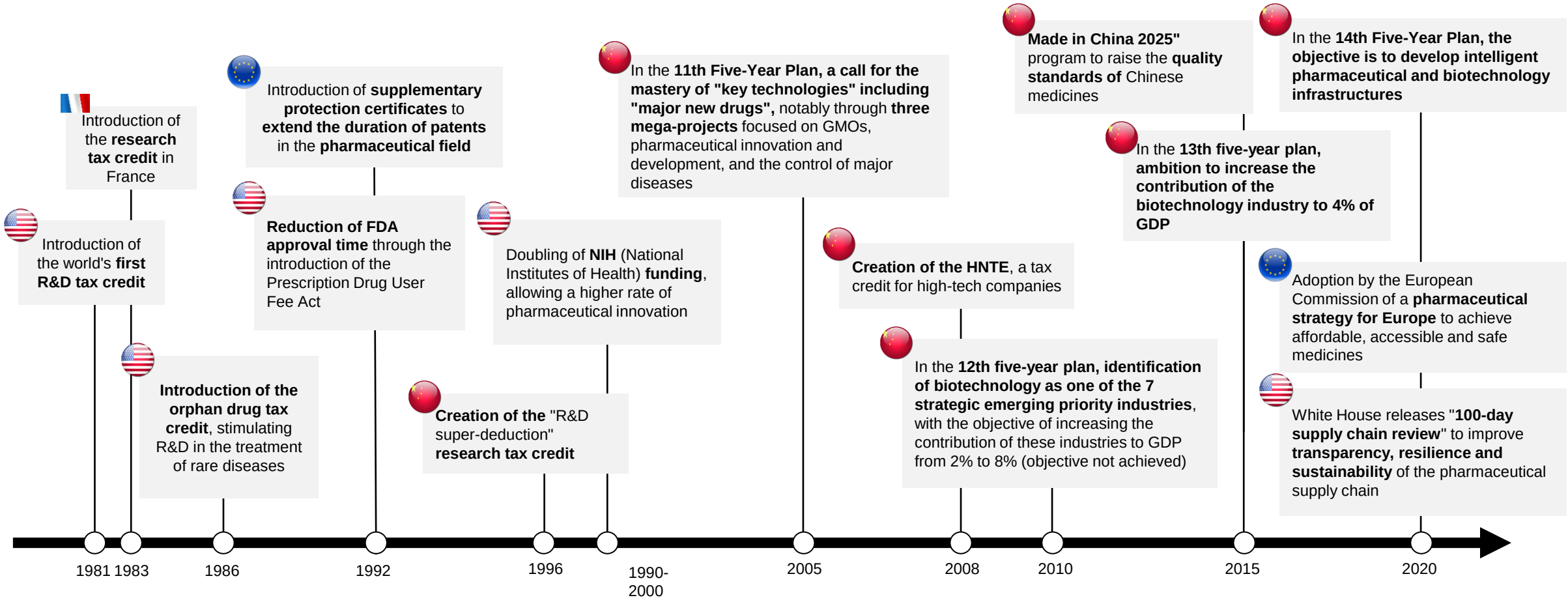
1. **The increasing complexity of pharmaceutical operations, especially R&D,** encourages subcontractors to offer services with increasing added value, making them true strategic partners (CDMOs)
2. **Low prices in European markets** make it necessary to optimize costs, encouraging the use of subcontracting
3. The **production costs and the constraints**, especially **environmental**, do not allow **the economic sustainability of** these productions in Europe

The increasing transfer of cost pressure to the downstream sector leads to a double movement

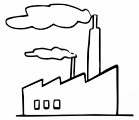
1. On the one hand, many subcontractors are forced to **relocate to emerging countries** (especially Asia) in order to remain competitive
2. On the other hand, there is a **movement of expansion towards the United States** in order to get closer to more lucrative markets (notably via acquisition strategies)

Unlike the United States and China, the European Union did not have a clear pharmaceutical strategy until the end of 2020

Major strategic events in the US, European and Chinese pharmaceutical industry, *1980-2021 (not exhaustive)*



A clear, coherent and detailed pharmaceutical strategy, combining R&D, Public Purchasers and Producers, is essential for success

Category	 R&D	 Financing	 Industrial fabric
Key success factors a positioning strategic	• Pharmaceutical positioning requires significant investment in **R&D** • **R&D must** be **driven by clusters** composed of **pharmaceutical companies, universities and funders in order to** achieve the best discovery results • **Coordination of the elements of these clusters is key** to success • The **ability to transform research into patents** is key to the development of the sector	• Successful financing of biomedical products relies on **public funding, private equity and alliances/M&A** depending on the stage of development of the product • **Public support** is particularly key to **initiating the process and funding basic research** in the preclinical phases • **Investor capital** is needed to **finance phases 1 to 3 of** development	• The **large number of producers** is essential for the development of the pharmaceutical sector • The **fabric of SMEs carrying this production represents ~2/3 of the production forces**, the nature of the activity often making **industrialization complex** • The **ability to mobilize large amounts of CAPEX** to finance dedicated and specific production lines is key to the success of the industrial network
Current challenges in France - focus on biomedicines	• The **amounts invested in R&D** seem to be **allocated less to biomedicines and** more to MedTech **and e-Health** companies • The **number and scope of clusters in France is less important** in Europe • The **transformation of R&D into patents is relatively low due to less coordination in the clusters**	• **Public funding for** basic research is **lower than in Germany and the UK**, resulting in a **weaker pipeline of** products in preclinical trials • Biomedical companies have **increased their use of the capital market** to overcome the lack of investor capital, impacting on the duration of the research phases	• The **number of production sites dedicated to** biomedicines is **relatively small**, **employing ~10k people** • The **structures** expected to carry the CAPEX for the creation of production lines **are mainly SMEs (+80%),** i.e. more small structures than the European partners

All 3 pillars must be activated at the same time to achieve a **successful strategy at the national/regional level**

Contents

Improved transparency in the chain and a review of AO, particularly in hospitals, would favor European production

Category		Type	Potential measures
Shortage	Transparency	Identification	• **Stricter categorization of** medicines of health and strategic importance (MISS) • **Clear definition of criteria for identifying** precursors and critical/strategic APIs, **common to EU countries** • **Mapping of** raw material production **sites** • **Monitoring** the **coverage of** high-risk MITMs • **Obligation to register** suppliers of raw materials supplying the European market in the EMA's EUDRA-GMDP database • Establishment of accelerated registration procedures for products in short supply and alleviation of certain requirements
		Cooperation	• **Optimization of exchanges** between manufacturers, authorities and health professionals **by ensuring** transparency on **the status of stocks** (centralized database on the distribution of MISS stocks) and reorganization of the dissemination of information to users through a "Drug Watch". • **Improved public access** to value chain data (e.g. possibility of origin marking...)
Request	Economic sustainability	Hospital tenders	• Valuing safety of supply, innovation and environmental criteria in drug AOs • Commitment on drug volumes • Optimization of the timing of health product RFPs, particularly between national and regional operators, and adoption of the multi-award aspect • Setting a minimum response time of 3 months for bidders to ensure compatibility with the organization and management time of companies
Offer		Price	• Limiting the decline in drug prices, especially for those undergoing commoditization • Setting a threshold price for medicines whose European supply is no longer assured
		Stock pilling	• Creation of a centralized safety stock for the most essential drugs
		Taxation	• **Support for the establishment** and **maintenance of pharmaceutical laboratories in Europe** through **tax and regulatory incentives** • Perpetuation and extension of the surcharge on productive investments for APIs and medicines
Techno.		Investment assistance	• Strengthening collaboration between public research and industrial innovation in the European biopharmaceutical ecosystem • Extension of the CIR in the form of CIDI to address the problem of industrial development, which is often costly for a biotherapy • Creation of a strategic fund for biomedicines

Sources: LEEM, GEMME, SICOS, Biot Report, G5, Strategy Analyses&.

Also, measures promoting the application of environmental standards to all actors could be beneficial

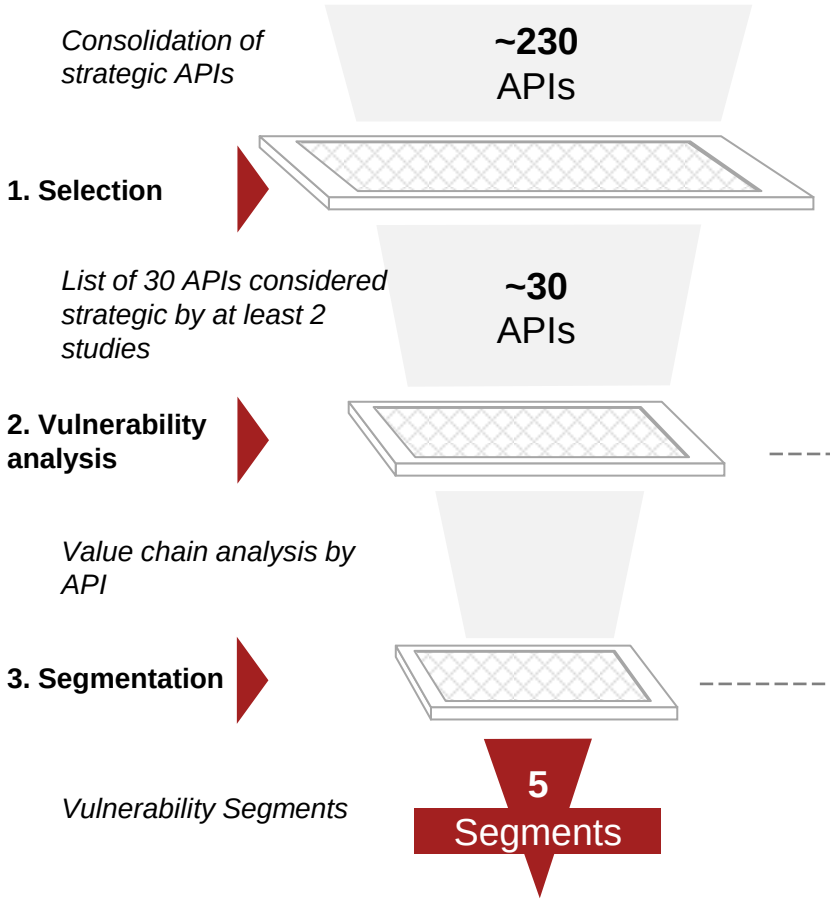
	Category	Type	Potential measures
Offer	HSE Sustainability	Legislation	• **Harmonization of the application of environmental standards** to **all products sold on European soil** • **Systematization and harmonization** of controls within and outside the EU • Elaboration of a benchmark including a series of criteria and requirements related to the circular economy and decarbonization of companies in the sector
		Taxation	• **Creation of a deduction for the environmental upgrading of industrial sites**
		Investment assistance	• Support for investment in production tools with high environmental standards

Sources: LEEM, GEMME, SICOS, Biot Report, G5, Strategy Analyses&.

Contents

We followed a 3-step approach to identify vulnerabilities in the API supply chain

Segmentation methodology followed



Constitution of a list of **~230 molecules** considered by **5 studies as strategic**. These studies have a **common scope of analysis** (APIs) but use **different sources and criteria**, including

- Quantitative criteria: volumes consumed, % of non-EU suppliers, supplier concentration
- Qualitative criteria: essential drug list, #breakdowns
- Sources: WHO, ANSM, BFARM, EU, EDQM, Qyobo, PharmaOffer, Customs, Purchasing data

Selection of **redundant APIs**, having been identified by at least 2 different studies as strategic by the 5 selected studies:

- **~30 APIs**
- **~20 therapeutic classes**

For each selected API, **conduct ~20 interviews** addressing vulnerabilities across the value chain with **industry experts:**

- **Private** (e.g. APIs manufacturers)
- **Public** (e.g. European Commission)

Segmentation of APIs by type of vulnerabilities identified based on :

- Expert interviews conducted
- Synthesized studies

The 5 studies that allowed the selection of APIs have a common scope but heterogeneous criteria and sources

Data available by source study

Study	Scope of analysis	#Priorities	Selection criteria	Sources
Sanofi	• **APIs**	**145**	Qualitative: • Presence on the WHO and European essential drug list • Adding drugs in recent shortage (FR/GR) Quantitative: • Addition of the most consumed drugs (EU)	• **WHO** • **ANSM** • **BFARM** • **EU**
ProGenerika	• **APIs**	**21**	Quantitative: • Share of Asian production (China + India) for these APIs • Estimated European demand for these APIs	• **Edqm** • **Qyobo** • **PharmaOffer**
IQVIA	• **APIs**	**23**	Qualitative: • Major therapeutic areas Quantitative: • Dependence outside the EU by APIs in these therapeutic areas	• **Expert Interviews**
DGE	• **Raw materials** • **Pdts. Synthesis** • **APIs** • **Finished products** • **Medical devices**	**54**	Quantitative: • Import volume • Share of non-EU imports • Supplier concentration Qualitative: • Level of therapeutic interest • Country of origin of supplier 1 and 2	• **Customs data**
G5 Health	• **Raw materials** • **Pdts. Synthesis** • **APIs** • **Packaging**	**36**	Quantitative: • Purchase volume - G5 Health • Geographical dependence • Supplier concentration Qualitative: • Major therapeutic areas	• **Purchasing French laboratories**

Fragile input supply" molecules depend on key materials and intermediates manufactured outside Europe

Detail by segment

Caption: ● Important vs. other molecules ○ Low

Ex. molecules	Consumption volume in Europe	API Award	Production complexity	Details of the problem	Potential levers
Docetaxel / Paclitaxel	4	1	2	• Products made by **hemisynthesis**, from **yew leaves** • The production of this natural material is today **almost exclusively carried out in India** with **little innovation of process possible**	• Price
Heparin	2	3	3	• **Natural product** made from **porcine inputs** produced almost **exclusively in China and Singapore** (although porcine heparin is **available in France**) • **Pork inputs are vulnerable to various diseases that can disrupt the production chain** (e.g. PRRS crisis in 2007 and ASF in 2018) • Biological pathway not synthesized **despite the R&D efforts** already implemented by the laboratories for several years	• Visibility on demand • Process innovation • Price
Macrolides *(e.g. Azithromycin)*	4	1	1	• Derived from the **erythromycin molecule tree** and produced in the **USA and China** • Erythromycin is also used to **create a dozen other antibiotics** and benefits from **scale effects in China**	• Process innovation (fermentation and synthesis routes)
Corticosteroids *(ex: Prednisolone)*	2	1	4	• The **manufacturing of the molecule** requires **30-40 steps,** increasing the probability of an incident along the chain (e.g. more than 6 months of shortage of oral corticoids in France due to a calibration problem between the Italian and French factories) • **7/8 key intermediates**, derived from fermentation and now produced in China, are **common to all corticoids**	• Innovative ways of synthesis

Molecules in "complex production" have unstable, regulated processes with a large number of manufacturing steps

Detail by segment

Caption: ● Important vs. other molecules ○ Low

Ex. molecules	Consumption volume in Europe	API Award	Production complexity	Details of the problem	Potential levers
Ibuprofen	3	1	3	• **Relatively complex** and **expensive manufacturing** process for which **non-European manufacturers** have **developed a critical size** and are very competitive • The **technology for manufacturing ibuprofen does not** exist in **Europe**, for a **key molecule in high demand** as an analgesic for the treatment of inflammation	• Process innovation • Price
Insulin			4	• The **inputs used** result from **biomedical manufacturing processes**, with a **high level of complexity** (continuous production from upstream to downstream) • **Non-European CEP** represent **90% of the total**, mastering the technology and having the scale to **compete in the market** • Because of its **complexity and the competitiveness of** the actors present, this production is **difficult to achieve** at the local level **without introducing process innovation**	• Innovative ways of synthesis
Fludarabine	1		4	• The molecule is subject to **EPO-5 classification**, requiring a **dedicated production environment** and a **large number of steps** • Supply is not able to follow the fluctuations of demand because of the **rigidity of the production chain**	• Calls for tender
Sartans *(ex: Candesartan, Losartan...)*	2		4	• **Current unstable manufacturing processes** leading to numerous cases of **impurities** caused by principles and reagents • **Ruptures resulting from** these impurities are **numerous** (e.g. 2018 with the worldwide recall of lots of major sartans due to an impurity in the valsartan prod.) • The **number of manufacturers** worldwide is **limited**, **aggravating the tension** on this molecule (e.g., only one production site for valsartan worldwide in 2018)	• Innovative ways of synthesis • Price

Sources: Interviews, Studies, Strategy Analyses&.

Molecules with a "Production including pollutants to treat" imply discharges and dangerous chemical reactions strongly regulated in the EU

Detail by segment

Caption: ● Important vs. other molecules ○ Low

Ex. molecules	Consumption volume in Europe	API Award	Production complexity	Details of the problem	Potential levers
5-FU	2	1	1	• **Manufacturing process involving old fluorination techniques** whose handling causes **inherent dangers** (high toxicity, corrosion...) • Fluoridation **discharges** are highly **toxic and polluting**	• Harmonized HSE regulations (outside the EU) • Process innovation (continuous production) • Price
Azathioprine				• **Manufacturing process** involving the potential for **significant releases of** toxic **metabolites** (e.g. 6-methylmercaptopurine), mainly performed in China today • As **environmental pressure increases**, **sites in China are closing**, creating **major supply problems** for the molecule and a **need for technological upgrades** in Europe to reduce environmental impact	• Harmonized HSE regulations (outside the EU) • Process innovation (continuous production) • Price
Estrogen				• Manufacturing process **with high hormone release** • When the **molecule is made outside Europe**, the hormones are untreated and **end up in the water system of the cities** because of the **lack of constraints** • The non-application of HSE rules to European manufactured products makes them more competitive on the market	• Harmonized HSE regulations (outside the EU)
Metronidazole		1	2	• The manufacturing process is carried out mainly in India, **in large** dedicated **bunkers** and is **based on an explosive chemical reaction** • These **explosive reactions** represent a **significant safety hazard that is not acceptable in Europe**	• Harmonized HSE regulations (outside the EU) • Process innovation (continuous production) • Price
Doxycycline	2			• The molecule is manufactured via a process of **fermentation of biological materials, which is polluting** and requires a **long cycle, mainly in India and China** • These **manufacturing units are closing** for **regulatory contingencies** and **environmental improvements**, leading to **tensions**	• Harmonized HSE regulations (outside the EU) • Process innovation (continuous production) • Price

Molecules with a "low API price" are generic, high volume and made outside Europe by players with critical size

Detail by segment

Caption: ● Important vs. other molecules ○ Low

Ex. molecules	Consumption volume in Europe	API Award	Production complexity	Details of the problem	Potential levers
Paracetamol	4	0	2	• Molecule **highly consumed in Europe** (35-40k tons/year) at a **very low price level** (5-10€/kg) experiencing **strong supply tensions** • **Production** is carried out **mainly in the United States, India and China** (the United States and India having served their **domestic markets as a priority** during the crisis) • **2 synthesis routes are used**, depending on the comparative advantage of each territory: the **USA** uses **benzene** (derived from petroleum), **China uses PNCB** (derived from the agricultural industry, used in fertilizers for rice cultivation) • Production in Europe is **possible**, but to **guarantee compliance with environmental standards** and to **compensate for more difficult access to inputs**, **innovation is essential** for a **competitive position in** relation to the competition, particularly from India	• Process innovation (e.g. continuous flow) • Price
Metamizole **Metformin**	4	0	1	• **A** group of molecules with **large volumes consumed in Europe** (5-20k tons/year in Europe) with **low price levels** (5-10€/kg) that are subject to **occasional tensions** • They **are old** (**discovered before 1980),** with **low production complexity** (<10 steps) and are among the first to **become generic** • Their **production** is mainly carried out in **Asian countries** by **large** players, achieving strong economies of scale with manufacturing costs **~30% cheaper than in Europe** (3-7€/kg) • **Innovation** is essential for a **competitive positioning on these molecules**	• Innovative ways of synthesis • Price

Molecules with "unstable demand" have fluctuating and complex hospital outlets in industrial planning

Detail by segment

Caption: ● Important vs. other molecules ○ Low

Ex. molecules	Consumption volume in Europe	API Award	Production complexity	Details of the problem	Potential levers
Propofol	1	1	1	• **Key molecule** for the treatment of patients in **intensive care,** which is under **strong pressure** in times of **health crises,** especially for injectable forms • The **production technology** is sufficiently **mastered** and the inputs (e.g. phenol, isopropanol) are not under **any particular pressure** • However, the **manufacture of** these molecules **is carried out on** non-dedicated **polyvalent lines** which are for the most part **not active in Europe** • The **lack of visibility on the demand for** this molecule, particularly in hospitals, is pushing players to **stop production** • **Restarting production** is a lengthy process, particularly because of the **time required to reconstitute** certification **files**, **order and receive inputs**	• More readable calls for tenders over time • Price • Building back-up capacity
Morphine **Codeine**	1	1	1	• These molecules are **poppy derivatives** whose **production is strongly regulated** by the ANSM • **Quantities are small** but **fluctuate** according to **hospital needs** • **Small poppy crops** exist in France for the national supply of the raw material necessary for the production of these molecules • However, an **existing aging and limited production tool reduces the potential to achieve economies of scale**, meet a large and fluctuating European demand • This is accentuated by the **strong competition from Indian producers**, who benefit from cheaper and more **abundant raw materials and a larger size** • The **prices charged by Indian** players **are 30-40% lower** than in Europe. They are better positioned to **respond to unexpected increases in demand**	• More readable calls for tenders over time • Process innovation (plant technology)

Contents

1 - Location of production

Zoom by measurement

Scope: ● APIs ● Finished products ● Entire chain

Related objectives		Details of the proposed measure	Segments covered
Maintain skills and resources (especially technologies) to ensure **resilience in the event of a crisis**, and **support** potential **innovations** in production processes or the use of the active substance	**Context**	• Guarantee the **security of supply** of **critical molecules** by introducing supply **criteria** (diversity of sources, bonus/malus for reliable and sustainable production in Europe, etc.) as well as (possibly European) **back-up production** (diversity of supply): – The European Agency and the national drug agencies must **secure supplies over the long term** and **list the manufacturers of active ingredients** and intermediates for the Member States' marketing authorizations. – Implement the development of shortage management plans for APIs of essential medicines – For critical molecules, in order to ensure sufficient availability of supply in Europe, **investments* should** also be **valued,** for example by allowing a **higher price for the drug** to **compensate for the higher cost** of production in Europe or of **safer** and **more environmentally friendly production** • **Supporting the development costs** of repatriated molecules or **obtaining new files through the CIR** (e.g.: CEP): – **Establish a fast-track procedure** to accelerate the qualification of a European supplier, even if it is only a back-up, in the modification of files. – **Financing by the CIR of the R&D costs for the constitution of the files (**closed part of the MA or CEP) in case of repatriation of **a molecule in Europe**	**Fragile input supply** *(e.g. heparin)* **Low price of the API** *(ex: Paracetamol)* **Unstable demand** *(ex: propofol)*
	Tools to use		

Ease of realization	Level of implementation	Conditions for implementation, success / Next steps
Ease of implementation: • Easier to require supplier diversity in relation to risk management than EU location **Estimated timeframe:** • < 1 year	• At the MS level • With European coordination	• Identify existing capacities and assets at risk in order to prioritize molecules for which a location in Europe is essential • Start by encouraging the localization of APIs in Europe (funding of DMF or CEP files, etc.) • Set up incentives to encourage the localization of APIs and medicines in Europe • Link to public tenders and innovation • Digitization and transparency of information in a designated receptacle to allow verification

Notes:
Made by European API providers to be competitive. If an API cost premium remains significant compared to non-European competition, consider a re-evaluation of the price of the critical drug to compensate for the additional cost of its production

2 - Harmonization (1/2)

Zoom by measurement

Scope: ● APIs ● Finished products ● Entire chain

Related objectives		Details of the proposed measure	Segments covered
The implementation of **shortage prevention plans** at the supplier level **Cooperation between MS** to improve demand predictability and limit shortages	Context	**1 - The implementation of shortage prevention plans at the level of Active and Intermediate Principles suppliers** For the most essential drugs, the list of which is established according to precise criteria in terms of medical need and patient risk in the event of a shortage, together with criteria relating to the ability of the drug to supply the French market (defined as drugs for which a shortage would entail an immediate and vital risk for patients suffering from a serious pathology, in the absence of a therapeutic alternative recommended by the authorities in this indication), it is recommended that reinforced Shortage Management Plans be put in place for raw materials, which could include • A mobilizable safety stock, available in France or in Europe, with distribution of quantities according to market shares, • Systematic identification of suppliers throughout the production chain, for active substances (incl. PM and intermediates) • An optional marking of the drugs on the box or via a QR code increasing the legibility and traceability on the value chain **2 - Cooperation between MS to improve demand predictability and limit shortages** • Optimization of order management and distribution practices • For hospital products: centralization of needs (as was done for critical drugs during the Covid period) to better distribute the allocation of available stocks among the states • AnticAPIte the needs to optimize the organization of the productions • Allow sufficient time between order and delivery to avoid shortages	**Fragile input supply** *(e.g. macrolides)* **Low price of the API** *(ex: Metformin)* **Unstable demand** *(e.g.: codeine)*
	Tools to use		

Ease of realization	Level of implementation	Conditions for implementation, success / Next steps
Ease of implementation: • Simple to implement, more difficult to apply in practice **Estimated timeframe:** • Depends on political will	• European	• Creation of a European authority independent of the Member States • Adequacy of the resources provided • Need for price increases to accompany these measures • Transparency of all actors is a necessary condition • The limitations are that these measures do not necessarily solve structural vulnerabilities (if the chain is already dependent on Asia, shifting responsibility will not change anything), and may make the value chain less profitable

2 - Harmonization (2/2)

Zoom by measurement

Scope: APIs; Finished products; Entire chain

Related objectives

The implementation of a **coordinated stock management strategy** at the European level
The establishment of a **centralized definition and monitoring of shortages** at the European level
Increased flexibilities for **emergency imports** needed in case of critical shortages

Details of the proposed measure

Context

Tools to use

3 - The implementation of a coordinated stock management strategy at the European level
- Earlier sharing of information regarding stock monitoring in the event of a strain, under the auspices of the health authorities
- The creation of a centralized information database on the distribution of stocks: under the aegis of the ANSM, this database would be filled in by all players in the pharmaceutical chain and would concern the status of stocks and supply plans,
- Pooling of information between EU states for enhanced European coordination on stock allocation
- Stopping national requirements in favor of measures to secure European stocks, in consultation with the ANSM

4 - The establishment of a centralized definition and monitoring of shortages at the European level
- Harmonization of practices between France and Europe, through harmonization of definitions and monitoring of shortages, currently underway at the EMA

5 - Increased flexibilities for emergency imports in case of critical shortages
- Simplifications and regulatory adaptations to shorten administrative registration times in case of tension
- Harmonization of information on primary packaging to encourage the development of multi-country packaging

Segments covered

Fragile input supply *(e.g. macrolides)*

Low price of the API *(ex: Metformin)*

Unstable demand *(e.g.: codeine)*

Ease of realization

Ease of implementation:
- Simple to implement, more difficult to apply in practice

Estimated timeframe:
- Depends on political will

Level of implementation

- European

Conditions for implementation, success / Next steps

- Creation of a European authority independent of the Member States
- Transparency of all actors is a necessary condition
- The limitations are that these measures do not necessarily resolve structural vulnerabilities

Request

3 - Hospital tenders

Zoom by measurement

Scope: APIs, Finished products, Entire chain

Related objectives

Ensure therapeutic management of patients for **MiTM drugs** for which **vulnerability and risk of shortages have been identified**. **Consolidate the robustness and sustainability of the** production **value chain of** these drugs from APIs / raw materials to finished products

Details of the proposed measure

Context

- In recent years, due to an increasingly constrained and unstable environment, hospitals have been facing more and more frequent procurement difficulties. Some of these difficulties could be solved through a revision of the clauses and criteria for tendering for certain health products.
- **Review the terms and conditions of public procurement practices** (volumes, award criteria, award deadlines, etc.),
- Set up **multi-tender calls** with **volume commitments** for each of the tenderers in order to **perpetuate the number of players and their production and ensure redundancy in case of crisis**
- **Enhance the value of environmental and societal criteria** in calls for tender; in fact, the purchasing strategies of hospitals are mainly based on price criteria
- **Valuing security of supply criteria in the** value chain

Tools to use

- The introduction and **enhancement of criteria for securing** supplies, such as "manufacturing in Europe for the entire production chain (from API to FP)" and **multi-sourcing**
- **The introduction and valorization of social and environmental criteria** linked to the production chain
- **Reciprocal volume commitments** to guarantee security of supply
- **Incentives for hospital structures** (CAQES type) to **resolve the contradictory injunction to reduce the** hospital drug **budget** and the **desire to secure supplies.**

Segments covered

Fragile input supply *(e.g. azithromycin)*

Unstable demand *(ex: propofol)*

Ease of realization

Ease of implementation:

- Difficult given the number of actors involved and the guiding principles of public procurement

Level of implementation

- National or European level (pharmaceutical strategy guidelines, guidelines for public purchasers for the award of intelligent and innovative contracts)

Conditions for implementation, success / Next steps

- Multidisciplinary working group (API and drug industry, hospital buyers, FHF, DGOS)
- Transparency and political will
- Volume, tariff construction and standardization (a single AO won will not allow the maintenance of a factory in Europe)
- Need for some transparency of suppliers and control capacity (e.g. for some Asian suppliers)

Request

4 - Legibility

Zoom by measurement

Scope: APIs, Finished products, Entire chain

Related objectives		Details of the proposed measure	Segments covered
Increasing transparency in the value chain	Tools to use	In order to smooth the flow of information and restore trust between actors, it is recommended: • **Early sharing of information** on **vulnerabilities** and tensions with authorities • **Sharing** of **information** between EU states for **enhanced European coordination** • An **extension of the information obligations** of the European databases to manufacturers of active substances outside the European Union who supply the EU. This will require the registration with the European Medicines Agency (EMA) of all suppliers of active ingredients who wish to market or stop marketing in Europe • **Knowledge of the value chain** • **Creation of an** optional **"Made in Europe" label** on drug boxes to promote the production origin of APIs, intermediates and raw materials	**Fragile input supply** *(ex: ramipril)* **Unstable demand** *(ex: morphine)*

Ease of realization	Level of implementation	Conditions for implementation, success / Next steps
Estimated timeframe: • Short term	• Europe	• The provision by ANSM of an electronic record system to obtain early information about tensions • Transparency and control of suppliers

5 - Capacity building

Zoom by measurement

Scope: APIs, Finished products, Entire chain

Related objectives

Encourage the modernization of existing capacities or the **installation of new** production **capacities** in Europe for certain **critical active ingredients** whose existing capacities in Europe are in **difficulty or at risk in the short/medium term** or for which there is no production in Europe

Details of the proposed measure

Context

- **Support for the construction or modernization** of facilities for the production of **critical molecules** in Europe
- **To maintain and develop the production capacity** in Europe of **essential active ingredients and intermediates at an acceptable cost** and in compliance with the strictest safety and environmental standards
  - Europe must **secure its supplies** in the long term and use **existing production capacities** for **medicines**, **active ingredients** or **intermediates** in Europe.
  - Failing that, for **technologies or value chains that no longer exist** in Europe (paracetamol, antibiotics), consider relocating to existing sites **based on technological innovations** and **direct or indirect support** (long-term contracts, price impact via impact on reimbursement of the finished product)
  - Similarly, for **weakened value chains,** support for **capacity expansion** or **capacity flexibilization** is needed to **strengthen the existing fabric** and ensure that it can respond, even in times of crisis
  - **Extend the CIR** to CEPs files
  - Include **Capex aid** in **calls for tenders**
  - Include the **scope of APIs** in the next health **IPCEI**

Tools to use

Segments covered

- **Fragile input supply** *(e.g. corticosteroids)*
- **Production including pollutants to treat** *(e.g. doxycycline)*
- **Complex production** *(e.g. sartans)*
- **Low price of the API** *(ex: Paracetamol)*

Ease of realization

Ease of implementation:
- Subject to compliance with state aid rules

Estimated timeframe:
- From now on

Level of implementation

- At the MS level
- With European coordination

Conditions for implementation, success / Next steps

- Identification of priorities
- Possibility of having a competitive unit (if the unit is not competitive, it is unrealistic to want to relocate without additional measures such as the level playing field or the incentive to buy in Europe)
- Safe and environmentally friendly technologies used (**highest safety and environmental standards**)
- Provide support over time to ensure the sustainability of production
- Potential limitations are the need for sufficient support for investment and explicit coordination at the European level

6 - Level-playing field

Zoom by measurement

Scope: APIs, Finished products, Entire chain

Related objectives

Improve the competitiveness of European industry by **fighting social and environmental dumping**.
To ensure the **sustainability and robustness** of the value chain by maintaining **healthy and efficient competition** on reliable, safe and environmentally friendly facilities

Details of the proposed measure

Context

- **To take into account, in** addition to quality requirements and in addition to price alone, **minimum criteria of respect for the environment, health and safety rules** and **quality for suppliers of medicines**, **APIs or raw materials**
- In the same way as quality, the **failure to respect a sufficient level of** employee safety and respect for the environment must **lead to the possibility of sanctions against** any unsustainable supplier

Tools to use

- **Additional taxes** paid to the State for these products by API suppliers wishing to sell in Europe without providing a guarantee of environmental and HSE compliance
- A **bonus system** in **public tenders**
- **Differentiated obligations** between suppliers to ensure the robustness of the value chain
- **Access** to the European market **conditional on compliance with minimum social and environmental standards**

Segments covered

Fragile input supply *(e.g. heparin)*

Production including pollutants to treat *(e.g. azathioprine)*

Complex production *(ex: Ibuprofen)*

Low price of the API *(e.g.: statins)*

Ease of realization

Ease of implementation:
- Very difficult due to the complexity of the value chain and the means of control

Estimated timeframe:
- 3 to 5 years

Level of implementation

- Necessarily European (border at European level)

Conditions for implementation, success / Next steps

- Implementation of laws or regulatory framework
- Establishment of resources to monitor suppliers' compliance with European quality, safety and environmental standards and identification of the sanctioning authority(ies) (addition of expertise/control/sanction areas to existing authorities or creation of an authority?
- Transparency and political will
- Simplicity
- The potential limitations are the need for control and transparency on the application of these criteria

7 - Drug and API pricing

Zoom by measurement

Scope: APIs, Finished products, Entire chain

Related objectives		Details of the proposed measure	Segments covered
Guarantee the sustainability of production lines for molecules and mature drugs located in Europe for drugs of major therapeutic interest. **Ensure the relocation of APIs**, their **raw materials** and **related technologies**	**Context**	• Until now, health policies have used pressure on prices to limit expenditure and meet ONDAM objectives, and the dimensions of "local production", "environmental footprint" and "health safety" have been given little or no consideration. • Recognize the **limits of price pressure on mature drugs** and **successive declines** (e.g., the 2019 median price of generic drugs was 11c/cp) • **Adapting the pricing doctrine for mature drugs by taking into** account **the industrial, environmental and social footprint** at the **European level** or **securing supply**	**Fragile input supply** *(e.g. docetaxel)* **Production including pollutants to treat** *(e.g. estrogen)*
	Tools to use	• Introduction of a **threshold price** for mature drugs • The possibility of **re-evaluating the price of** a drug for a therapeutic class (Framework Agreement 2021) • A price that allows commitments to guarantee **security of supply** • A **tax incentive policy** that values **the industrial, environmental and social footprint** • **CSIS credits** linked to the production of mature products, which compensate for the lack of competitiveness and the additional cost of manufacturing expenses linked to the European location of API and drug production facilities (taking into account environmental and societal constraints) • The optional introduction of a **mark of origin** and/or a **label** on the boxes of medicines or via a QR code allowing transparency and traceability for the patient	**Complex production** *(e.g. insulin)* **Low price of the API** *(e.g. metoprolol)*

Ease of realization	Level of implementation	Conditions for implementation, success / Next steps
Ease of implementation: • Difficult due to budgetary constraints but facilitated by the implementation of a well-defined perimeter of molecules **Estimated timeframe:** • 3 to 5 years in Europe	• National, at the state level	• Initiate reflection at the European level • Transparency and political will • Targeting the higher price • CEPS, Social Security Department • Transparency and control capacity of the actors (difficulty in determining the "fair price" of production)

8 - Innovation and adaptation

Zoom by measurement

Scope: APIs, Finished products, Entire chain

Related objectives		Details of the proposed measure	Segments covered
Guarantee the **sustainability of production lines** for mature molecules located in Europe Ensure, in a competitive, efficient and environmentally friendly way, the **relocation of APIs** to consolidate the robustness of the CoP. Supporting the **transformation of the** healthcare **ecosystem** and the **development of** therapeutic **innovations**	**Context**	• **To support innovation in new manufacturing process technologies** (inputs and APIs) combining competitiveness, reliability, durability, safety, quality and respect for the environment. • **Accelerate the transformation** of industrial processes to **relocate** or **strengthen the** value chain of major molecules of therapeutic interest that are highly vulnerable in Europe • Promote **technology transfer** between academia and industry on the one hand, and within industry on the other (intra-disciplinary cross-fertilization) • **Support the evolution of employee skills** in the appropriation of these new technologies • Encourage all organizational and regulatory innovations through **digital transformation and artificial intelligence**. • of new technologies	**Fragile input supply** *(e.g. heparin)* **Production including pollutants to treat** *(ex: formoterol)*
	Tools to use	• A **IPCEI in health that focuses on** the "resilience of the value chain" to ensure the financing of R&D/IDF risk-taking and the expected acceleration to meet the need for sovereignty at European level • **Calls for industrial projects to support innovative solutions that** reduce the environmental footprint and improve the performance (efficiency / competitiveness) of our industrial facilities • Support in the framework of the new **European program Horizon** • Support for **multidisciplinary research** in chemistry • The **Research Tax Credit** • Set up **continuous training** to support employees in the appropriation of new technologies	**Complex production** *(e.g. corticosteroids)* **Low price of the API** *(e.g.: statins)*

Ease of realization	Level of implementation	Conditions for implementation, success / Next steps
Ease of implementation: • Ease of implementation subject to alignment at European level **Estimated timeframe:** • <1 year depending on political will	• European and national	• Supporting industrialization with a view to ensuring the sustainability of production • Develop a new manufacturing technique • Include APIs in the scope of the next health IPCEI • Ensure that there is a receptacle for innovation, not just the leaders but the entire value chain • The limits are that it supposes to have the skills and the industrial fabric, the profitability in the long run, and potentially to review the state aid schemes