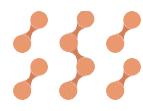


# Sicos data on the WW production of API



**SICOS**  
LA VOIX DES INDUSTRIES  
CHIMIE FINE ET BIOTECH

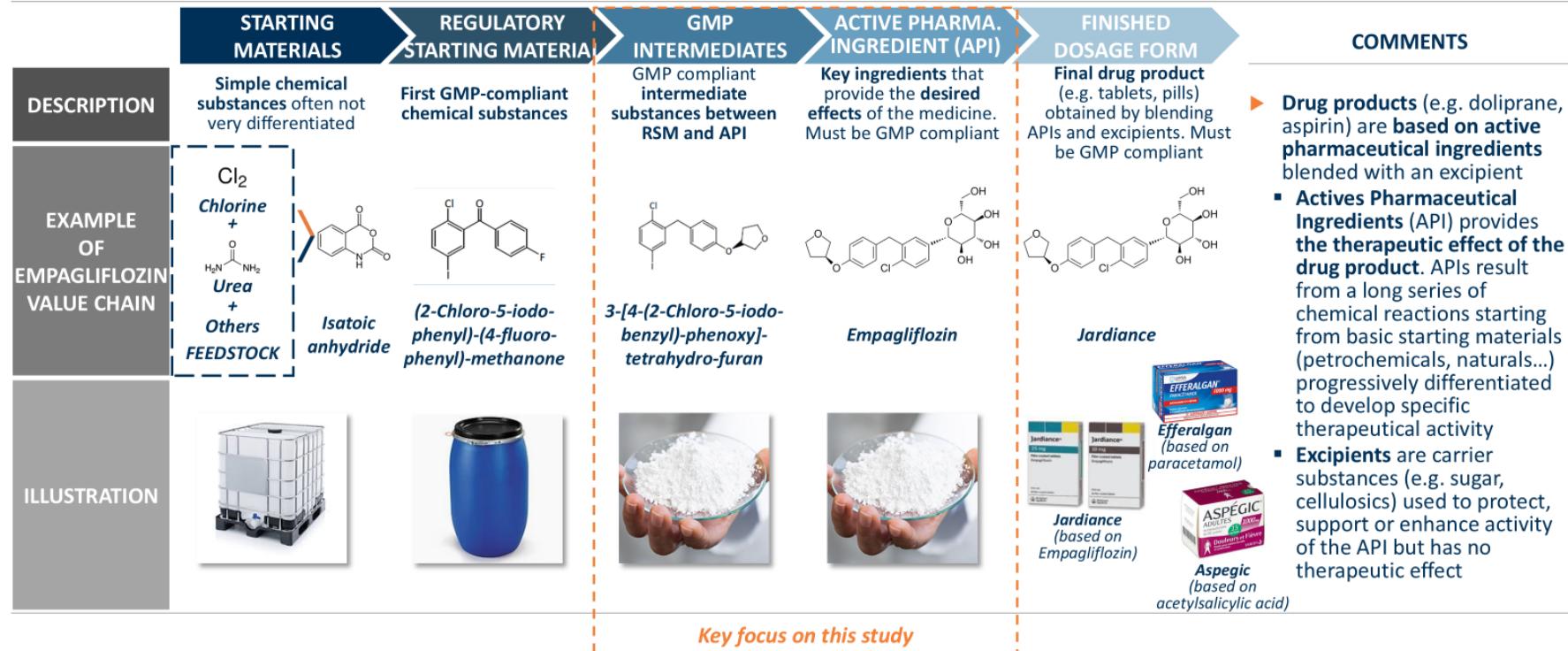


# Etude advancy – the supply chain of drug product – focus on GMP and API

## OVERVIEW

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

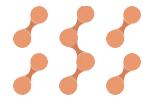


Key focus on this study

Sources: Ashford's Dictionary, EFPIA, Science Direct, Advancy

advancy

This study focusses on matures APIs (small molecules mainly generics) which represent 60bn€ market ww vs a total APIs and intermediate market of 160 bn€ ww

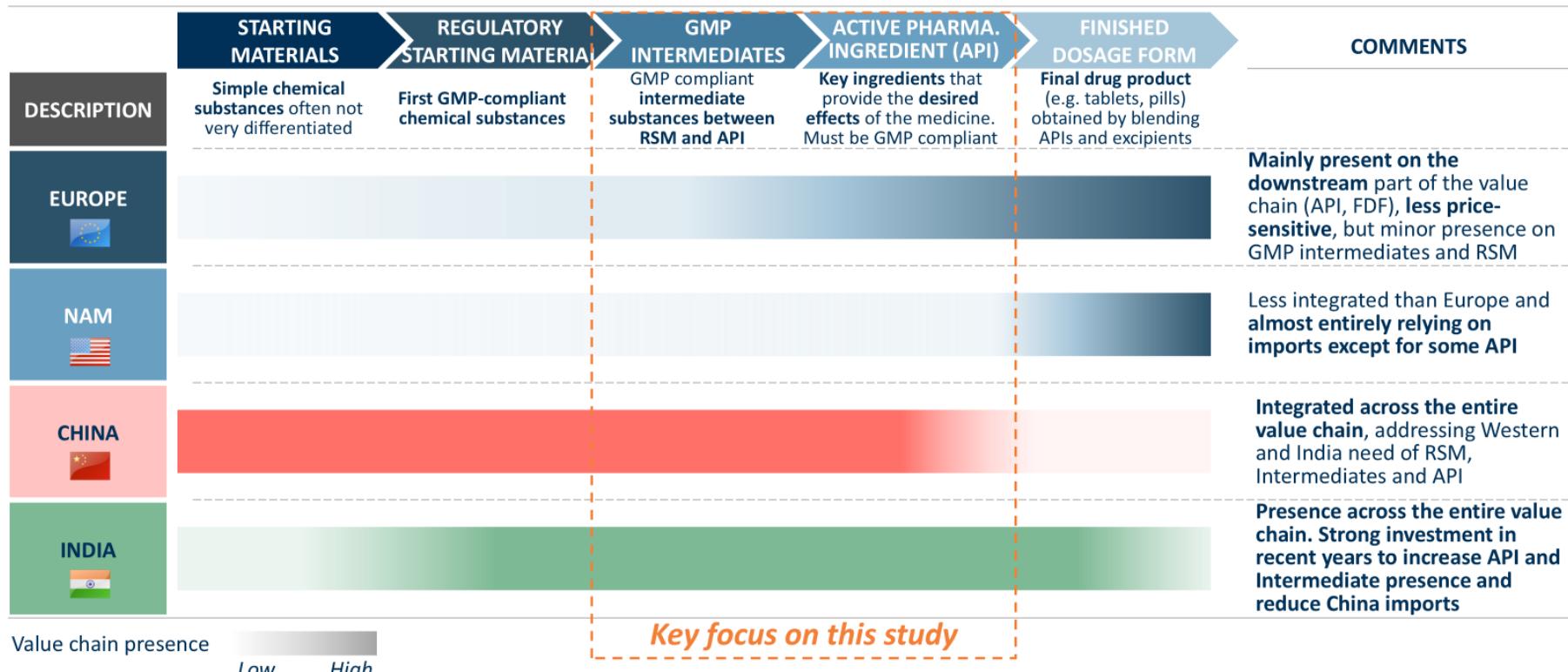


# Etude advancy – WW presence

## OVERVIEW

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



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

advancy

China focuses at the beginning on the starting materials and developed during the last 10 years the downstream production to address the final drug product.

India started from final drug product and developed the upstream value chain.

The starting value chain disappears progressively in EU and NAM.

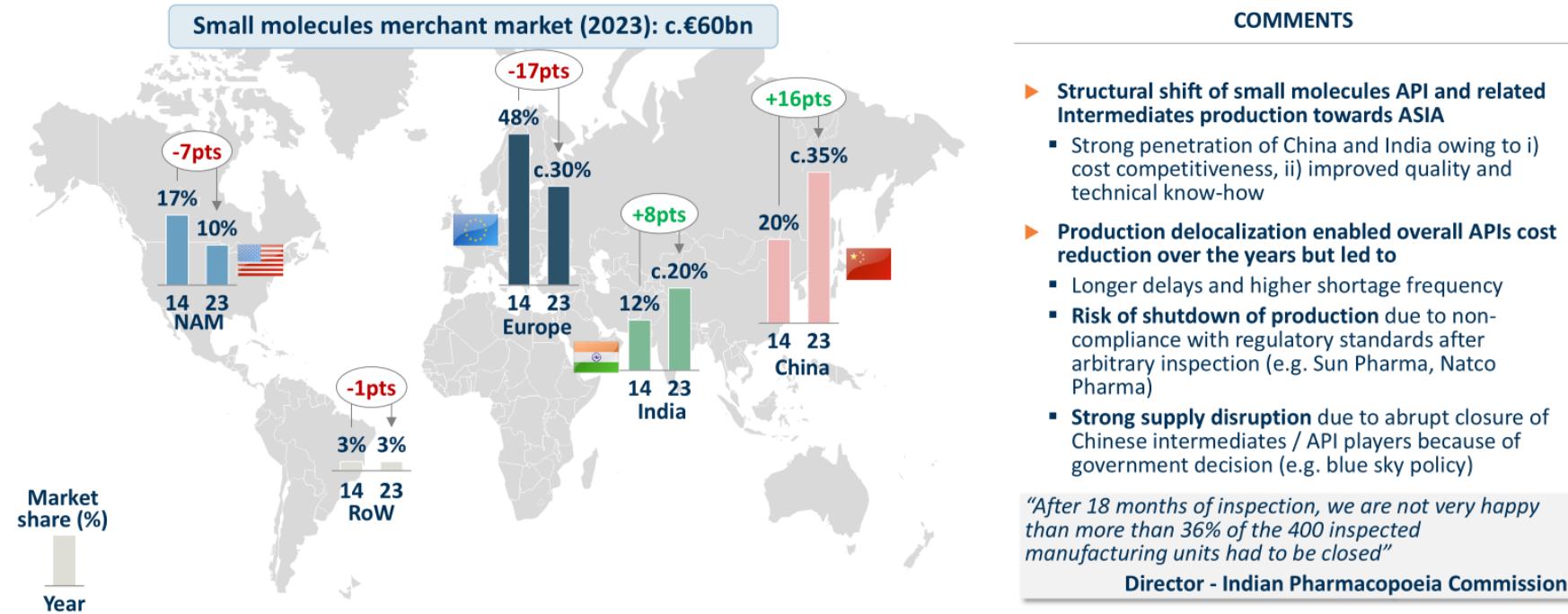


# Etude advancy – WW presence of API manufacturers

## OVERVIEW

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

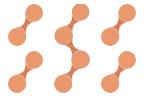


Sources: Company data, External Interviews, IQVIA, Advancy

advancy

There is only 3 regions producing API : NAM, Europe and Asia,

During the last 10 years, EU and US production decreased to the benefice of Asia!

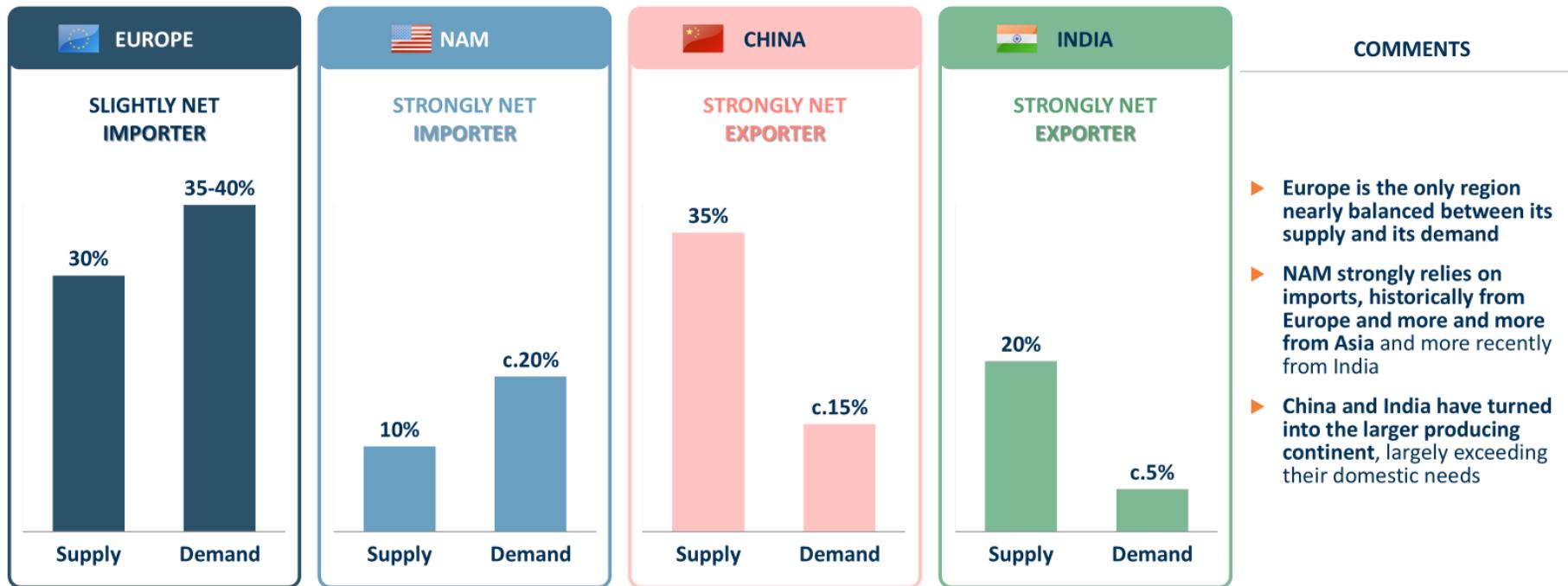


# Etude advancy - dependencies

## OVERVIEW

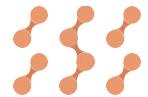
... Which resulted in a net importer position for Europe and NAM in a much larger extent while China and India have become strong net exporting geographies

| Small molecules APIs and Intermediates supply and demand per region <sup>1</sup> | merchant, small molecules, %value, 2023, World



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

advancy



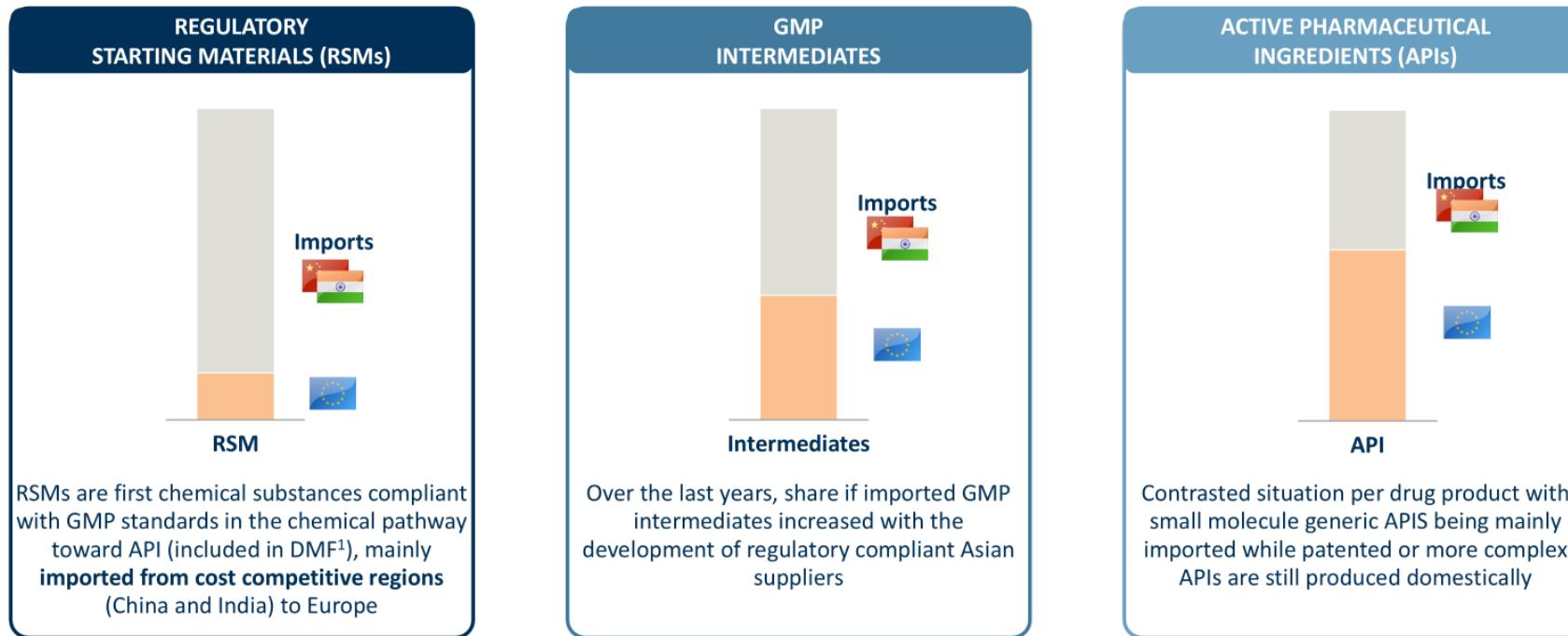
# Etude advancy- Dependency of Europe : ratio of production versus importation

## 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



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

advancy

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



# Etude advancy – global support and barriers

## OVERVIEW

**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%)	<ul style="list-style-type: none"> <li>€1bn through the IPCEI Med4Cure to support 4 pharmaceutical R&amp;D axis, only &lt;25% is directed toward small molecules participating the open market</li> <li>Investments at national levels in most countries, e.g. €50m to reshore essential medicines (France 2030)</li> <li>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<sup>1</sup> in Dec 23)</li> </ul>	<ul style="list-style-type: none"> <li>European market fully open to foreign competition</li> <li>c.7% import tariffs</li> </ul>
US	>€1bn (c.15%)	<ul style="list-style-type: none"> <li>Large investment (&gt;€1bn) in manufacturing assets on domestic soil           <ul style="list-style-type: none"> <li>€910m during COVID-19 crisis for APIs and FDF production in the US</li> <li>€40m for essential medicines through Defense Production act</li> </ul> </li> <li>In progress: "Pills act", promotes US generic medicine production via tax credits</li> </ul>	<ul style="list-style-type: none"> <li>Restrict some federal market to Chinese players (Buy American act)</li> <li>May be expanded to a broader scope if Biosecure act is passed</li> <li>c.7%<sup>2</sup> import tariffs</li> </ul>
CHINA	>€1.5bn (c.7%)	<ul style="list-style-type: none"> <li>Large investment at national level (€1.5bn) and province level (e.g. Shanghai: c.€2.5m R&amp;D investment) to support new drug development</li> <li>Boost local players' cost competitiveness via investments in infrastructure (SEZs<sup>3</sup>, R&amp;D parks) and very advantageous loan from state-controlled banks</li> </ul>	<ul style="list-style-type: none"> <li>No formal barriers, but disclosing process details limits foreign players' participation in the Chinese market</li> <li>5-10% import tariffs</li> </ul>
INDIA	>c.€3bn (25%)	<ul style="list-style-type: none"> <li>Large investment (€2.5bn) to stimulate domestic production and reduce exposure to imports from China (PLI<sup>4</sup>)</li> <li>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<sup>5</sup>)</li> </ul>	<ul style="list-style-type: none"> <li>Indian market fully open to foreign competition</li> <li>15-30%<sup>6</sup> tax</li> </ul>

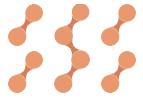
Importance (xx%): Support intensity defined as support measure budget divided by the value of the domestic industry

Importance

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

advancy



# Etude advancy

DEFENCE OF  
PRODUCTION

- 3 Zoom on China: Government creates favorable conditions to boost domestic players and has implemented unofficial barriers for foreign companies preventing them to serve its market



## | Government initiatives to develop local API production | 2023, China

LEVER	ACTION	SPENDING	DESCRIPTION
SUPPORT LOCAL PRODUCTION	STATE SUBSIDIES	€1 500m	<ul style="list-style-type: none"> <li>Investment of Chinese government to support new drug development in China and secured long-term competitiveness</li> </ul>
	SEZ	-	<ul style="list-style-type: none"> <li>Funding of seven SEZs (<i>Special Economic Zones</i>) offering China manufacturers access to discounted land acquisition, electricity, tax rates,...</li> </ul>
	R&D PARKS	-	<ul style="list-style-type: none"> <li>Funding of R&amp;D parks offering China manufacturers offering subsidies, tax incentives, low interest loans...</li> </ul>
	REGIONAL LEVEL POLICY	No total budget available	<p>Many regional initiatives focused on R&amp;D and innovation including for example:</p> <ul style="list-style-type: none"> <li>Guangzhou: Up to €13m for national projects, €600m interest-subsidized for global ones</li> <li>Shanghai: Up to €2.5m R&amp;D investment for innovative drugs post-clinical trials; rental subsidies for Shanghai-based companies</li> <li>Jiangsu: €1-4m subsidies for innovative drugs post clinical trials and in production</li> <li>Hebei Xiong'an: €6m subsidies for certified locally produced innovative drugs</li> </ul>
BARRIER TO ENTRY	PROCESS	-	<ul style="list-style-type: none"> <li>Obligation for foreign players to disclose confidential information about their production process to participate to China market</li> </ul>
	TAXES	-	<ul style="list-style-type: none"> <li>5-10% imports tariffs</li> </ul>
TOTAL INVESTMENT		>€1 500m	

The establishment of special economic zones (SEZs) to provide economic and/or infrastructure-related benefits to China-based manufacturers. The benefits may include lower-than-market prices for land acquisition; facilitated and/or discounted access to electricity, water and other utilities; access to common waste processing and/or disposal facilities; relief from import duties with respect to materials and/or equipment used for export-related activities; preferential tax rates; subsidies; access to low-cost employee housing, and/or; facilitated access to transport services. There are a variety of different approaches to the specific benefits of the SEZs, which change from time to time.

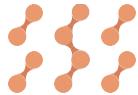
The establishment of R&D parks that provide economic and/or infrastructure-related benefits to research-oriented entities located within the R&D parks. These R&D parks may be established at the provincial and/or local level, and the benefits vary. These may include making available low-cost facilities; R&D grants or subsidies; facilitated access to loans; tax benefits, and/or, organization of conferences.

KU is Dentons' Preferred Law Firm in China.

No.	Target Objects	Incentive Policies
1.	Research and development projects on innovative drugs and devices	<ul style="list-style-type: none"> <li>Offer a maximum amount of RMB 30 million as financial support for eligible projects</li> </ul>
2.	Breakthroughs in key and core technologies, building of key professional service platforms and major product industrialization projects in the field of biomedicine	<ul style="list-style-type: none"> <li>Offer a maximum amount of RMB 15 million as financial support for eligible projects</li> </ul>
3.	Establishment of headquarters, research and development centers and production bases by biotech and pharmaceutical companies	<ul style="list-style-type: none"> <li>Encourage the introduction of major functional headquarters.</li> <li>Enhance support for projects that introduce headquarters of innovative and trade-oriented companies, headquarters of private companies, as well as regional headquarters and research and development centers of multinational companies</li> <li>Encourage all districts to provide a maximum subsidy of 10 million RMB for the company headquarters making their first purchases of office space, and a maximum subsidy of 5 million RMB for renting their office space.</li> </ul>

Sources: Advancy

advancy



# Etude advancy

DEFENCE  
OF  
PRODUCTION

## 4 India is heavily investing to boost local API and intermediate production, including c.€2.5bn PLI incentive scheme and investment in infrastructures



### | Government initiatives to develop local API production | 2023, India

LEVER	ACTION	SPENDING	DESCRIPTION
SUPPORT LOCAL PRODUCTION	PLI	€2 400m	<ul style="list-style-type: none"> <li>PLI (<i>Production Linked Incentive</i>) is a <b>€2.4bn incentive program to support the growth of Indian APIs and intermediates production</b> <ul style="list-style-type: none"> <li><b>€1.6bn for all Indian pharma players</b>, subsidies amounting to 6-15% of the incremental sales realized from one year to the other</li> <li><b>€0.8bn specifically targeting 41 products (53 APIs)</b>, subsidies amounting to 5-20% of the incremental sales realized from one year to the other</li> </ul> </li> </ul>
	SPI	€55m	<ul style="list-style-type: none"> <li>SPI (<i>Strengthening of pharmaceutical industry</i>) is a series of initiatives to support development of the domestic APIs and related intermediates industry including:           <ul style="list-style-type: none"> <li><b>APICF<sup>1</sup></b>: R&amp;D facilities with shared services to host R&amp;D teams/projects</li> <li><b>PTUAS<sup>2</sup></b>: 5%-interest or 10% capital subsidy for MSMEs<sup>3</sup> meet regulatory standards</li> <li>Incl. <b>€35m for upgrading production facilities</b> of pharma companies with sales &lt;€55m</li> </ul> </li> </ul>
	BULK DRUG PARKS	€330m	<ul style="list-style-type: none"> <li><b>Three mega bulk drug parks</b> set up to reduce manufacturing costs including shared services : solvent recovery, effluent treatment plants, distillation units...</li> </ul>
BARRIER TO ENTRY	TAXES	-	<ul style="list-style-type: none"> <li><b>c.10% import tariff</b></li> <li><b>5-20% Good and services tax</b></li> </ul>
TOTAL INVESTMENT		€2 800m	

The Union Cabinet chaired by the Prime Minister, Shri Narendra Modi has approved the following schemes:

- The scheme on Promotion of Bulk Drug Parks for financing Common Infrastructure Facilities in 3 Bulk Drug Parks with financial implication of Rs. 3,000 crore for next five years.
- Production Linked Incentive (PLI) Scheme for promotion of domestic manufacturing of critical KSMs/Drug Intermediates and APIs in the country with financial implications of Rs6.940 crore for next eight years.

The Scheme has 3 components / sub-schemes: **Assistance to Pharmaceutical Industry for Common Facilities (APICF)**, to strengthen the existing pharmaceutical clusters' capacity for their sustained growth by creating common facilities; **Pharmaceutical Technology Upgradation Assistance Scheme (PTUAS)** to facilitate Micro, Small and Medium Pharma Enterprises (MSMEs) of proven track record to meet national and international regulatory standards and **Pharmaceutical & Medical Devices Promotion and Development Scheme (PMPDS)** to facilitate growth and development of Pharmaceutical and Medical Devices Sectors through study/survey reports, awareness programs, creation of database, and promotion of industry. The scheme will provide financial incentives on the incremental sales (over Base Year) of pharmaceutical goods and in-vitro diagnostic medical devices to selected applicants based on pre-defined selection criteria. The incentives will be paid for a maximum period of 6 years for each participant depending upon the threshold investments and sales criteria to be achieved by the applicant. The total quantum of the incentive for the scheme is Rs 15,000 crore. SIDBI is the Project Management Agency for the Scheme.

*"To reduce dependency to import, India is focusing on production of high value pharmaceuticals and high-end medical devices."*

Minister of labor and Employment of India

Notes: (1) Assistance to Pharmaceutical Industry for Common Facilities (2) Pharmaceutical Technology Upgradation Assistance (3) Micro and small companies  
 Sources: Advancy

advancy



# Etude advancy

DEFENCE OF  
PRODUCTION

- 4 Zoom on India: €2.5bn Production Linked Incentive (PLI) scheme aims at increasing domestic production and reduce India dependency on Chinese imports



## | Focus on PLI Schemes | 2020-2029, €bn, India

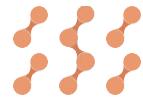
PLI TIMELINE		CONTEXT AND DESCRIPTION	FOCUS ON PLI SCHEME FOR BULK DRUGS		
			DRUG CLASS	MOLECULE	COMPANY
	PASSED	<p>► PLI Scheme introduced in 2020 to reduce dependency on China for RSM, Intermediate and API supply (c.€3bn in 2023) and increase local production</p> <ul style="list-style-type: none"> <li>▪ PLI Scheme for Pharmaceuticals: c.€1.6bn (until 2029) <ul style="list-style-type: none"> <li>▪ Incentive based on incremental sales over the base year</li> <li>▪ Used to promote <b>high value drugs sales</b> (e.g. complex generics, biological)</li> </ul> </li> <li>▪ PLI Scheme for Bulk Drugs: c.€0.8bn <ul style="list-style-type: none"> <li>▪ Allocation provided for <b>6 years to 51 manufacturers</b> (covering 41 products<sup>1</sup> used to manufacture 53 APIs)</li> <li>▪ <b>Used to develop production of bulk drugs</b> (Key Starting Materials, Intermediaries and APIs)</li> <li>▪ Incentive based on <b>incremental sales over the base year</b></li> </ul> </li> </ul>	ANTIBIOTIC 13 manufacturers	Ciprofloxacin Clindamycin Base Levofloxacin Meropenem Norfloxacin Other (Ofloxacin etc.)	SREEPATHI PHARMACEUTICALS LIMITED PHARMAKAR PHARMACEUTICALS LIMITED MSN Research for Better Medicines HETERO Globela Industries Pvt. Ltd. Vital Health Care Naturally Global Pharma Healthcare Ltd. INDIA
	2020	Launch of the PLI Scheme under the <i>Atmanirbharta</i> (self-reliant India) initiative	CORTICOSTEROID 4 manufacturers	Betamethasone Dexamethasone Prednisolone	NATURAL BIOGENEX PVT LTD SYMBIOTEC Alta Laboratories Ltd.
	2029	End of PLI scheme	NSAID 4 manufacturers	Aspirin Diclofenac Sodium	Kreative Organics Ananda Biotech
			INTERMEDIATE 8 manufacturers	Para amino phenol (PAP), 7-ACA and others	KARNATAKA PHARMACEUTICALS N LTD OrchidPharma MEGHMANI
			VITAMIN 4 manufacturers	Vitamin B1, B6	HAZELO LAB PRIVATE LTD Sudarshan Pharma HONOUR
			OTHER API 18 manufacturers	Carbidopa, Losartan, Valsartan and others	Anasia HONOUR

Likehood to pass → High

Notes: (1) RSM, Intermediates and APIs  
Sources: Advancy

Full list of APIs and intermediates provided in appendix

advancy



# Etude advancy -

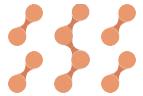
THE KEYS API STUDIED

**APIs among the most sold and/or most critical have been investigated in this report to illustrate cost-competitiveness API production in Europe vs. oversea competition**

CLASS	EXAMPLE OF KEY MOLECULES	COMMENTS
NSAID	Paracetamol, Aspirin, Metamizole, Ketoprofen, Ibuprofen, Codeine, Morphine,...	<ul style="list-style-type: none"> <li>▶ Include some of the most prescribed drug products in Europe</li> <li>▶ Very large volume (up to c.50kt), low-mid value (€5-100/kg) molecules</li> </ul>
CARDIOVASCULAR ANTITHROMBOTICS DIURETICS	Atorvastatin, Rivaroxaban, Ramipril, Clopidogrel, Dronaderone, Candesartan, Irbesartan, Losartan, Furosemide,...	<ul style="list-style-type: none"> <li>▶ Large volume, mid value molecules with strong capacity increase in Asia for some products in recent years leading to pressure on price</li> </ul>
RESPIRATORY	Budesonide, Fluticasone, Ephedrine,...	<ul style="list-style-type: none"> <li>▶ Notably include several products on WHO list of essential medicines, limited shortage in recent years</li> </ul>
ANTI HISTAMINIC	Cetirizine, Bilastine, Desloratadine, Fexofenadine,...	<ul style="list-style-type: none"> <li>▶ Large volume, mid value molecules with strong price pressure from Asia</li> </ul>
DIABETES	SGLT2i (e.g. Empagliflozine), Insulin, Metformin, DPP4 inhibitors (Sitagliptine), GLP1 (Semaglutide),...	<ul style="list-style-type: none"> <li>▶ Include several patented products with large share of production remaining in Europe (for both API and precursor)</li> </ul>
STEROIDS	Methylprednisolone, prednisolone, hydrocortisone, dexamethasone,...	<ul style="list-style-type: none"> <li>▶ Numerous shortages in Europe for various corticoids</li> <li>▶ Europe sustainability at risk owing to historical under-investments</li> </ul>
ANTIBIOTICS	Amoxicillin, Spiramycin, Cefixime, Meropenem, Ceftriaxone, Rifampicine,...	<ul style="list-style-type: none"> <li>▶ On the list of essential medicines but many recent shortage events</li> <li>▶ Large volume molecule. Most of the Europe demand no longer addressed by local producer. Remaining production at risk</li> </ul>
ONCOLOGY (OEB>3)	Capecitabine, Florouacil, Paclitaxel,...	<ul style="list-style-type: none"> <li>▶ Product requiring specific safety requirements to protect workers (OEB 3/4) given their toxicity</li> </ul>
NEUROLOGY	Midazolam, Amisulpride, Ketamine, Methylphenydate,...	<ul style="list-style-type: none"> <li>▶ Low volume medicine (high value) with small batches production cycle where Europe is still a key supplier</li> </ul>
GASTRO-INTESTINAL	Mesalamine, Ondansetron, Loperamide PPI: Omeprazole, Esomeprazole, Lantoprazole,...	<ul style="list-style-type: none"> <li>▶ Include products with high risk of delocalization which experienced recurring shortages in recent years for some products</li> </ul>
HORMONES (>OEB3)	Fulvestrant, Tamoxifen, Estradiol, Trenbolone,...	<ul style="list-style-type: none"> <li>▶ Europe and US as leading producers for several products</li> <li>▶ Some Indian authorization removed due to quality issue</li> </ul>
TOTAL		

This study compares the cost production of several APIs in Europe vs oversea competition

advancy



# Etude advancy – 1st exemple

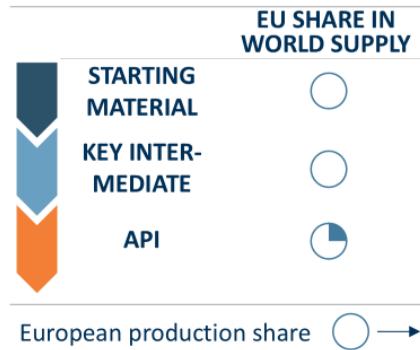
NSAID

Europe can become economically viable and if minimum offtake price can be guaranteed to secure investment economics in a competitive chemical route requiring less labor

## API overview

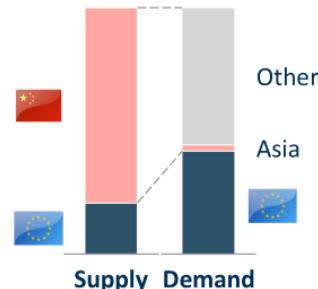
- ▶ NSAID<sup>1</sup> class drug
- ▶ Large volume API, alternative to most prescribed NSAID to relieve high fever and painkiller after paracetamol and aspirin
- ▶ Lifecycle status: Generics in all region
- ▶ Mainly used in LATAM and Europe with limited shortage in recent years

## Value chain



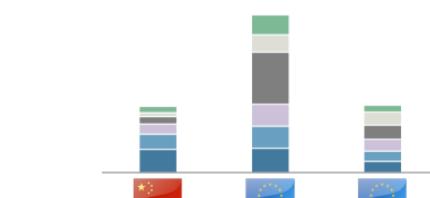
Note: (1) NonSteroidal Anti-Inflammatory Drug; (2) relative production capacity  
Sources: IQVIA, Tradedata, Company information, Ashford's Dictionary, Advancy

## API demand and supply | t, %, 2023, world



- ▶ Very high supply/demand dissymmetry with China accounting for c.80% of global supply
- ▶ European demand (40%) only partially supplied by domestic player (20% of supply)

## Cost structure | costs in €/kg, 2023



- ▶ LOW economic viability
  - European player suffers mainly from more expensive labor force and higher use of FTE/kg and unfavorable energy prices
  - At threat to be discontinued with no more supply in Europe given that necessary investment (R&D, equipment) have no payback

advancy

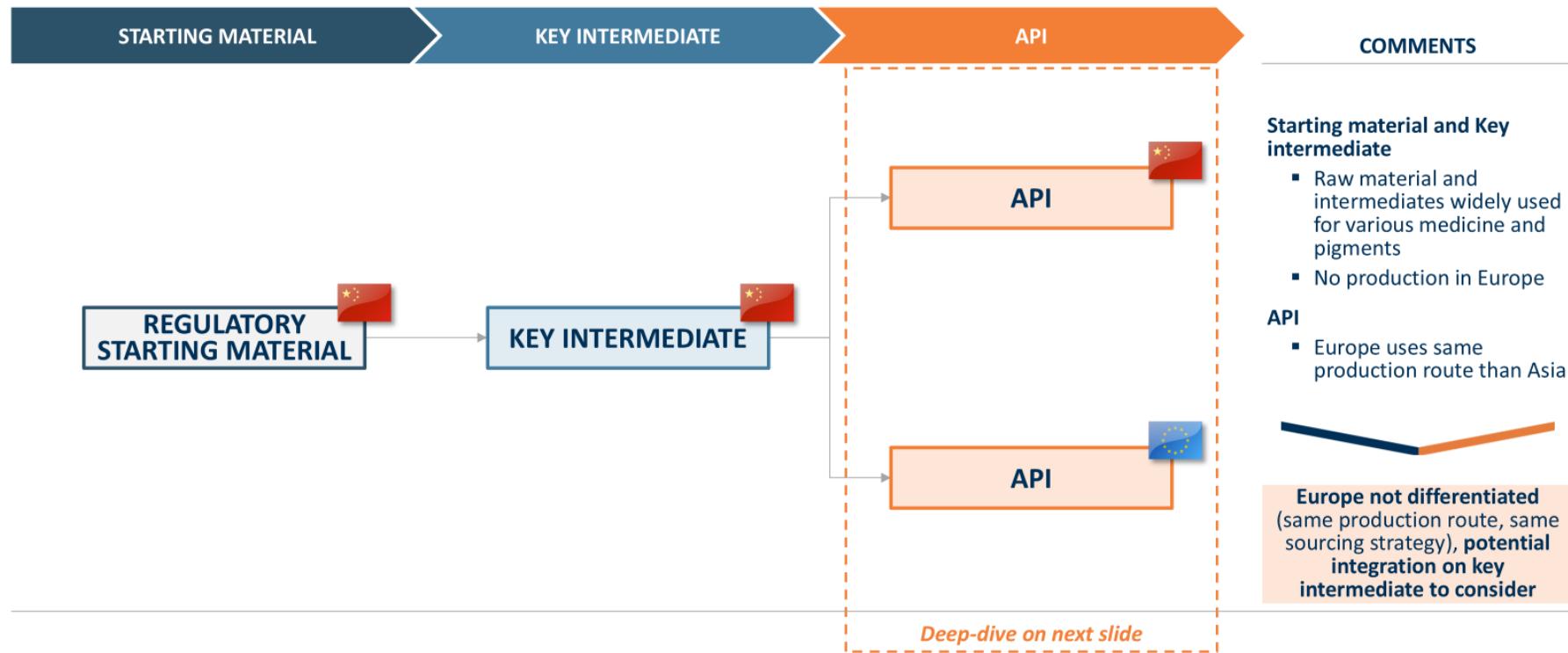


# Etude advancy – 1st exemple the routes of the supply chain

NSAID

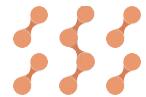
Europe route is not differentiated (production process, sourcing) on molecule 2 and most of the supply chain is already delocalized in China

Molecule 2 value chain | 2023



Sources: Tradedata, Ashford's Dictionary, Advancy

advancy

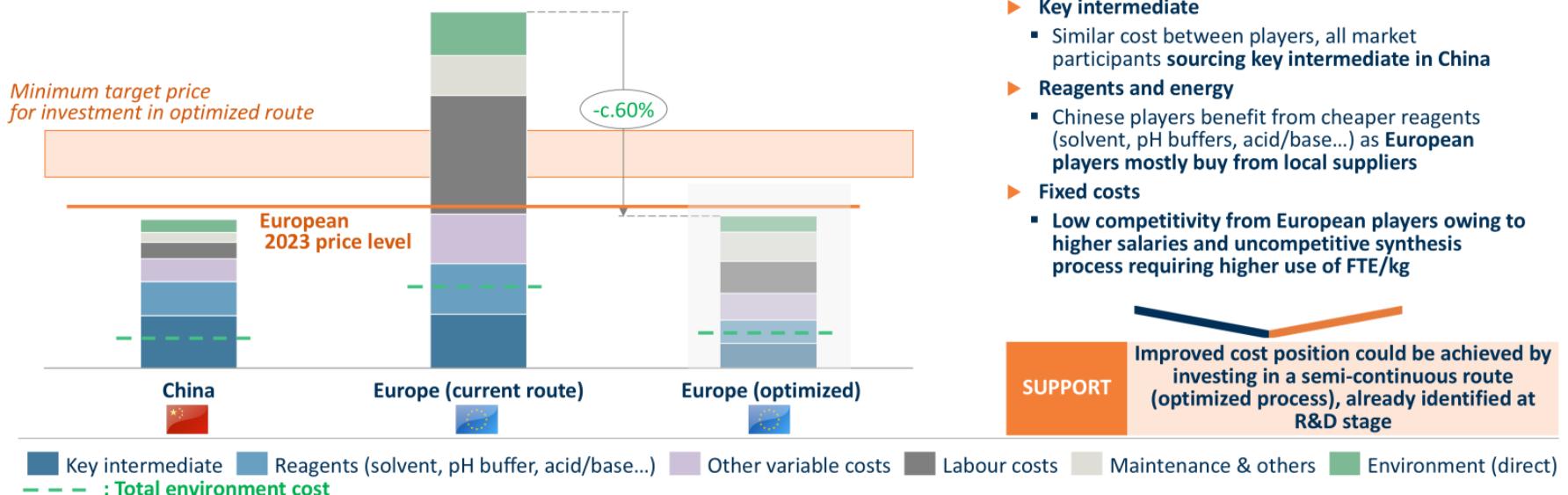


# Etude advancy – 1st exemple prices comparison Europe vs China

NSAID

Europe is not cost-competitive vs. China but cost gap can possibly be bridged by investing in new route development; Secured investment economics would be necessary to trigger such investment

| Cost structure by players | Costs in €/kg, 2023



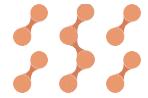
## MAIN COST DRIVERS

- ▶ European and Chinese players are using the same production route, limited investments conducted over the recent years in Europe given unfavorable cost position
- ▶ Key intermediate
  - Similar cost between players, all market participants sourcing key intermediate in China
- ▶ Reagents and energy
  - Chinese players benefit from cheaper reagents (solvent, pH buffers, acid/base...) as European players mostly buy from local suppliers
- ▶ Fixed costs
  - Low competitiveness from European players owing to higher salaries and uncompetitive synthesis process requiring higher use of FTE/kg

**SUPPORT** Improved cost position could be achieved by investing in a semi-continuous route (optimized process), already identified at R&D stage

Sources: Tradedata, Company information, Ashford's Dictionary, Advancy

advancy



# Etude advancy – 2<sup>nd</sup> exemple

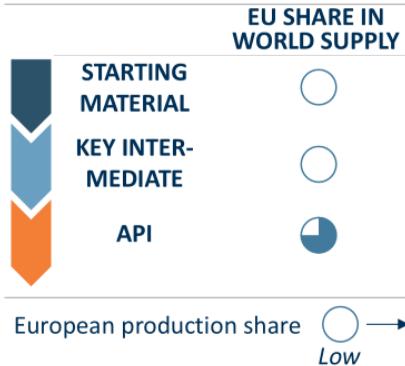
NEUROLOGY

## Europe economic viability seems challenging even considering investment in process optimization

### API overview

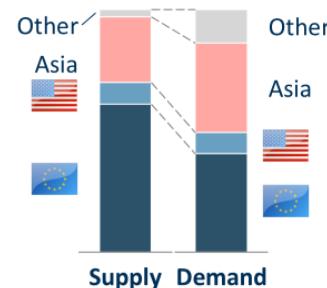
- Neurology class drug
- Small volume API, one of the **most consumed benzodiazepine** in the intensive care unit
- Mainly employed in seizures, anesthesia and anxiety disorders
- Lifecycle status: **Generic** in all regions
- **Strong increase of demand during Covid-19 leading to shortages**

### Value chain



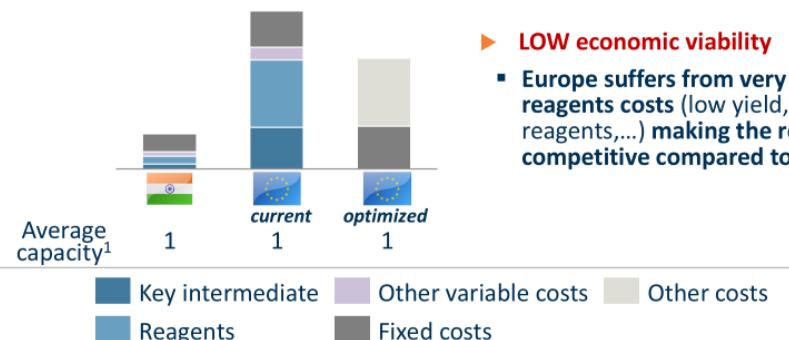
Note: relative production capacity  
Sources: IQVIA, Tradedata, Company information, Ashford's Dictionary, Advancy

### API demand and supply | t, %, 2023, world



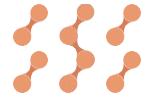
- Europe is the main supplier of Molecule 9 (60% of total supply) benefitting from limited capacity abroad
- Regional supply and demand mainly aligned
- **Europe supply** (c.60% of total supply) sufficient to address local demand (c.40%)

### Cost structure | costs in €/kg, 2022



- **LOW economic viability**
- Europe suffers from very high reagents costs (low yield, old reagents,...) making the region not competitive compared to India

advancy

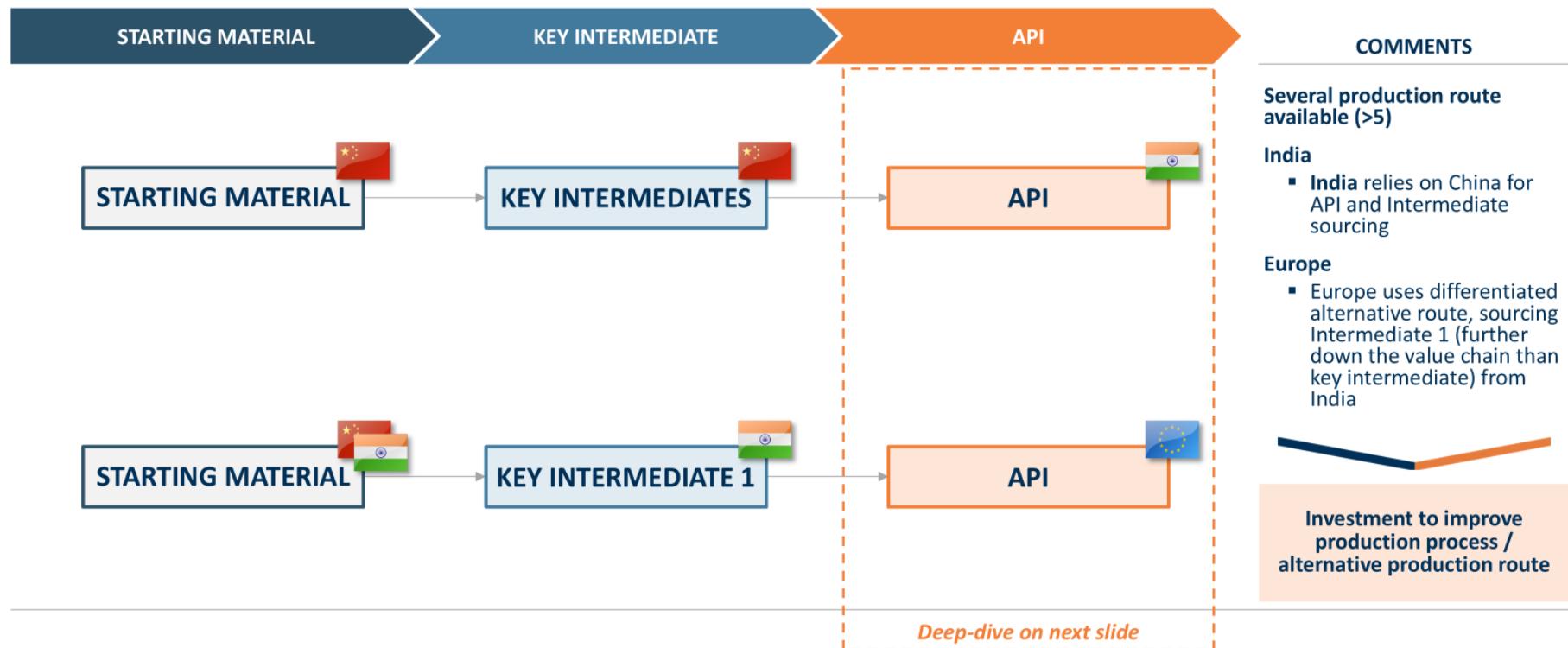


# Etude advancy – 2<sup>nd</sup> exemple the routes of supply chain

NEUROLOGY

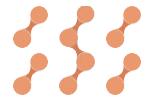
Europe is sourcing key intermediate in Asia but is not using the same route as India competitors to manufacture Molecule 9

Molecule 9 value chain | 2023



Sources: Tradedata, Ashford's Dictionary, IHS Markit, Advancy

advancy



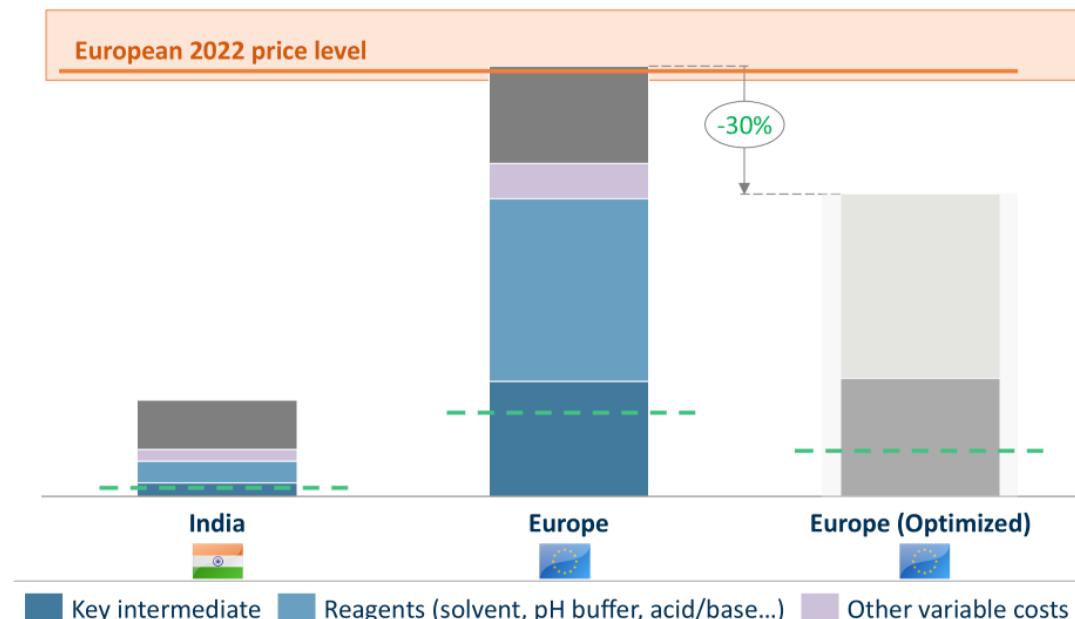
# Etude advancy - 2<sup>nd</sup> exemple prices comparison Europe vs India

NEUROLOGY

Europe is not competitive vs. India and investment is required to develop a more competitive production route and bridge the gap (at least partly)

| Cost structure by players | Costs in €/kg, 2022

Minimum target price  
for investment in optimized route



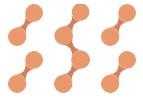
## MAIN COST DRIVERS

- Complex production synthesis requiring handling of explosive and other dangerous chemicals (e.g. Nitro-compound)
- Key intermediate and reagents
  - Main driver behind Europe lack of competitiveness. Europe suffering from low yield and high reagents prices compared to India
- Fixed costs
  - Europe has (i) higher labor costs and (ii) produces in small batches, leading to higher fixed costs versus India and specific safety requirements have to be met

**LEVEL THE PLAYING FIELD + SUPPORT** Investment to develop alternative production route and improve production yield could improve Europe competitiveness

Notes: 1) for 10 years amortization period  
Sources: Tradedata, Company information, Ashford's Dictionary, Advancy

advancy



# Etude advancy – 3rd exemple

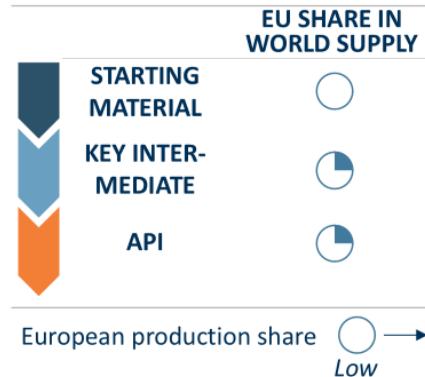
HORMONES

Europe economic viability seems challenging vs. Chine competition due to high labor cost and less efficient route; Possible competitiveness rejuvenation if investment economics can be secured

## API overview

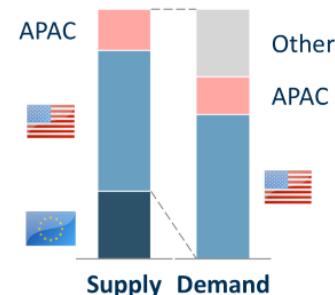
- ▶ Anabolic-androgenic steroid
- ▶ Small volume API, used as a **feed supplement** in cattle to promote **faster weight gain and enhance meat production** (forbidden in most countries for usage on humans, muscle growth promoter)
- ▶ Lifecycle status: **Generics in all regions**
- ▶ Limited shortage in recent years

## Value chain



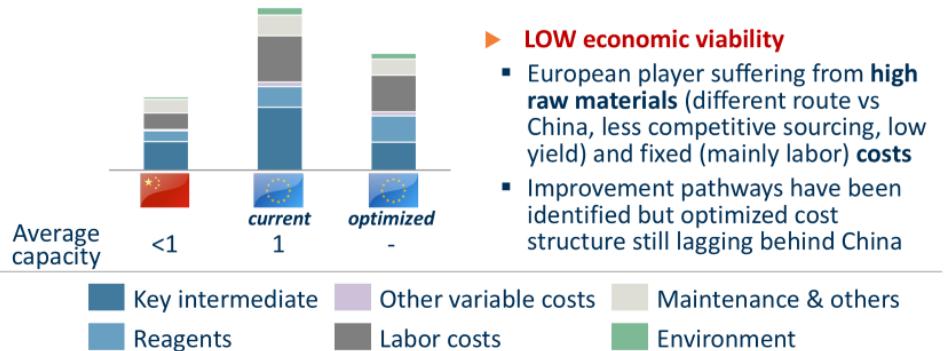
Note: (1) relative production capacity  
Sources: IQVIA, Tradedata, Company information, Ashford's Dictionary, Advancy

## API demand and supply | t, %, 2023, world



- ▶ Europe represents c.25% of world production but no demand due to ban on usage both for human and feedstock
- ▶ Demand mainly driven by meat production in authorized regions (USA, Argentina, South Africa)
- ▶ Asia supply addresses primarily unregulated markets

## Cost structure | costs in €/kg, 2023



- ▶ **LOW economic viability**
- European player suffering from **high raw materials** (different route vs China, less competitive sourcing, low yield) and **fixed (mainly labor) costs**
- Improvement pathways have been identified but optimized cost structure still lagging behind China

advancy

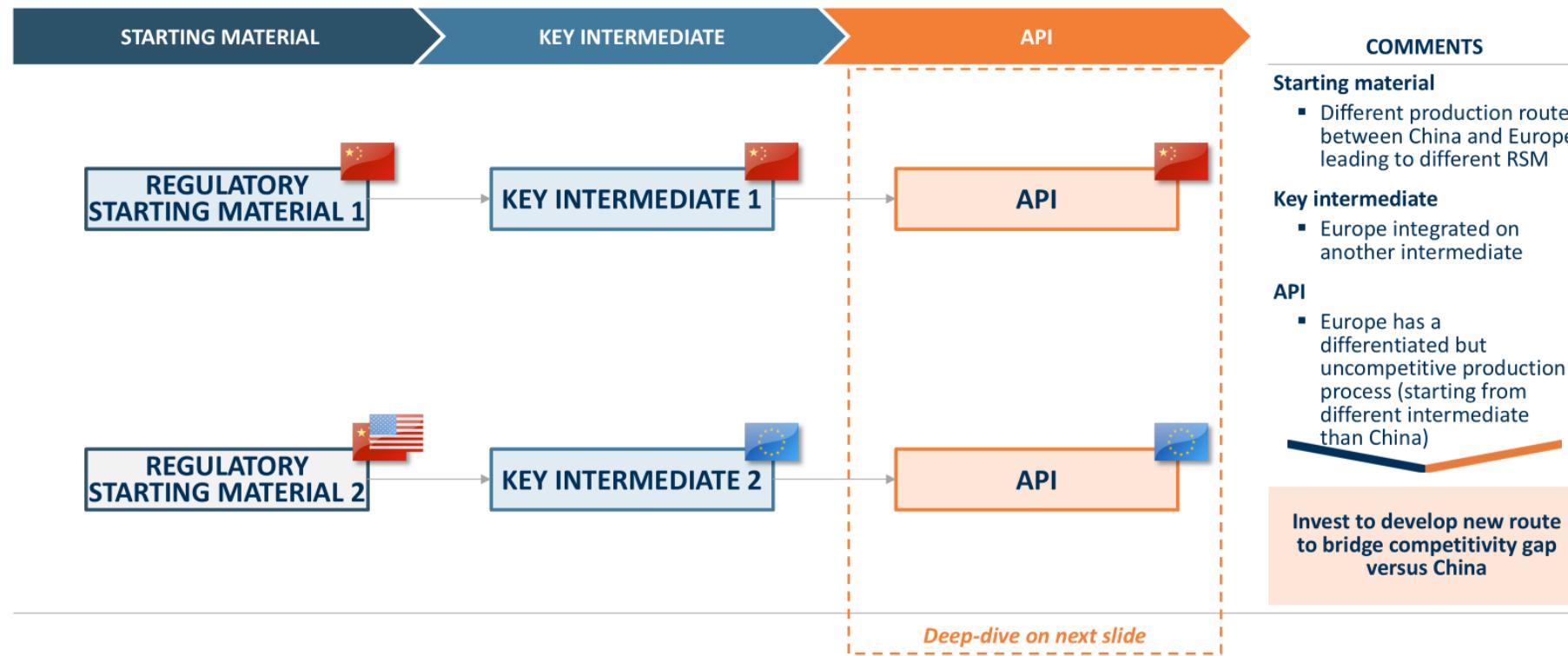


# Etude advancy - 3rd exemple the routes of the supply chain

HORMONES

Europe and China routes are based on different chemical paths not starting from same starting material and not going through same key intermediate

Molecule 12 value chain | 2023



Sources: Tradedata, Ashford's Dictionary, Advancy

advancy

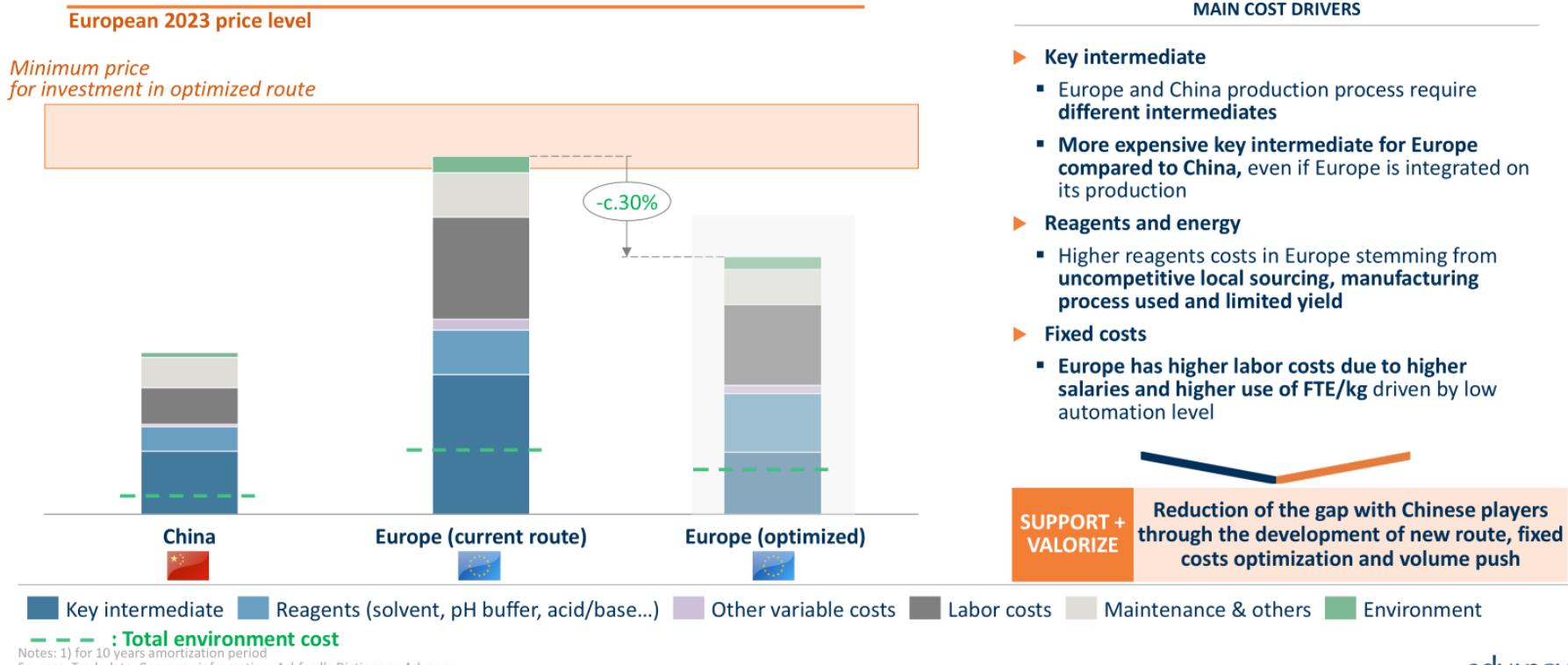


# Etude advancy – 3rd exemple – prices comparison Europe vs china

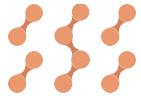
## HORMONES

Europe is less competitive than China due to high fixed costs resulting from less efficient production route which also induces higher raw material costs

### Cost structure by players | Costs in €/kg, 2023



advancy



# Etude advancy – overall opex comparison

GENERAL CONCLUSIONS ON THESE 12 APIs

**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
	2	100	200 (->85) <sup>1</sup>	85	-	► Europe is not cost-competitive vs. China but cost gap can possibly be bridged by investing in new route development
	3	100	55 (->15) <sup>1</sup>	15	-	► Europe long term economic viability is not secured, but investment in new process could enable to be on par with India competition
CARDIOVASCULAR	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) <sup>1</sup>	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) <sup>1</sup>	25	-	► Europe is not competitive and investment is required to develop a more competitive production route and partly bridge the gap
	10	100	100 (->50) <sup>1</sup>	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) <sup>1</sup>	30	-	► Europe is less competitive than China due to high fixed costs resulting from less efficient production route

XX: Europe on par with Asia

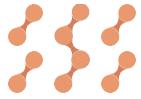
XX: Europe not cost competitive vs. Asia

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

Global comparison  
on 12 APIs.

On the examples  
studied

advancy



# Etude advancy

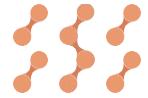
GENERAL CONCLUSIONS ON THESE 12 APIs

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													<ul style="list-style-type: none"> <li>Europe can be on-par with Asian peers when <b>being more integrated and using efficient production routes</b></li> </ul>	
EUROPE IS NOT COST COMPETITIVE													<ul style="list-style-type: none"> <li><b>UNDER-INVESTED PRODUCTION PROCESS</b></li> <li>Investment in more efficient processes and/or world-scale assets not realized due to <b>insufficient business case economics</b> resulting from higher competitive intensity, volume volatility and regulatory constraints</li> <li>In addition, <b>investing in Europe is more expensive</b> due to higher environment, regulatory, safety requirements vs. other regions <b>and provides less return revenues and lower profitability</b></li> </ul>	<ul style="list-style-type: none"> <li>SEVESO, DCE, IED (water, air)</li> <li>REACH, CLP, BPR, POP/PIC...</li> <li>CPR and other regulations related to construction (Biodiversity, Protected Natural Areas...)</li> </ul>
													<ul style="list-style-type: none"> <li><b>COST OF LABOR</b></li> <li>Higher <b>minimum wages in Europe</b> vs. Asia</li> <li>More direct FTE per kg of product to <b>met local work rules</b> and as a result from <b>smaller production units vs. world-scale units operated in Asia</b></li> </ul>	<ul style="list-style-type: none"> <li>EU Directive on Safety and Health at Work, EU social policies, Pregnant Workers Directive, employment code...</li> </ul>
													<ul style="list-style-type: none"> <li><b>LACK OF UPSTREAM INTEGRATION</b></li> <li>Low <b>integration</b> on intermediates and regulated starting materials <b>usually increase access cost</b> which led to the vanishing of related manufacturing capacities and related technology know-hows</li> </ul>	<ul style="list-style-type: none"> <li>EU-ETS, IED, SEVESO</li> <li>ADR, AND, RID</li> <li>Quality guidelines of the European pharmacopeia...</li> </ul>
													<ul style="list-style-type: none"> <li><b>UNCOMPETITIVE FEEDSTOCK AND REAGENTS</b></li> <li>Locally sourced materials are more expensive <b>due to higher energy and/or petrochemical feedstock costs in Europe</b> vs. other regions</li> </ul>	<ul style="list-style-type: none"> <li>EU-ETS, SEVESO, IED,</li> <li>REACH, CLP, BPR, POP/PIC, ADR, AND, RID, WFD...</li> </ul>
													<ul style="list-style-type: none"> <li><b>ENVIRONMENT, SAFETY, ADMINISTRATIVE BURDEN</b></li> <li>Higher <b>cost</b> in Europe vs. other geographies to <b>met more stringent (liquid and gaseous) effluents and solid wastes compliance standards</b> and <b>manage all the related administrative workload</b></li> </ul>	<ul style="list-style-type: none"> <li>EU-ETS, SEVESO, IED, REACH, CSRD, NIS2...</li> </ul>

Sources: Advancy

advancy



# Etude advancy – impact of EU regulation on cost

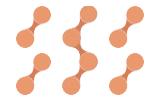
## GENERAL CONCLUSIONS

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

advancy

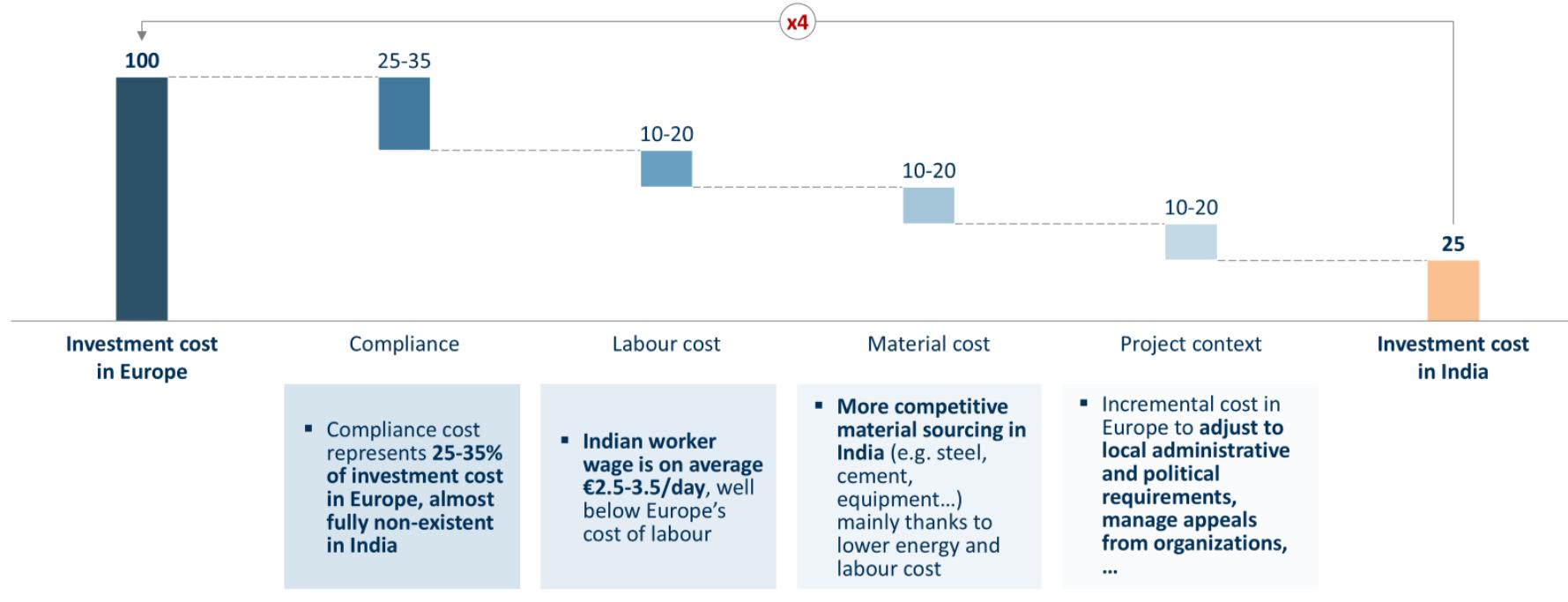


# Etude advancy – comparison of EU and India investment cost

## GENERAL CONCLUSIONS

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



Sources: Advancy analysis

advancy