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CHIMIE FINE ET BIOTECH

Strengthen the API production industry in France and Europe

Final report| September 5th 2024

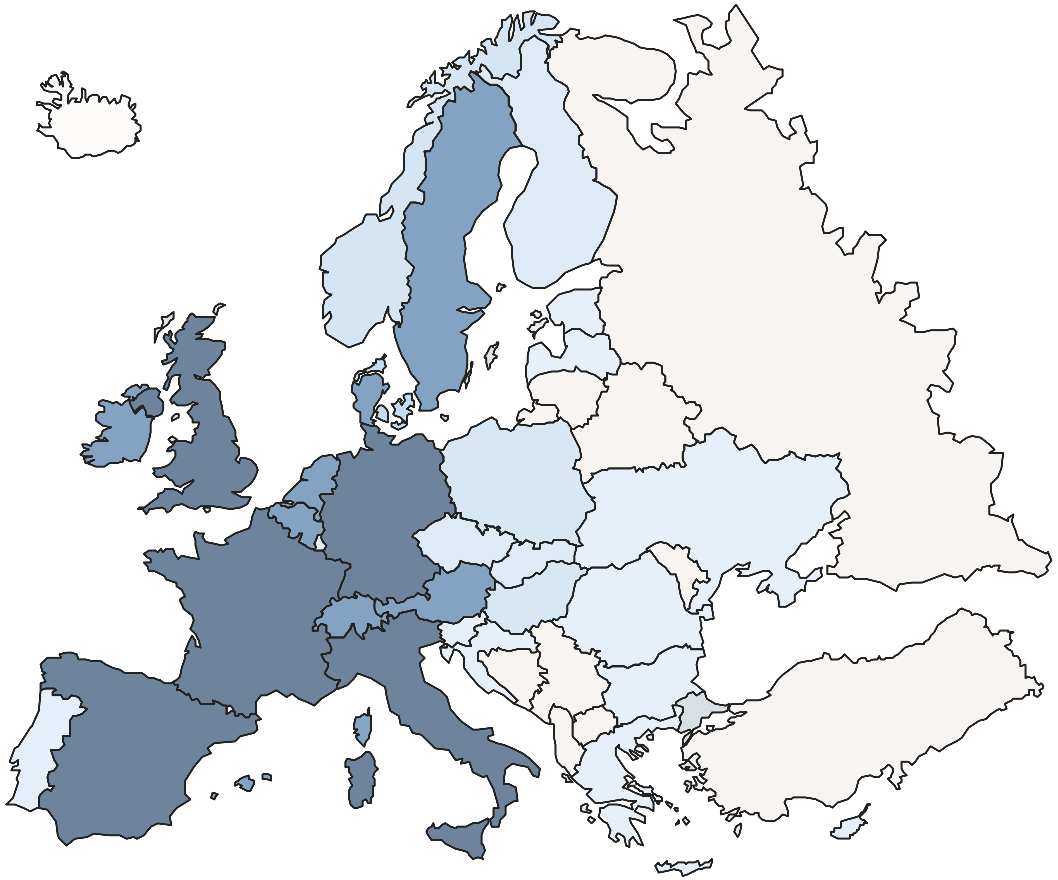
Agenda

OVERVIEW

Active Pharmaceutical Ingredients manufacturing generates €160bn (o/w €70bn for the merchant market) per year and employes 150.000+ people throughout Europe

European CDMO facilities | 2024, # production sites per country, Europe

API & INTERMEDIATES PRODUCTION FOOTPRINT (C. 440 SITES)



< 10 sites | 10-20 sites | > 30 sites

c.30%
of Global API and intermediate CDMO manufacturing market

c.20%[1]
of European Chemical market

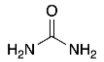
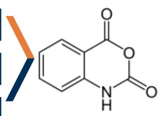
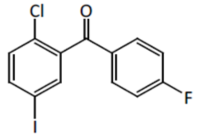
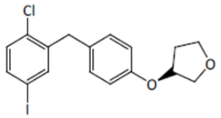
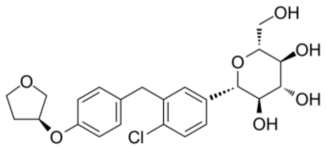
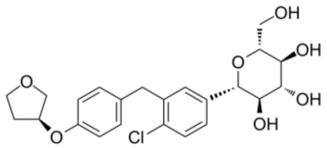
c.440
manufacturing sites in European

>150K[2]
People employed

Notes: (1) c.3% of European industrial production, (2) for the merchant market (c.€70bn)
Sources: Cefic, Eurostat, Policy Department for Economic, Scientific and Quality of Life Policies Directorate, Advancy

Finished Dosage Form (FDF) are drug products used to treat patients which are based on Active Pharmaceutical Ingredients (API), the chemical substances providing the desired efficacy

Pharmaceutical value chain

	STARTING MATERIALS		REGULATORY STARTING MATERIA	GMP INTERMEDIATES	ACTIVE PHARMA. INGREDIENT (API)	FINISHED DOSAGE FORM
DESCRIPTION	**Simple chemical substances** often not very differentiated		**First GMP-compliant chemical substances**	GMP compliant **intermediate substances between RSM and API**	**Key ingredients** that provide the **desired effects** of the medicine. Must be GMP compliant	**Final drug product** (e.g. tablets, pills) obtained by blending APIs and excipients. Must be GMP compliant
EXAMPLE OF EMPAGLIFLOZIN VALUE CHAIN	Cl_2 *Chlorine* +  *Urea* + *Others* *FEEDSTOCK*	 *Isatoic anhydride*	 *(2-Chloro-5-iodo-phenyl)-(4-fluoro-phenyl)-methanone*	 *3-[4-(2-Chloro-5-iodo-benzyl)-phenoxy]-tetrahydro-furan*	 *Empagliflozin*	 *Jardiance*
ILLUSTRATION						 *Efferalgan* (based on paracetamol)  *Jardiance* (based on Empagliflozin)  *Aspegic* (based on acetylsalicylic acid)

Key focus on this study

COMMENTS

- **Drug products** (e.g. doliprane, aspirin) are **based on active pharmaceutical ingredients** blended with an excipient
  - **Actives Pharmaceutical Ingredients** (API) provides **the therapeutic effect of the drug product**. APIs result from a long series of chemical reactions starting from basic starting materials (petrochemicals, naturals…) progressively differentiated to develop specific therapeutical activity
  - **Excipients** are carrier substances (e.g. sugar, cellulosics) used to protect, support or enhance activity of the API but has no therapeutic effect

OVERVIEW

Pharmaceutical value chain is global, fragmented and served by large number of suppliers with most of them only focused on one or few steps of the value chain

Pharmaceutical value chain

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VALUE CHAIN	INEOS, Formosa, Sinopec, Lanxess, TotalEnergies, Shell, LyondellBasell, Mitsui Chemicals	Hovione; olon, Weylchem, Seqens, FIS, Priya Chemicals, Porton, Ajinomoto, Interor, aspen, Kyowa Kirin	Cambrex; teva, Boehringer Ingelheim, Thermo Fisher Scientific, Centrient; Neuland, Laurus Labs, Pharmaron, Apeloa, axplora, Asymchem, Porton, Suven Pharma	Siegfried; polpharma, AstraZeneca, Piramal, Sanofi; olon, Seqens, Divi's, FIS, euroAPI, Solara, Minakem, Sai, WuXi AppTec	Curia; Pfizer, gsk, Lonza; Patheon, Famar, Synerlab, Jubilant Pharmova, Fareva, axplora, Recipharm, aenova, Delpharm
MARKET SIZE	-	€20-30bn	c.€50bn	c.€110bn	€1 000-1 500bn
MARGIN					
REGULATION					

Key focus on this study

COMMENTS

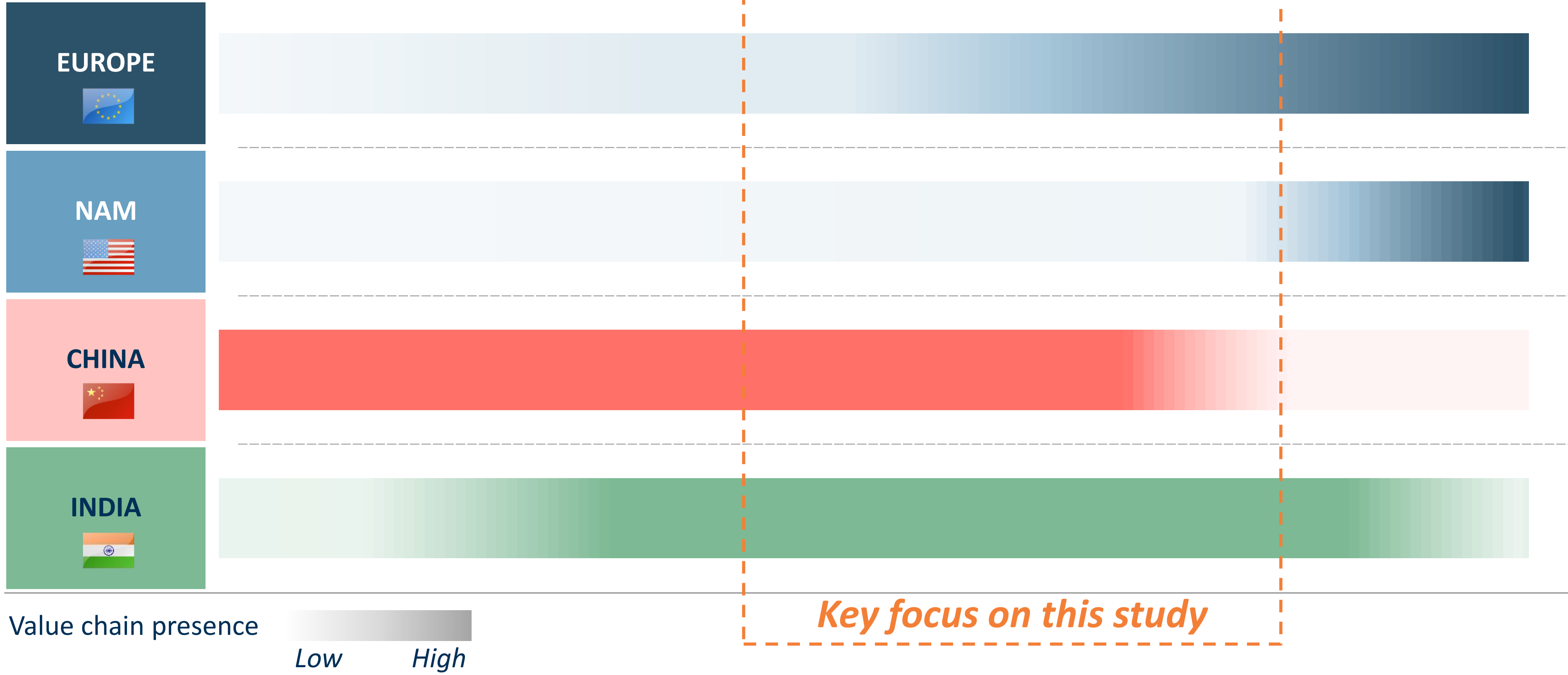
- Pharmaceutical value chain starts with **basic chemical companies** (Shell, Ineos, Nouryon, Dow…)…
- …which are **converted into Regulatory Starting Material, GMP intermediates then API by fine chemical companies** (Olon, Seqens, EuroAPI, Piramal, Minakem, FIS, Interor, Weylchem…)…
- …and finally turned into final drug products (FDF), by **big pharmaceutical laboratories** (Pfizer, Sanofi, Merck…) **or FDF contractors** (Patheon, Famar, Fareva…)
- Within the pharmaceutical value chain, **APIs is** a €100bn market accounting **for 10% of the global FDF market** (€1000-1500bn)

Sources: EFPIA, IQVIA, APIC, Investor Presentations, External Interviews, Advancy

Europe is still present on API and FDF manufacturing which are less price-sensitive and still more driven by innovation while most of the upstream part of the value chain is done in Asia

Pharmaceutical value chain

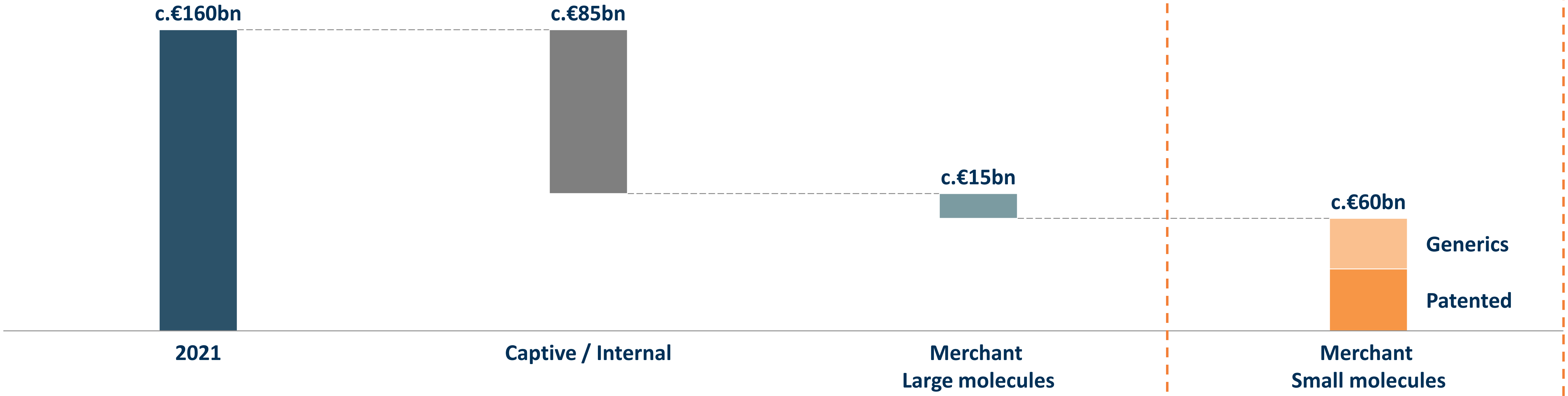
	STARTING MATERIALS	REGULATORY STARTING MATERIA	GMP INTERMEDIATES	ACTIVE PHARMA. INGREDIENT (API)	FINISHED DOSAGE FORM	COMMENTS
DESCRIPTION	**Simple chemical substances** often not very differentiated	**First GMP-compliant chemical substances**	GMP compliant **intermediate substances between RSM and API**	**Key ingredients** that provide the **desired effects** of the medicine. Must be GMP compliant	**Final drug product** (e.g. tablets, pills) obtained by blending APIs and excipients	
EUROPE						**Mainly present on the downstream** part of the value chain (API, FDF), **less price-sensitive**, but minor presence on GMP intermediates and RSM
NAM						Less integrated than Europe and **almost entirely relying on imports except for some API**
CHINA						**Integrated across the entire value chain**, addressing Western and India need of RSM, Intermediates and API
INDIA						**Presence across the entire value chain. Strong investment in recent years to increase API and Intermediate presence and reduce China imports**



Sources: EFPIA, IQVIA, APIC, Investor Presentations, External Interviews, Advancy

Out of c.€160bn APIs and Intermediates market, c.€60bn are exposed to global competition, mainly small molecules, less complex to produce and more price-driven

Global API and Intermediates market size | €bn, World, 2023



2021
- **Global APIs (c.€110bn) and Intermediates (c.€50bn) market**

Captive / Internal
- **APIs and Intermediates manufactured by big Pharma laboratories** (e.g. Pfizer, GSK) and large **FDF generics** player (e.g. Teva, Sandoz) for internal consumption

Merchant Large molecules
- **Large size molecules (e.g. peptides, mAbs…) complex to manufacture**
- Low exposure to Asian competition, high value products with players competing **more on technical capabilities than price**

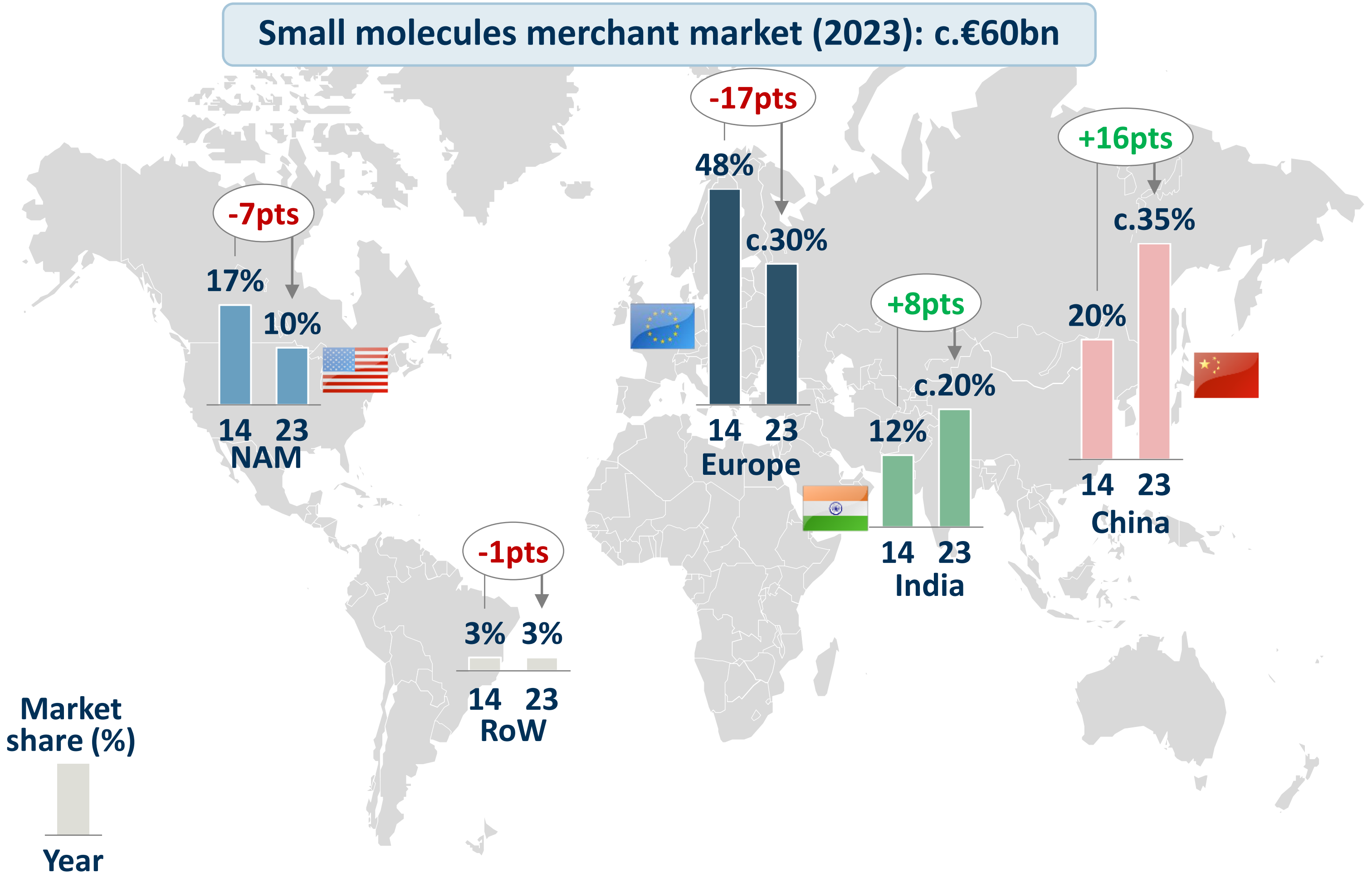
Merchant Small molecules
- **Old and/or less complex molecules mainly price-driven**
- **Global market since China and India** ramped-up on technical and regulatory compliance while preserving favorable cost position
- **ASIA mainly addressing generics**

Key focus on this study

Sources: Cefic, Company data, External Interviews, Advancy

On the €60bn merchant small molecules APIs and intermediates market, Europe is #2 player after production moved towards Asia over the last decade to optimize manufacturing costs...

Small molecules APIs and Intermediates market dynamics | merchant market, small molecules, €bn, %, 2014-2023, World



COMMENTS

- **Structural shift of small molecules API and related Intermediates production towards ASIA**
  - Strong penetration of China and India owing to i) cost competitiveness, ii) improved quality and technical know-how
- **Production delocalization enabled overall APIs cost reduction over the years but led to**
  - Longer delays and higher shortage frequency
  - **Risk of shutdown of production** due to non-compliance with regulatory standards after arbitrary inspection (e.g. Sun Pharma, Natco Pharma)
  - **Strong supply disruption** due to abrupt closure of Chinese intermediates / API players because of government decision (e.g. blue sky policy)

"After 18 months of inspection, we are not very happy than more than 36% of the 400 inspected manufacturing units had to be closed"

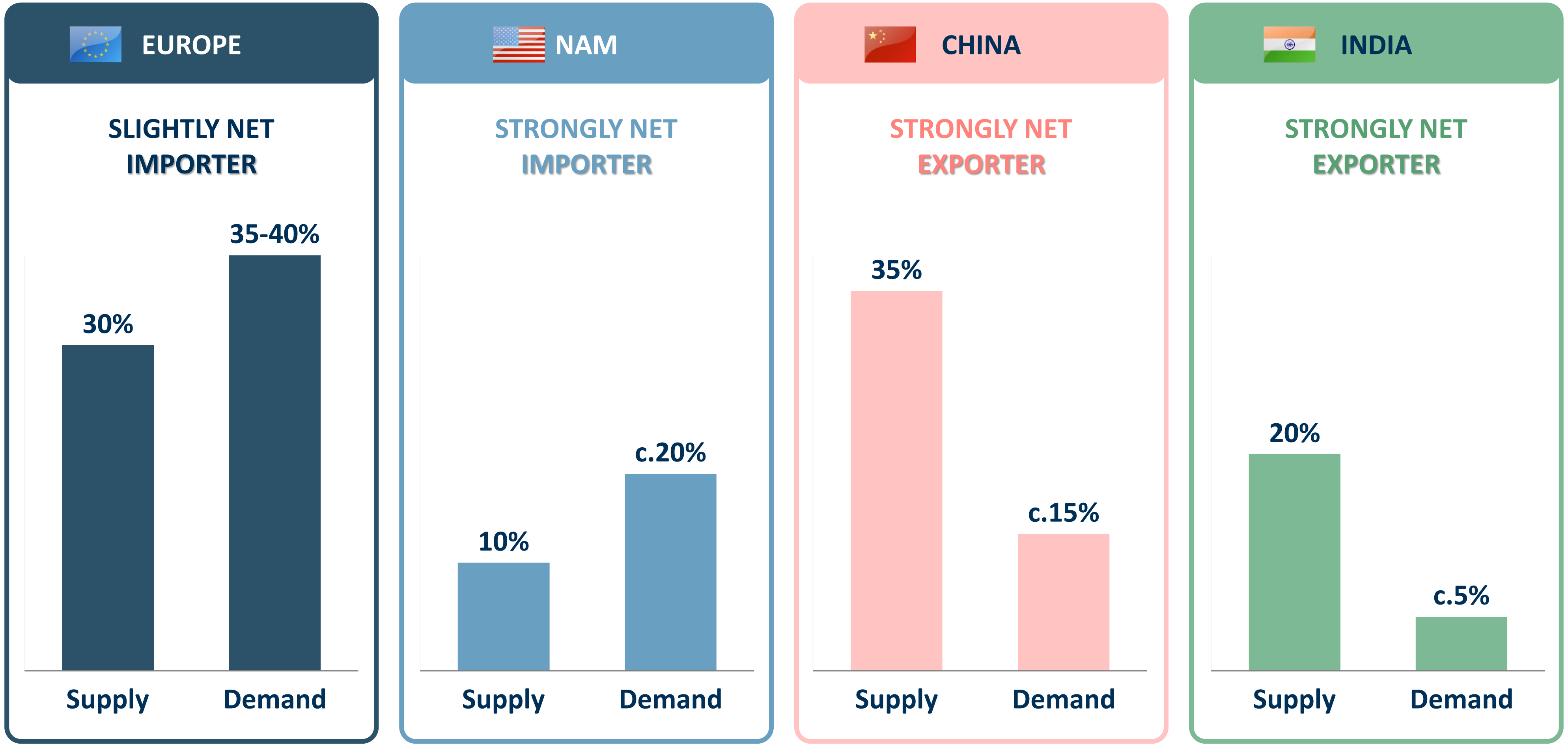
Director - Indian Pharmacopoeia Commission

Sources: Company data, External Interviews, IQVIA, Advancy

OVERVIEW

… Which resulted in a net importer position for Europe and NAM in a much larger extent while China and India have become strong net exporting geographies

Small molecules APIs and Intermediates supply and demand per region [1] | merchant, small molecules, %value, 2023, World



COMMENTS

- **Europe is the only region nearly balanced between its supply and its demand**
- **NAM strongly relies on imports, historically from Europe and more and more from Asia** and more recently from India
- **China and India have turned into the larger producing continent**, largely exceeding their domestic needs

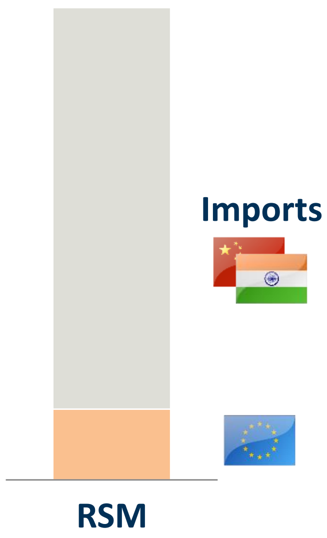
Notes: (1) RoW excluded. leading to Supply and Demand not summing to 100%
Sources: Company data, External Interviews, IQVIA, Advancy

OVERVIEW

Zooming on Europe, exposure to Asian imports is very high for RSMs but more balanced for GMP intermediates and APIs, yet >74% of the European medicine value chain depends on imports

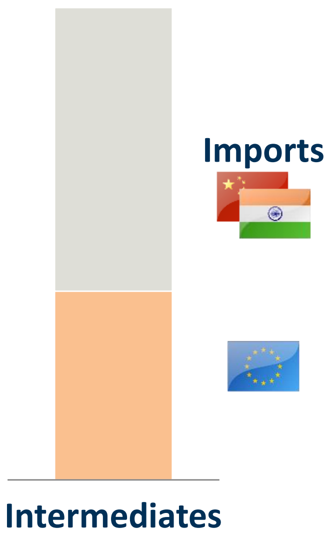
Share of imports along the European API value chain | Base 100, in value, Europe, 2023

REGULATORY STARTING MATERIALS (RSMs)



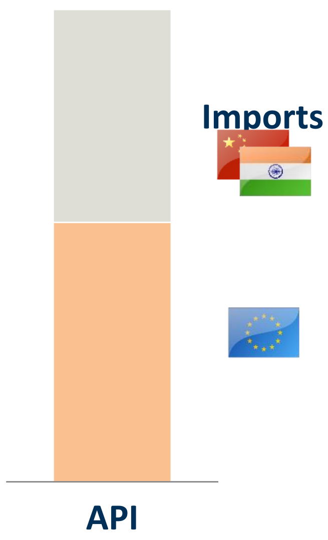
RSMs are first chemical substances compliant with GMP standards in the chemical pathway toward API (included in DMF[1]), mainly **imported from cost competitive regions** (China and India) to Europe

GMP INTERMEDIATES



Over the last years, share if imported GMP intermediates increased with the development of regulatory compliant Asian suppliers

ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)



Contrasted situation per drug product with small molecule generic APIS being mainly imported while patented or more complex APIs are still produced domestically

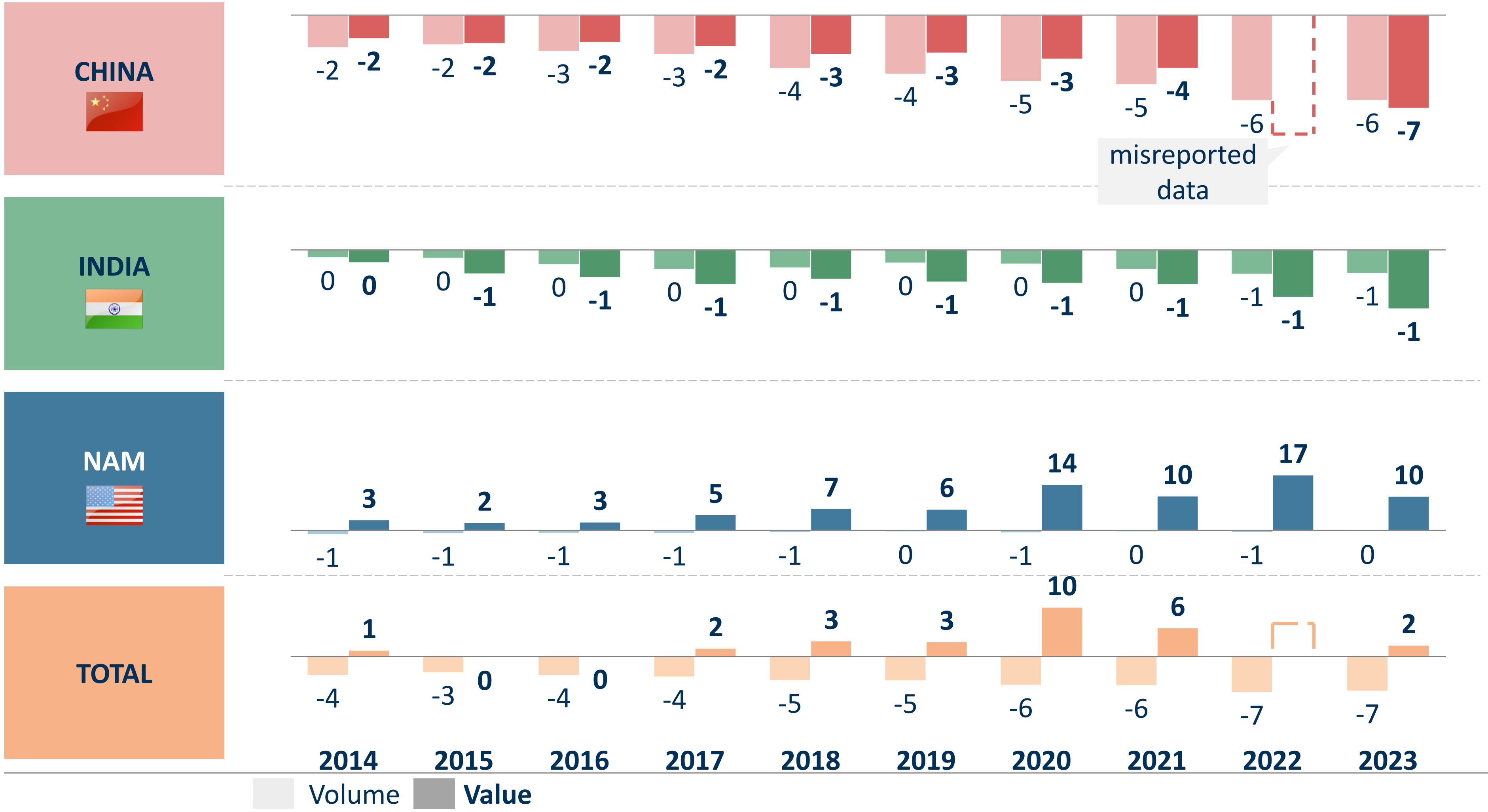
>74% of the European medicine value chain depends on imports,
could it be at the API, GMP intermediate or Regulatory starting Material step

Notes: (DMF) Drug master files
Sources: External Interviews, Advancy

OVERVIEW

On API (excl. Intermediates and RSM): Europe have been increasingly relying on China and India to supply the API and intermediate demand and thus depending more and more on Asia

Europe API[1] net trade[2] evolution by volume and value | €bn, mt, 2014-2023, API only (excl. Intermediates and RSM), World[3]



COMMENT

- **Continuously growing trade imbalanced between China and Europe driven by steady import increase** in both volume and value
- **Similarly, Indian imports have grown significantly which** led to increasing Europe net importer position
- Regarding NAM, **Europe has been net exporter in value since at least 2014, and NAM dependency on Europe even increased** from €2-4bn to €c.10bn after 2019

Notes: (1) defined as list of 102 Combined Nomenclatures (CN 8 digit) included in ECIPE list of APIs, (2) Net trade = Exports – Imports, (3) excluding regions other than China, India and NAM
Sources: Eurostat, ECIPE, Advancy

OVERVIEW

Since 2016, 80% of the top 10 best-selling, all generics, have experienced shortages and more generally >300 molecules were concerned in recent years, mainly due to supply issues from China

Shortages dynamics | 2016-2024, Europe

	CLASS	MOLECULE	EU SHARE OF PRODUCTION	SHORTAGE ON 2016-24
TOP 10 API IN EU5[1,2]	NSAID[3]	Paracetamol		YES
		Aspirin		YES
		Diclofenac		YES
	CARDIO-VASCULARY[4]	Atorvastatin		YES
		Ramipril		YES
		Bisoprolol		NONE REPORTED
	DIABETES	Metformin		NONE REPORTED
	RESPIRATORY	Salbutamol		YES
	GASTRO-INTESTINAL	Omeprazole		YES
	HORMONES	Levothyroxine sodium		YES

European production share — Low → High

European Commission

Commission steps up actions to address critical shortages of medicines and strengthen security of supply in the EU

The Commission has adopted today a set of actions to better prevent and mitigate critical medicine shortages in the EU, this winter, next winter and beyond. Recent critical shortages, including of certain antibiotics last winter, show that continued coordinated action is needed to address supply challenges and to make Europe's medicine supply chains more resilient in the long run. The key goals of today's Communication are to prevent and mitigate **critical shortages** at EU level. It puts a particular focus on the most **critical medicines**, for which security of supply in the EU must be ensured at all times.

This Communication builds on the work under the European Health Union, notably the reinforced mandate of the European Medicines Agency and the recently published pharmaceutical reform. It follows a strong call by Member States at the 2023 June European Council, confirmed in Granada in October 2023, and from the European Parliament.

Mitigating critical shortages this winter and beyond

To better prepare for this winter, a lot of measures have already been taken. For instance, the European Health Emergency Preparedness and Response Authority (HERA) and the European Medicines Agency (EMA) have identified **key antibiotics** (including specific paediatric formulations) for which they anticipate the risk of critical shortages ahead of the winter. Measures have been put in place to assure the availability of these antibiotics.

However, more needs to be done. This is why we are stepping up our actions with:

- The launch of **a European Voluntary Solidarity Mechanism for medicines** (October 2023): the mechanism flags a Member State' needs for a given medicine to other Member States, that can respond by redistributing medicines from their available stock.
- A **Union list of critical medicines** (available by the end of 2023): Once established, this list will be the first step to analyse the supply chain of selected medicines by April 2024. This analysis will then show where additional measures are needed.

The Guardian

The Guardian view on medicine shortages: a global issue for which Britain needs a plan

The UK is not alone in facing drug supply-chain challenges. This is a global issue, which has been rising up the agenda of EU states and the US as well. Rich western countries, along with much of the rest of the world, are heavily reliant on the pharmaceuticals manufacturing capacity of India and China for sufficient quantities of generic, off-patent drugs. During the pandemic the risks of this model became obvious when countries were forced to compete for vaccines, and India placed export restrictions on many items, including paracetamol.

Both the EU and US have responded with significant moves towards reshoring. France is building a paracetamol factory large enough to meet half of all European demand. Belgium has made the issue a theme of its EU presidency. Rules about state aid look set to be altered, and pharmaceuticals recategorised as a strategic industry like semiconductors. While European manufacturing will make supplies more secure, it is also expected to make drugs more expensive and reduce carbon emissions and other environmental damage associated with them.

"We need to be able to see what the crises are and respond to them effectively before they happen"

Health Commissioner - Stella Kyriakides

"We will then identify the best measures to address and avoid shortages, […] to increase manufacturing in Europe"

Commission President - Ursula von der Leyen

SHORTAGES OBSERVED FOR MORE THAN 300 MOLECULES IN RECENT YEARS

Notes: (1) In standard units (2) EU5: France, Germany, Italy, Spain, UK (3) Nonsteroidal anti-inflammatory drugs (4) Include antithrombotics
Sources: IQVIA, EFCG, Advancy

Europe is the region which less supports domestic production and, has no clear plan to limit the access to its market to oversea competition or defend domestic production while other have €bn plan accounting for 10-20% of their domestic production value

		LEVER 1: SUPPORT DOMESTIC PRODUCTION	LEVER 2: BARRIER TO ENTRY ON API MARKET
EU	**<€0.25bn** *(c.1%)*	▶ **€1bn through the IPCEI Med4Cure** to support 4 pharmaceutical R&D axis, only <25% is directed toward small molecules participating the open market ▶ **Investments at national levels in most countries**, e.g. €50m to reshore essential medicines (France 2030) ▶ ***In progress: "Critical Medicine Alliance" launched in April 2024*** *to pave the way to future* ***"Critical Medicine Act"*** *to support local API production (by EESC[1] in Dec 23)*	▶ European market fully open to foreign competition ▶ **c.7% import tariffs**
US	**>€1bn** *(c.15%)*	▶ **Large investment (>€1bn) in manufacturing assets on domestic soil** ▪ **€910m** during COVID-19 crisis for **APIs and FDF production in the US** ▪ **€40m** for essential medicines through **Defense Production act** ▶ ***In progress: "Pills act"****, promotes US generic medicine production via tax credits*	▶ **Restrict some federal market to Chinese players** (Buy American act) ▶ *May be expanded to a broader scope if Biosecure act is passed* ▶ **c.7%[2] import tariffs**
CHINA	**>€1.5bn** *(c.7%)*	▶ **Large investment at national level (€1.5bn) and province level** (e.g. Shanghai: c.€2.5m R&D investment) to support **new drug development** ▶ Boost local players' cost competitiveness via **investments in infrastructure** (SEZs[3], R&D parks) and **very advantageous loan from state-controlled banks**	▶ No formal barriers, but **disclosing process details limits foreign players' participation** in the Chinese market ▶ **5-10% import tariffs**
INDIA	**>c.€3bn** *(25%)*	▶ **Large investment (€2.5bn) to stimulate domestic production and reduce exposure to imports from Chain** (PLI[4]) ▶ Boost local players' cost competitiveness via **i) investment (€330m) in infrastructure,** financing of 3 chemical parks, and **ii) €55m in pharmaceutical infrastructure**, incl. 35m for production facility upgrades (SPI[5])	▶ Indian market fully open to foreign competition ▶ 15-30%[6] **tax**

Importance → *Low* *High*

(xx%): Support intensity defined as support measure budget divided by the value of the domestic industry

Importance → *Low* *High*

Note: (1) European Economic and Social Committee; (2) Customs Processing Fees; (3) Special Economic Zones; (4) Production Linked Incentive; (5) Strengthening of Pharmaceutical Industry ; (6) Tariffs rate cumulated with Good and service tax
Sources: Advancy

Europe competitiveness on API production has been assessed via the analysis of the production costs of 12 APIs among the most sold and/or most critical in Europe vs. oversea locations

CLASS	EXAMPLE OF KEY MOLECULES	COMMENTS	DEEP-DIVE IN NEXT SECTION
NSAID	Paracetamol, Aspirin, Metamizole, Ketoprofen, Ibuprofen, Codeine, Morphine,…	▶ Include some of the most prescribed drug products in Europe ▶ Very large volume (up to c.50kt), low-mid value (€5-100/kg) molecules	3
CARDIOVASCULARY ANTITHROMBOTICS DIURETICS	Atorvastatin, Rivaroxaban, Ramipril, Clopidogrel, Dronaderone, Candesartan, Irbesartan, Losartan, Furosemide,…	▶ Large volume, mid value molecules with strong capacity increase in Asia for some products in recent years leading to pressure on price	1
RESPIRATORY	Budesonide, Fluticasone, Ephedrine,…	▶ Notably include several products on WHO list of essential medicines, limited shortage in recent years	-
ANTI HISTAMINIC	Cetirizine, Bilastine, Desloratadine, Fexofenadine,…	▶ Large volume, mid value molecules with strong price pressure from Asia	1
DIABETES	SGLT2i (e.g. Empagliflozine), Insulin, Metformin, DPP4 inhibitors (Sitagliptine), GLP1 (Semaglutide),…	▶ Include several patented products with large share of production remaining in Europe (for both API and precursor)	1
STEROIDS	Methylpredinosolone, prednisolone, hydrocortisone, dexamethasone,…	▶ Numerous shortages in Europe for various corticoids ▶ Europe sustainability at risk owing to historical under-investments	1
ANTIBIOTICS	Amoxicillin, Spiramycin, Cefixime, Meropenem, Ceftriaxone, Rifampicine,…	▶ On the list of essential medicines but many recent shortage events ▶ Large volume molecule. Most of the Europe demand no longer addressed by local producer. Remaining production at risk	1
ONCOLOGY (OEB>3)	Capecitabine, Florouacil, Paclitaxel,…	▶ Product requiring specific safety requirements to protect workers (OEB 3/4) given their toxicity	-
NEUROLOGY	Midazolam, Amisulpride, Ketamine, Methylphenydate,…	▶ Low volume medicine (high value) with small batches production cycle where Europe is still a key supplier	2
GASTRO-INTESTINAL	Mesalamine, Ondansetron, Loperamide PPI: Omeprazole, Esomeprazole, Lantoprazole,…	▶ Include products with high risk of delocalization which experienced recurring shortages in recent years for some products	1
HORMONES (>OEB3)	Fulvestrant, Tamoxifen, Estradiol, Trenbolone,…	▶ Europe and US as leading producers for several products ▶ Some Indian authorization removed due to quality issue	1
TOTAL			**12**

Europe is almost always more expensive than Asia and in the few cases where Europe is cost competitive, aggressive Asian players strategy jeopardizes long-term viability of European assets

CLASS	MOLECULE #	MARKET PRICE (BASE 100)	OPEX POSITION (BASE 100)			COMMENTS
			EUROPE	ASIA	US	
NSAID	1 *(intermediate)*	100	90	85-100	-	Europe is well positioned on cost yet losing market share due to aggressive pricing from Asian players
NSAID	2	100	200 *(->85)*[1]	85	-	Europe is not cost-competitive vs. China but cost gap can possibly be bridged by investing in new route development
NSAID	3	100	55 *(->15)*[1]	15	-	Europe long term economic viability is not secured, but investment in new process could enable to be on par with India competition
CARDIOVASCULARY	4	100	90	80	-	Europe is slightly less competitive than China, yet new capacity addition in China can lead to price dumping in the short-term future
ANTI HISTAMINIC	5	100	90	45	-	Europe heavily lagging behind India yet upstream integration and more automation could be considered to bridge the gap
DIABETES	6 *(intermediate)*	100	70	25-45	-	Lower Europe cost-competitiveness results from lack of integration on RSM and higher labor costs
STEROIDS	7	100	60 *(->45)*[1]	40	-	Europe economic viability is not secured, but investment in a more competitive route is possible if investment economics can be secured
ANTIBIOTICS	8	100	155	90	-	Europe is suffering from higher cost position which could be partly mitigated by upstream integration on intermediate
NEUROLOGY	9	100	100 *(->70)*[1]	25	-	Europe is not competitive and investment is required to develop a more competitive production route and partly bridge the gap
NEUROLOGY	10	100	100 *(->50)*[1]	45	40-50	New proprietary route could allow Europe to be cost competitive in the future if investment economics can be secured
GASTRO-INTESTINAL	11	100	70	35	-	Europe is suffering higher cost position, mainly resulting from a higher labor costs and uncompetitive reagents
HORMONES (>OEB3)	12	100	70 *(->50)*[1]	30		Europe is less competitive than China due to high fixed costs resulting from less efficient production route

XX: Europe on par with Asia

XX: Europe not cost competitive vs. Asia

Note: 1) Achievable OPEX position after investment in more performant process when business case is viable and secured
Source: External interviews, Advancy analysis

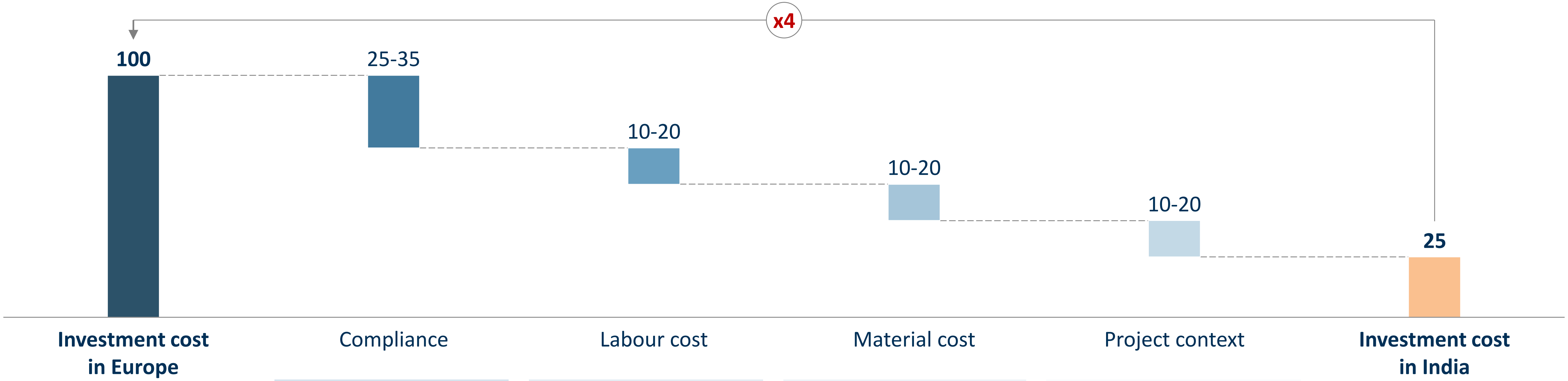
For most of APIs highlighted in this report, economic viability seems challenging and at the mercy of oversea competition, especially Asian one, not playing with the same rules

		1	2	3	4	5	6	7	8	9	10	11	12	DESCRIPTION	RELATED EU REGULATIONS
EUROPE IS ON-PAR WITH ASIA		X			X						X			▪ Europe can be on-par with Asian peers when **being more integrated and using efficient production routes**	
EUROPE IS NOT COST COMPETITIVE	UNDER-INVESTED PRODUCTION PROCESS		X	X		X		X	X	X			X	▪ Investment in more efficient processes and/or world-scale assets not realized due to **insufficient business case economics** resulting from higher competitive intensity, volume volatility and regulatory constraints ▪ In addition, **investing in Europe is more expensive** due to higher environment, regulatory, safety requirements vs. other regions **and provides less return revenues and lower profitability**	▪ SEVESO, DCE, IED (water, air) ▪ REACH, CLP, BPR, POP/PIC… ▪ CPR and other regulations related to construction (Biodiversity, Protected Natural Areas…)
	COST OF LABOR		X					X	X	X		X		▪ **Higher minimum wages in Europe** vs. Asia ▪ **More direct FTE** per kg of product to **met local work rules** and as a result from **smaller production units vs. world-scale units operated in Asia**	▪ EU Directive on Safety and Health at Work, EU social policies, Pregnant Workers Directive, employment code…
	LACK OF UPSTREAM INTEGRATION			X			X	X	X			X	X	▪ **Low integration** on intermediates and regulated starting materials **usually increase access cost** which led to the vanishing of related manufacturing capacities and related technology know-hows	▪ EU-ETS, IED, SEVESO ▪ ADR, AND, RID ▪ Quality guidelines of the European pharmacopeia…
	UNCOMPETITIVE FEEDSTOCK AND REAGENTS					X		X	X			X		▪ Locally sourced materials are more expensive **due to higher energy and/or petrochemical feedstock costs in Europe** vs. other regions	▪ EU-ETS, SEVESO, IED, ▪ REACH, CLP, BPR, POP/PIC, ADR, AND, RID, WFD…
	ENVIRONMENT, SAFETY, ADMINISTRATIVE BURDEN		X			X		X					X	▪ **Higher cost** in Europe vs. other geographies to **met more stringent** (liquid and gaseous) **effluents and solid wastes compliance standards** and **manage all the related administrative workload**	▪ EU-ETS, SEVESO, IED, REACH, CSRD, NIS2…

Sources: Advancy

On average, investment in Europe is c.4x higher compared to India due to a multiple cumulative drivers

European and Indian investment cost compared | index 100, 2023



- Compliance cost represents **25-35% of investment cost in Europe, almost fully non-existent in India**

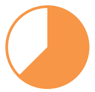
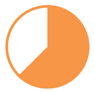
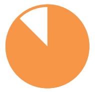
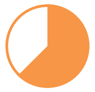
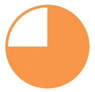
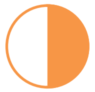
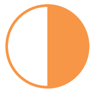
- **Indian worker wage is on average €2.5-3.5/day**, well below Europe's cost of labour

- **More competitive material sourcing in India** (e.g. steel, cement, equipment…) mainly thanks to lower energy and labour cost

- Incremental cost in Europe to **adjust to local administrative and political requirements, manage appeals from organizations, …**

Sources: Advancy analysis

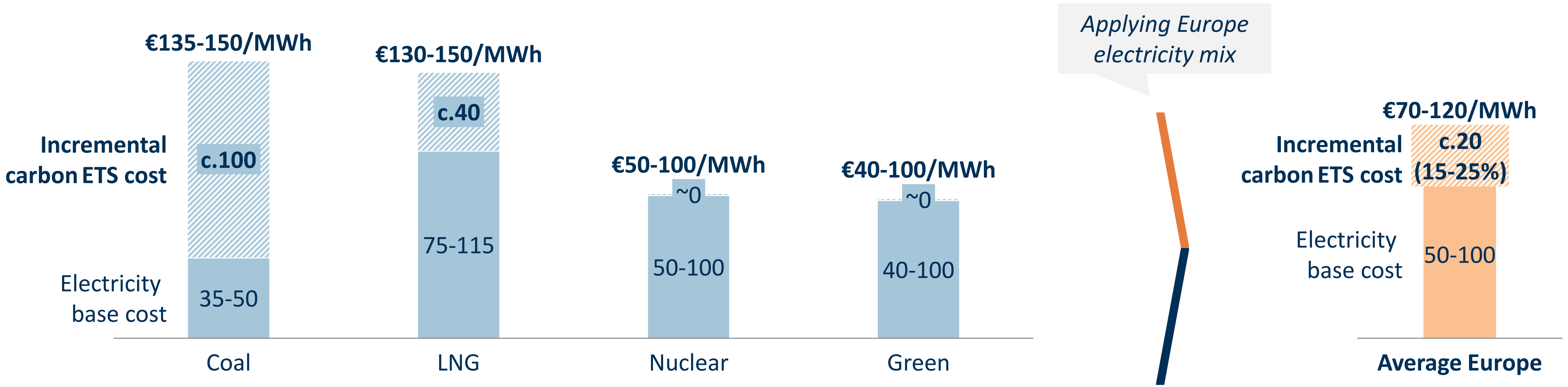
European regulations are numerous and have strong impacts on cost competitiveness in Europe

THEME	MAIN SOURCES OF BURDEN	IMPACT	
		OPEX	CAPEX
WATER & AIR PROTECTION	▪ IED, WFD		
WASTE MANAGEMENT	▪ Waste burning regulations, waste recycling regulations, overall industry structure		
ENERGY & CO2 EMISSIONS CONTROL	▪ Carbon credit mechanism (EU-ETS)		
WORKFORCE SAFETY AND WELLBEING	▪ European Directive on Safety and Health at Work, CMR directive, CAD, Machine directive, European social policies, Pregnant Workers Directive, employment code, Work-life balance and gender equality, administrative (CSRD, NIS2) …		
PROCESS SAFETY	▪ Operational risks: SEVESO ▪ Transport of hazardous substances: ADR, AND, RID ▪ Other hazardous substances regulations: REACH, CLP, BPR, POP/PIC		
OTHER REGULATIONS & FRAMEWORKS	▪ Construction: CPR, Biodiversity regulation, Protected Natural Areas regulation, Flora and Fauna Protection, Environmental Assessment Regulations, Impact Study assessment, RED, Preventive archeology, water consumption… ▪ Other: DCE, Quality guidelines of the European pharmacopeia, Nagoya protocol, GMM, DSI, taxations and customs…		

Sources: Advancy analysis

On average in most European countries, electricity includes environment compliance cost, due to carbon cost, accounting for 15-25% of electricity price

Case of environment compliance cost in electricity price | €/MWh, Europe, 2023



- **Fossil-based power plants are essential to the EU mix**, as nuclear capacity can only serve c.25% of demand and green power is intermittent
- Carbon ETS mechanism is making **fossil-based power uncompetitive** and as per electricity market design, **electricity price is set by the marginal power plant which is mainly fossil-based in Europe**
- And, green power will generate **additional costs for electricity consumers** (network costs, storage costs, capacity costs, supports costs, etc.) which will impact the overall electricity bill of EU industrials
- This is why, despite increasing decarbonized power production capacity, electricity market prices in EU will continue to bear an important carbon ETS cost and **electricity bill in EU will remain uncompetitive**

- On average, carbon cost represents **15-25% of total electricity cost**

Sources: IEA, RTE, Advancy analysis

Europe must provide a common answer to defend the domestic production of small molecule API, critical for its model of society

Lessons learnt

- **Rules of the game are not the same in Europe** compared to the large Asian competitors, namely China and India for both manufacturing of RSMs and APIs
- **Competitivity deficit mainly results from**:
  - **European model of society** guaranteeing higher standards of living, healthcare systems, protection of workers and environment…
  - And in a lesser extend **higher energy and feedstock costs in Europe** than in China or India…
- Resulting in structural under-investment in **world-scale unit and efficient processes** as well as **closure of key RSM production capacities** and **loss of some related know-how** (e.g. nitration)

Pre-requisite to domestic API production defense measures

- In order to **defend European model of society,** and **make sustainable and safe the medicine value chain** for the common good**,** member states have to join forces and **provide a common answer at the European level:**
  - API manufacturing **needs a critical market size with common rules of the game** to foster the **emergence of cost-competitive European champions vs. Asian unfair competition**
  - API manufacturers need to **secure minimum/critical volumes to cover higher fixed costs and labor costs**
- Securing sustainable domestic production of critical APIs is the **cornerstone of European citizens protection system** shared across all member states and recent shortage events tend to further reinforce this need… while **APIs value only accounts for 10% FDF value**

Advancy view on possible measures to defend domestic API and intermediates manufacturing which could be considered

Europe suffers from a lack of cost competitiveness and situation is expected to deteriorate further with the European regulations currently in preparation (CSRD, NIS2, PFAS,…)

LEVERS	DESCRIPTION	PROPOSALS	UNDER-INVESTED PROD. PROCESS	COST OF LABOR	LACK OF INTEGRATION	UNCOMPETITIVE PRODUCTS	ENVIRO., SAFETY, ADMIN. BURDEN
SUPPORT	Stimulate API innovation and production in Europe	▪ **Support investment in innovative process for key APIs and RSM production** (e.g. corticoids, antibiotics,…), : improved IPCEI, dedicated EU funds,…	✓		✓		
		▪ **Support production increase and capacity development:** tenders, *"European-PLI", SGEI, EU FAB,…*	✓		✓		
		▪ **Participate to investment extra cost driven by safety, environment, quality standards**					✓
		▪ **Facilitate/support** dossier instruction for new APIs or new process validation	✓		✓		✓
		▪ Support the constution of an **"Airbus of RSMs"** to **guarantee sustainable cost-competitive supply i) at scale** and **ii) in which know-how could be re-build/secured on the long term**	✓	✓	✓		
		▪ **Simplify/streamline procedure** for new dossier submission[1] for critical APIs for EU players only	✓		✓		✓
VALORIZE	Valorize domestic API production according to high ESG and quality standards	▪ **Include MadeinEU or environmental criteria in public tenders** and/or **any EU support scheme**	✓	✓	✓	✓	✓
		▪ **Set differentiated reimbursement rate by social security system based MadeinEU or environmental criteria**	✓	✓	✓	✓	✓
		▪ **Impose API geographic origin or "*environmental score*" labelling** for consumer to be informed	✓	✓	✓	✓	✓
		▪ Constrain member states to **purchase at >30% of their critical medicines with drug products using API made in Europe and/or include ESG criteria related to API production**	✓	✓	✓	✓	✓
		▪ **Guidance on minimum price per API domestically produced with high ESG standards**	✓				✓
		▪ For critical API, **set quotas of domestic sourcing to guarantee long-term Europe sovereignty**	✓		✓	✓	✓
		▪ **Impose reciprocity in international trade agreements**	✓	✓			✓
		▪ **Encourage diversification[1] of supply** from (or to) countries operating according to EU standards			✓		
		▪ **Strengthen partnerships with US, Japan, South Korea** and countries with high production standards	✓				
		▪ **Valorize upstream integration** to de-risk whole supply chain	✓		✓	✓	
LEVEL THE PLAYING FIELD	Secure fair competition conditions in Europe	▪ **Introduce an *European biosecure Act*** to restrict access to EU market to unfair competition			✓	✓	
		▪ **Introduce purchase quota of domestically produced critical APIs**	✓	✓	✓	✓	
		▪ **Include environment criteria, workers' safety and health standards in GMP standards**	✓	✓		✓	✓
		▪ **Impose reciprocity in international trade agreements**	✓	✓			✓
		▪ **Grant market access only to a positive list of virtuous non-European suppliers** based on their compliance with European standard for environment, workers' safety,…	✓	✓			✓
		▪ **Ban API made through polluting process** when cleaner processes exist	✓	✓			
		▪ **Enforce an *ESG-passport*** *(similar to battery passport)* per molecule		✓	✓		✓
		▪ **Enforce a European-GDFUA for non-European market participants** to fund EU control agency					✓

Note: 1) when there is no European supplier
Source: External interviews, Advancy analysis

Possible measures suggested by Advancy should have direct positive impacts on economic viability of investigated molecules sample

LEVERS	DESCRIPTION	PROPOSALS	1	2	3	4	5	6	7	8	9	10	11	12
SUPPORT	Stimulate API innovation and production in Europe	**Support investment in innovative process for key APIs and RSM production** (e.g. corticoids, antibiotics,…), : improved IPCEI, dedicated EU funds,…		P1	P1			P1	P1	P1	P2	P1		P1
		Support production increase and capacity development: tenders, *"European-PLI", SGEI, EU FAB,…*		P1	P1				P1		P2	P1		P1
		Participate to investment extra cost driven by safety, environment, quality standards		P1	P1				P1		P2	P1		P1
		Facilitate/support dossier instruction for new APIs or new process validation		P1	P1				P1		P2	P1		P1
		Support the constution of an **"Airbus of RSMs"** to **guarantee sustainable cost-competitive supply i) at scale** and **ii) in which know-how could be re-build/secured on the long term**					P3	P1		P1	P2	P1		P1
		Simplify/streamline procedure for new dossier submission[1] for critical APIs for EU players only	*Not applicable for analyzed molecules*											
VALORIZE	Valorize domestic API production according to high ESG and quality standards	**Include MadeinEU or environmental criteria in public tenders** and/or **any EU support scheme**	P1	P2	P2	P2	P1	P3	P2	P2	P3	P2	P2	P3
		Set differentiated reimbursement rate by social security system based MadeinEU or environmental criteria	P1	P2		P2	P1	P3	P2	P2	P3	P2	P2	P3
		Impose API geographic origin or "*environmental score*" labelling for consumer to be informed	P1	P2		P2	P1	P3	P2	P2	P3	P2	P2	P3
		Constrain member states to **purchase at >30% of their critical medicines with drug products using API made in Europe and/or include ESG criteria related to API production**	P1	P2	P2	P2	P1	P3	P2	P2	P3	P2	P2	P3
		Guidance on minimum price per API domestically produced with high ESG standards	P1	P2			P1		P2	P2		P2	P2	
		For critical API, **set quotas of domestic sourcing to guarantee long-term Europe sovereignty**	P1	P2	P2	P2	P1	P3	P2	P2	P3	P2	P2	P3
		Encourage diversification[1] of supply from countries operating according to EU standards	P1			P2	P1	P3		P2	P3	P2	P2	P3
		Strengthen partnerships with US, Japan, South Korea and countries with high production standards	P1	P1	P3	P3	P3					P3	P2	
		Valorize upstream integration to de-risk whole supply chain	P1	P1	P3	P3	P3					P3	P2	
LEVEL THE PLAYING FIELD	Secure fair competition conditions in Europe	**Introduce an *European biosecure Act*** to restrict access to EU market to unfair competition	P2	P3	P3	P1	P2	P2	P3	P3	P1	P3	P1	P2
		Introduce purchase quota of domestically produced critical APIs	P2	P3	P3	P1	P2	P2	P3	P3	P1	P3	P1	P2
		Include environment criteria, workers' safety and health standards in GMP standards	P2	P3	P3	P1	P2	P2	P3	P3	P1	P3	P1	P2
		Impose reciprocity in international trade agreements	P1	P2	P2	P2	P1	P3	P2	P2	P3	P2	P2	P3
		Grant market access only to a positive list of virtuous non-European suppliers based on their compliance with European standard for environment, workers' safety,…	P2	P3	P3	P1	P2	P2	P3	P3	P1	P3	P1	P2
		Ban API made through polluting process when cleaner processes exist	*Not applicable for analyzed molecules*											
		Enforce an *ESG-passport* *(similar to battery passport)* per molecule	P2	P3	P3	P1	P2	P2	P3	P3	P1	P3	P1	P2
		Enforce a European-GDFUA for non-European market participants to fund EU control agency	P2	P3	P3	P1	P2	P2	P3	P3	P1	P3	P1	P2

Proposals: P1 : Priority 1 P2 : Priority 2 P3 : Priority 3

Note: 1) when there is no European supplier
Source: External interviews, Advancy analysis

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