EU Fine Chemical Commercial KPI

Executive summary

11th December, 2020

Agenda

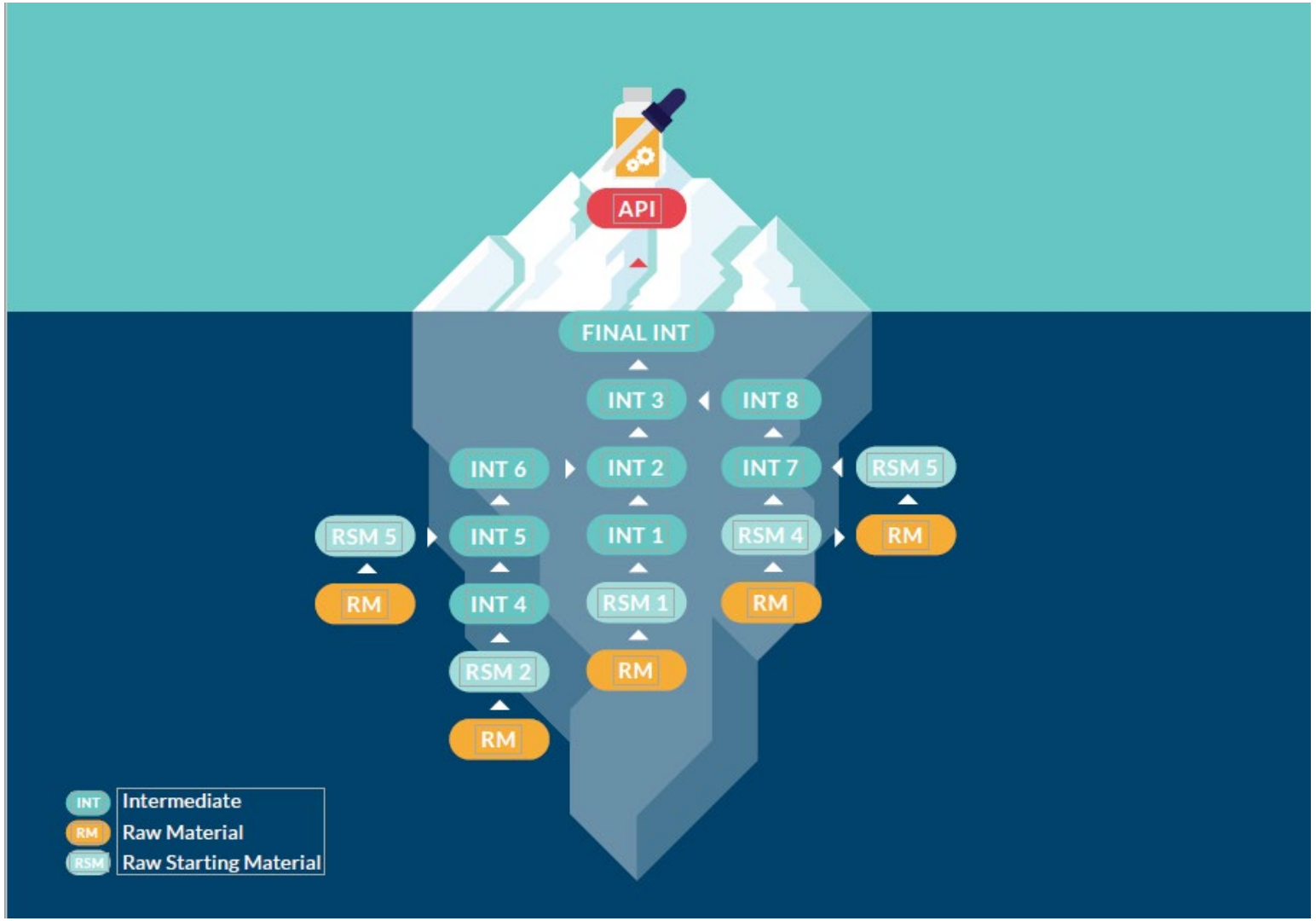
+ **Background, objectives and project approach**
+ Sample description
+ Executive summary
+ Key detailed results
+ Glossary

Active Pharmaceutical Ingredients are the essential part of the pharmaceutical supply chain

Active Pharmaceutical Ingredients are the components in a medicine that provide therapeutic effects

Source: EFCG Website https://efcg.cefic.org/

The production of a single Active Pharmaceutical Ingredient is the result of a complex process



Raw Starting Materials, Raw Materials and **Intermediates** represent **APIs precursors**

Source: EFCG Website https://efcg.cefic.org/

European manufacturers play a key role in the APIs market, representing 30% of Global APIs production

European manufacturers play a key role in the APIs market, representing **30% of Global APIs production**. However, a **large proportion of precursors** needed for producing APIs are currently **sourced from Asia**

API | Drug Product | Sponsor | Packaging & Distribution | Intermediates | Primary & Secondary Packaging | Starting Material | Excipients

Source: EFCG Website https://efcg.cefic.org/

EFCG sought IQVIA's support in assessing the potential risk of shortage of precursors and APIs for the production of drugs in EU

BACKGROUND

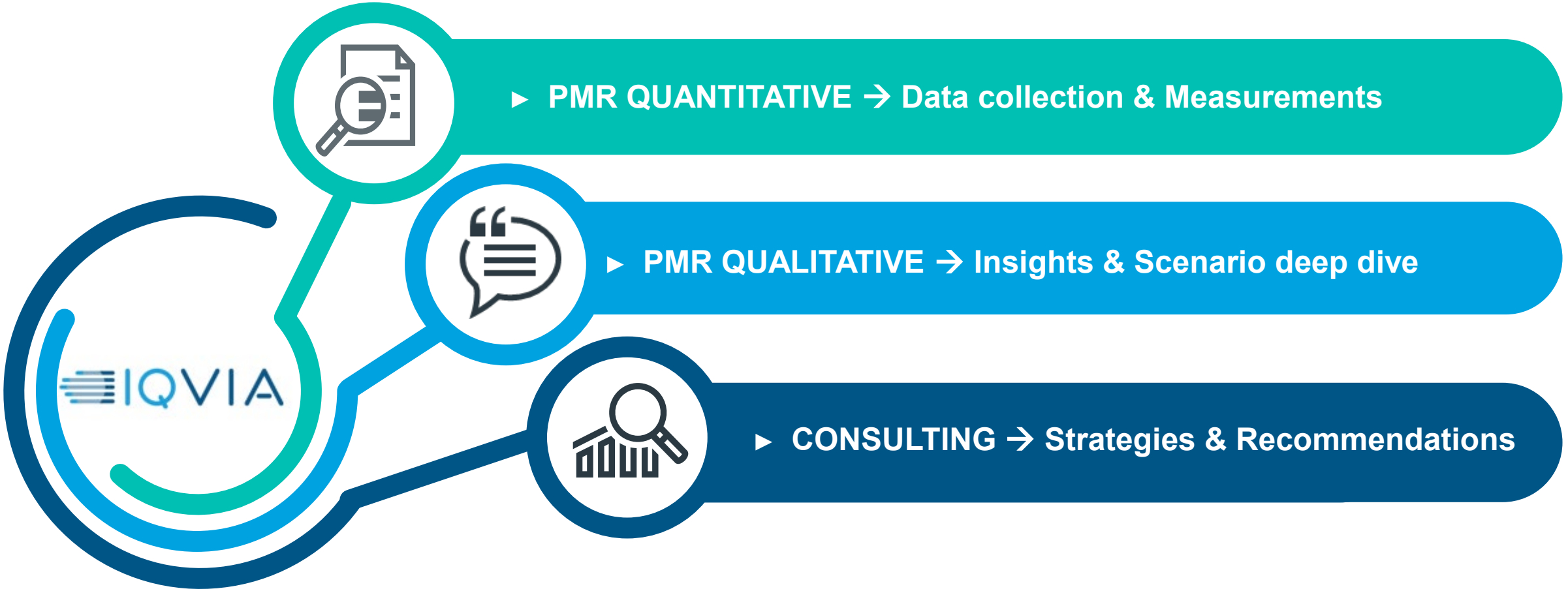
- EFCG (European Fine Chemical Groups) is working with the European Commission to assess the **risk of shortages of precursors and APIs for the production of drugs** (for human and veterinary use), with particular reference to expired patent drugs (generics).
- One of the relevant topics to this assessment is the **dependency of the API supply chain from non-European countries**, in particular from India and China

OBJECTIVES

- EFCG has appointed IQVIA to collect the missing data and information necessary to complete the **potential risk assessment of shortage at EU level**
- In particular, the main areas of interest are:
  - **Overall pharmaceutical market overview** in both volumes and values and relative key trends taking place during last years (e.g. generics penetration evolution, main growing areas, etc.)
  - General information about companies (total employees, overall sales, etc.)
  - High level assessment of EU internal production capacity and its evolution over the past years
  - **Degree of dependence of the EU from other world regions** for the supply of precursors and Active Pharmaceutical Ingredients (APIs) to produce drug products
  - Based on **supplier countries market evolution**, **scenario design will be performed to assess the risk of shortages**
  - High level **recommendations to mitigate the risk of shortage** of raw materials
  - High level criteria to identify essential molecules and exemplify the arguments deployed in this report

IQVIA has reached its objectives thanks to a unique and integrated approach, built to answer all business questions

Integrated approach to business questions



The project has been developed integrating two PMR streams and strategic Consulting analysis

Project approach

QUANTITATIVE SURVEY – Key objectives

- **Identify how much EU depends from overseas** for the production of drugs
- **Identify how much of this sourcing is done from China, India** and other ROW Countries
- Verify risk on raw materials, intermediates and APIs shortages

QUALITATIVE SURVEY – Key objectives

- **Investigate and understand the opportunities and critical issues** of the current market regarding **supply of raw materials from overseas** (particularly from China and India)
- Deep dive on issues and how companies are thinking to manage or minimise possible risks of shortage
- **Understand possible future market scenarios** and expectations of intervention regarding risk of shortage

CONSULTING – Key objectives

- Overall EU5 pharmaceutical market overview in both volumes and values, **key trends identification** (e.g. generics penetration evolution, main growing areas, etc.) over the past years
- Leveraging results from qualitative and quantitative surveys, we will design a future scenario in terms of production capacity (supply) of a selection of therapeutic areas
- High level **estimation of the "market at risk"** for the supply of drug substances will be provided and high-level strategic recommendation on how to mitigate it will be developed

Agenda

+ Background, objectives and project approach
+ **Sample description**
+ Executive summary
+ Key detailed results
+ Glossary

Out of a long list provided by EFCG, 52 stakeholders participated in the quantitative PMR and 18 in the qualitative PMR

Quantitative and qualitative sample

QUANTITATIVE SURVEY Data collection & Measurements

- **Methodology**: WEB questionnaire sent to 120 stakeholders
- **Responses: 52 stakeholders** from relevant companies in the fine chemicals, APIs manufacturing and pharmaceuticals (Innovative & Generics) industry

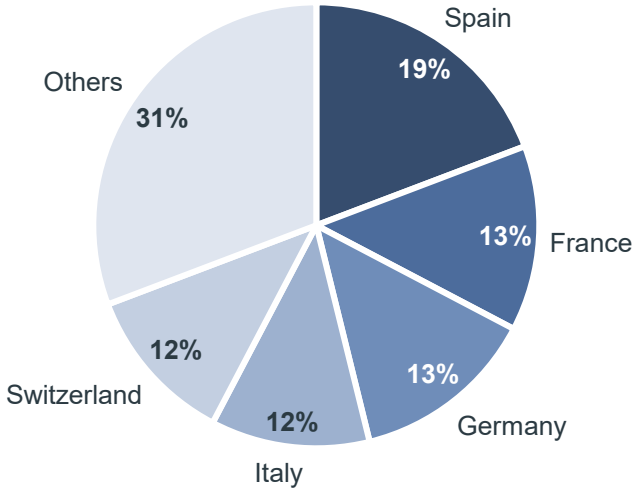
QUALITATIVE Insights & Scenario deep dive

- **Methodology**: in depth personal phone or web interviews (length of 1 hour approximately)
- **Sample: 18 stakeholders** from relevant companies in the fine chemicals, APIs manufacturing and pharmaceuticals (Innovative & Generics) industry

List of respondents provided by EFCG, also including manufacturers of finished drugs and companies that are not members of EFCG and APIC

All respondents operate in Europe but 44% also have operations overseas

WHERE ARE RESPONDENTS BASED?



WHERE DO THEY OPERATE THEIR API PLANTS?

100%

Companies operating their APIs plants at least in one EU country

(EU26 + UK, Norway and Switzerland)

44%

Companies operating their APIs plants both in EU and other countries

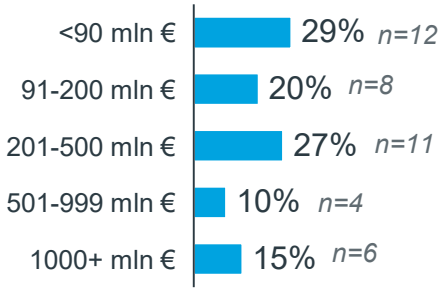
Bases: 52 respondents

The report is based on input provided by a representative sample of EU-based manufacturers

Sample: companies description

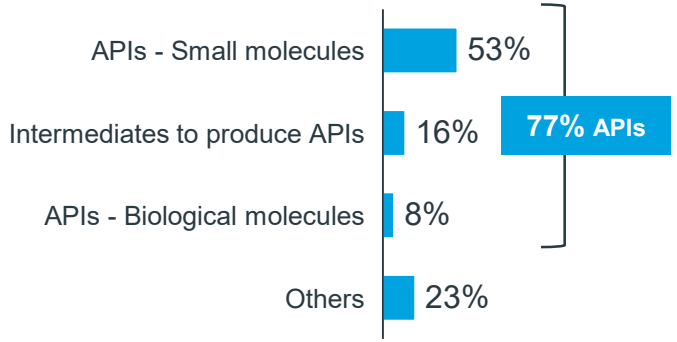
ANNUAL REVENUE

4. Can you please indicate the approximate 2019 Annual Revenue of your company, overall? (*)



Total rev. **51.000 mln €**

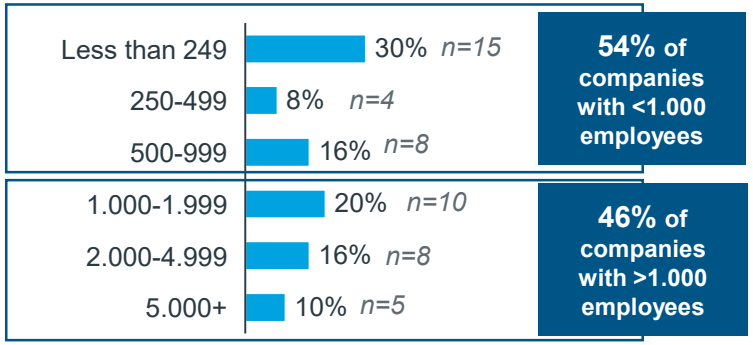
% of REVENUES coming from…



Average calculated among all respondents and not weighted for revenues

NR OF EMPLOYEES

3. Can you please indicate the approximate number of employee of your company? (**)



Sampled companies include manufacturers of intermediates, APIs and finished drugs.

Bases: 52 respondents (*) 11 respondents did not answered (**) 2 respondents did not answered

Agenda

+ Background, objectives and project approach
+ Sample description
+ **Executive summary**
+ Key detailed results
+ Glossary

European dependency from Asian Countries for the supply of APIs and precursors is growing

1 **Europe is highly dependent from Asia for Active Pharmaceutical Ingredients and precursors**

- Currently, European **direct and indirect dependency from Asia**, in terms of both APIs and precursors, is estimated to be around 74% of total market volume (in kg). Within Asia, China represents the most relevant country, being responsible for almost 70% of total Asian dependency (cf. slide 25)
- This trend of dependency from Asia has grown over time, more than doubling since the eighties, up to 74% currently (cf. slide 27)
- Most of the innovative APIs are still manufactured in Europe. Innovative API customers highly value European manufacturers' robustness of supply, including strict compliance with Environmental, Safety and Quality regulations.
- Constant price pressure on generic drug product manufacturers pushed them towards the lowest price API suppliers. Some of these are based outside of Europe but even those that are still based in Europe have to rely on cheap precursors sourced in Asia. This race to the bottom goes against value chain robustness and Environmental or Safety performance. (cf. slide 26)

Environmental regulation and price pressure are main root causes for the increasing dependence on overseas supplies

2 **Main root causes** for this phenomenon can be identified (cf. slide 28 and slide 29):

- **Stringent environmental and safety regulations within the EU:**

  Fully supported by EFCG members, the more stringent EHS standards in the EU are not respected to the same degree by a fully global industry – creating an uneven playing field for EU companies

- **Strong price pressure**: most public tenders in the payer system of EU member states currently award the market to the cheapest offer for the final drug product without full consideration to other criteria
- **Growth of China and India's domestic markets**: in case of shortages of certain APIs that have a high domestic demand, local authorities might decide to restrict the export of certain medicines, as has been witnessed during the Covid-19 pandemic.

While in Europe price pressure and regulations have become increasingly stringent, Asian Countries, mainly China and India, have leveraged advantageous cost structures, lower regulatory and environmental controls, economies of scale and preferential access to the domestic market to attract foreign investments.

This leads to an exacerbation of European vulnerability and low resilience of European Pharma Industry

3 **European dependency from Asia generated crucial consequences:**

- **Key processes and technologies for the production of APIs**, such as fermentation, fluorination, chlorination and nitration, **have totally or partially moved to Asia, losing the European API value chain its critical mass.** (cf. slide 30)
- More recent laudable government measures to **raise environmental and safety standards in Asia, have led to shutdown of many non-compliant plants in Asia, increasing shortages over the last decade.**
- In addition to this dependency from Asia, other factors **increasingly expose Europe‘s vulnerability.** These include **increasing supplier consolidation** to only 1 or 2 for the global demand, **lack of visibility and control** on Asian producers, leading to the inability to identify weaknesses that can lead to shortages further down the line. (cf. slide 31)

4 **Issues along the supply chain potentially led to its vulnerability:**

- The **majority of European companies reported to have experienced shortages** – mainly from China and India – over past years with high/very high **impact on their business continuity. This is expected to worsen** as **China and India** are foreseen to present the **highest shortage risk in the future** (cf. slide 33 and slide 35)
- Among the possible causes for shortage risk from Asia, **unexpected company closures**, **new environmental laws**, **quality issues** and **shortage of precursors** have been identified as the most crucial. Politically motivated border closures, already witnessed during COVID-19 pandemic, can potentially worsen the situation. (cf. slide 36 and slide 37)
- **Potential impact on Europe could be dramatic:** looking at the **top 10 molecules** by volume in EU5 market, dependency from Asia is estimated to be around 78% (cf. slide 38)

COVID exacerbated European vulnerability, and created the need to re-shape the supply chain

5 **In light of this situation, a re-shoring trend has been detected at Global level**

- **COVID-19 undermined the global value chain**, and represented a **trigger to re-think trade models, especially for the pharmaceutical supply chain**
- In response to the Global pandemic, **many countries started to put in place strict re-shoring measures**. (cf. slide 42) For instance:
  - › **USA**: In August 2020 the US administration issued an "Executive Order on Ensuring Essential Medicines, Medical Countermeasures, and Critical Inputs Are Made in the United States". This project led to the development of a long-term, national stockpile to secure key ingredients to manufacture the most essential medicines in the U.S.
  - › **China**: unveiled "dual circulation" and will rely mainly on "internal circulation" - the domestic cycle of production, distribution, and consumption. Moreover, some local regulations do not allow foreign companies to produce only intermediates but forces them to produce the API as well.
  - › **India**: On May 12, 2020 prime minister Modi presented a 'Self Reliant India Initiative' that would enable India to become more self-reliant, with a stimulus package of $260 billion to revive the Indian economy.

These protective measures initiated by the afore-mentioned countries have the potential to undermine the competitiveness of EU-based manufacturers, at a time Europe desperately needs to reinforce the critical mass of its industrial base. In order to maintain its sovereignty and independence of pharma supplies, Europe has to take the necessary measures that will maintain its global competitiveness.

COVID exacerbated European vulnerability, and created the need to re-shape the supply chain

6 **Following Global trends, Europe is trying to re-shape its supply chain** (cf. slide 43 and slide 44)

- The economic model governing the supply of generic medicines discourages investments in the European API value chain.
- Multiple and sometimes unclear regulations governing new investments on chemistry manufacturing capacity further hinders investments in Europe
- To overcome these barriers, **European intervention is needed and should take place with urgency**

Not all molecules can and should be re-shored. Europe has to concentrate on essential technologies and molecules to secure existing productions and relative value chain

What are the key actions that can be evaluated?

Critical pharmaceutical value chains have to be identified according to objective and transparent criteria set at European level, and common to all Member States. This list needs to be regularly updated and should form the basis of the selective re-shoring. Criteria for the choice can include:

- **Therapeutic interest**: molecules for which therapeutic interest has been demonstrated (e.g. WHO list of essential medicines, FDA's "Drug and Biological Essential Medicines List")
- **Existence of shortages**: molecules that are regularly in short supply, which can result from failures throughout the value chain
- **Vulnerability of the supply chain**: it can be measured by the dependency on countries outside Europe, on the concentration on a few producers or on the complexity of the supply chain
- **Technology used**: the analysis of the technologies implemented enables us to assess the risk of supply disruption in the short or medium term:
  - On the one hand, the lack of suitable skills or appropriate technologies in Europe jeopardises a long-term resilience of Europe's supply of essential molecules.
  - On the other hand, if the technologies are only deployed in countries with low environmental constraints, beyond the environmental aspect of relocation, there is a real risk for these units to be closed down, either for safety reasons or because of tightening local regulations (e.g. the Blue Sky program deployed in China in 2015-2017, which has led to a large number of plant closures and very significant disruptions of the supply chain).
  - Europe needs to make the necessary technological investments that would enable it to be ready for any future crisis or change in global market dynamics.

Main recommendations from the survey respondents: production, innovation and regulation

- To ensure the full long-term resilience of Europe's pharmaceutical supplies, we should ensure:
  - A level playing field not only on quality but on safety and environment regulations and a better consideration for the reliability / environmentally friendly processes of European producers
  - A strong support to existing manufacturers to reduce timelines while accelerating their process innovations and develop their capabilities
- For these reasons, we recommend:
  - To lead actions at EU level and **clearly define the criteria to identify critical/strategic precursors and APIs, common to EU countries**
  - To **support the investment** into new API / RSM capacity in Europe with highest environmental standards **to protect certain technologies from a shift toward Asia**
  - To implement rules **supporting European production,** e.g. :
    - › Reserving a percentage of products with a European supply chain on therapeutically important and potentially critical APIs
    - › Embed in the pricing/reimbursement policy components to reflect the use of sustainable production technologies and adherence to environmental and EHS standards - i.e. call for tenders should include criteria beyond pricing, e.g. environmental compliance

Agenda

+ Background, objectives and project approach
+ Sample description
+ Executive summary
+ **Key detailed results**
+ Glossary

A two-fold analysis has been performed to dimension European APIs market

To size the European APIs market a 2-fold analysis has been performed: APIs contained in finished pharmaceutical products and APIs not yet transformed in pharmaceutical products

Finished pharmaceutical products

The first part of the analysis focuses on **finished pharmaceutical products produced and partially consumed in Europe**. We **converted** volumes of finished pharmaceutical products in Tons of APIs.

- Tons of **APIs contained in finished pharmaceutical products consumed** in Europe have been quantified leveraging IQVIA data (A)
- Tons of **APIs contained in imported** (B) **and exported** (C) **finished pharmaceutical products** in / from Europe have been quantified
- **APIs contained in finished pharmaceutical products produced** in Europe have been consequently derived (A – B + C = D)

Active Pharmaceutical Ingredients

In addition to the finished pharmaceutical products market, to complete the European APIs market understanding, we sized the market of **Active Pharmaceutical Ingredients not yet transformed into finished pharmaceutical products**.

- Tons of **APIs imported** in Europe needed to produce finished pharmaceutical products (E)
- Tons of **APIs exported** from Europe needed to produce finished pharmaceutical products elsewhere (F)
- Tons of **APIs produced** in Europe (D – E + F = G)

Several items have been analyzed to map European APIs market

		Item	Description
Finished pharmaceutical products	A	Finished pharmaceuticals products **sold** in European market	Consumption in Europe of finished drugs (converted in Tons of APIs)
	B	**Import** in Europe of finished pharmaceuticals products	Import in Europe of finished drugs (converted in Tons of APIs)
	C	**Export** from Europe of finished pharmaceutical products	Export from Europe of finished drugs (converted in Tons of APIs)
	D	European **production** of finished pharmaceutical products	European production of finished drugs (converted in Tons of APIs)
Active Pharmaceutical Ingredients	E	European **import** of APIs	Import in Europe of APIs (not converted in finished drugs yet)
	F	European **export** of APIs	Export from Europe of APIs (not converted in finished drugs yet)
	G	European **production** of APIs	European production of APIs

European production of APIs for European market is estimated to be ~ 545,5 K Tons in 2019

		Item	Thousand Tons of API (2019)	Source
Finished pharmaceutical products	A	Finished pharmaceuticals products **sold** in European market	**350,0**	IQVIA Database[1]
	B	**Import** in Europe of finished pharmaceuticals products	**142,4**	ECIPE Report[2]
	C	**Export** from Europe of finished pharmaceutical products	**959,6**	ECIPE Report[2]
	D	European **production** of finished pharmaceutical products	**1.167,2**	Calculation: A – B + C
Active Pharmaceutical Ingredients	E	European **import** of APIs	**1.532,5**	ECIPE Report[2]
	F	European **export** of APIs	**910,8**	ECIPE Report[2]
	G	European **production** of APIs	**545,5**	Calculation: D – E + F

Source 1: IQVIA sales database
Source 2: https://ecipe.org/wp-content/uploads/2020/07/Pharmaceutical-data_July-2020.pdf

Europe is dependent from Asia for ~ 70% for APIs and for ~ 79% for precursors

		Thousand Tons of API (2019)		Dependency from Asia (%)		Dependency from Asia (Tons)
E	European **import** of APIs	1.532,5	×	~ 70% EU dependency from Asia for APIs[3]	=	1.072,8
F	European **export** of APIs	910,8				
			+	~ 79% EU dependency from Asia for precursors used to produce APIs[4]	=	1.145,9
G	European **production** of APIs	545,5	×			

Source 3: European dependency % from Asia for APIs has been derived from **ECIPE report** and multiplied by European import of APIs to obtain EU dependency from Asia for APIs (in Tons)

Source 4: European dependency % from Asia for precursors used to produce APIs has been derived from the **quantitative PMR results** and multiplied by the sum between European production of APIs and European export of APIs to obtain EU dependency from Asia for precursors (in Tons)

Overall European dependency from Asia (for APIs and precursors) is estimated to be ~ 74% of total volumes

EU dependency from Asia for APIs	1.072,8	2.218,7
EU dependency from Asia for precursors	1.145,9	

÷

E	European **import** of APIs	1.532,5	2.988,8
F	European **export** of APIs	910,8	
G	European **production** of APIs	545,5	

=

Overall EU dependency from Asia	**~74%** (of which ~ 70% from China)

While recently launched molecules are still produced in the EU, generic APIs are mainly manufactured in other world regions

Top therapeutic areas

A short list of top therapeutic areas have been identified bases on volumes, values as PMR results

Top areas by volumes in EU5

Top areas by values in EU5

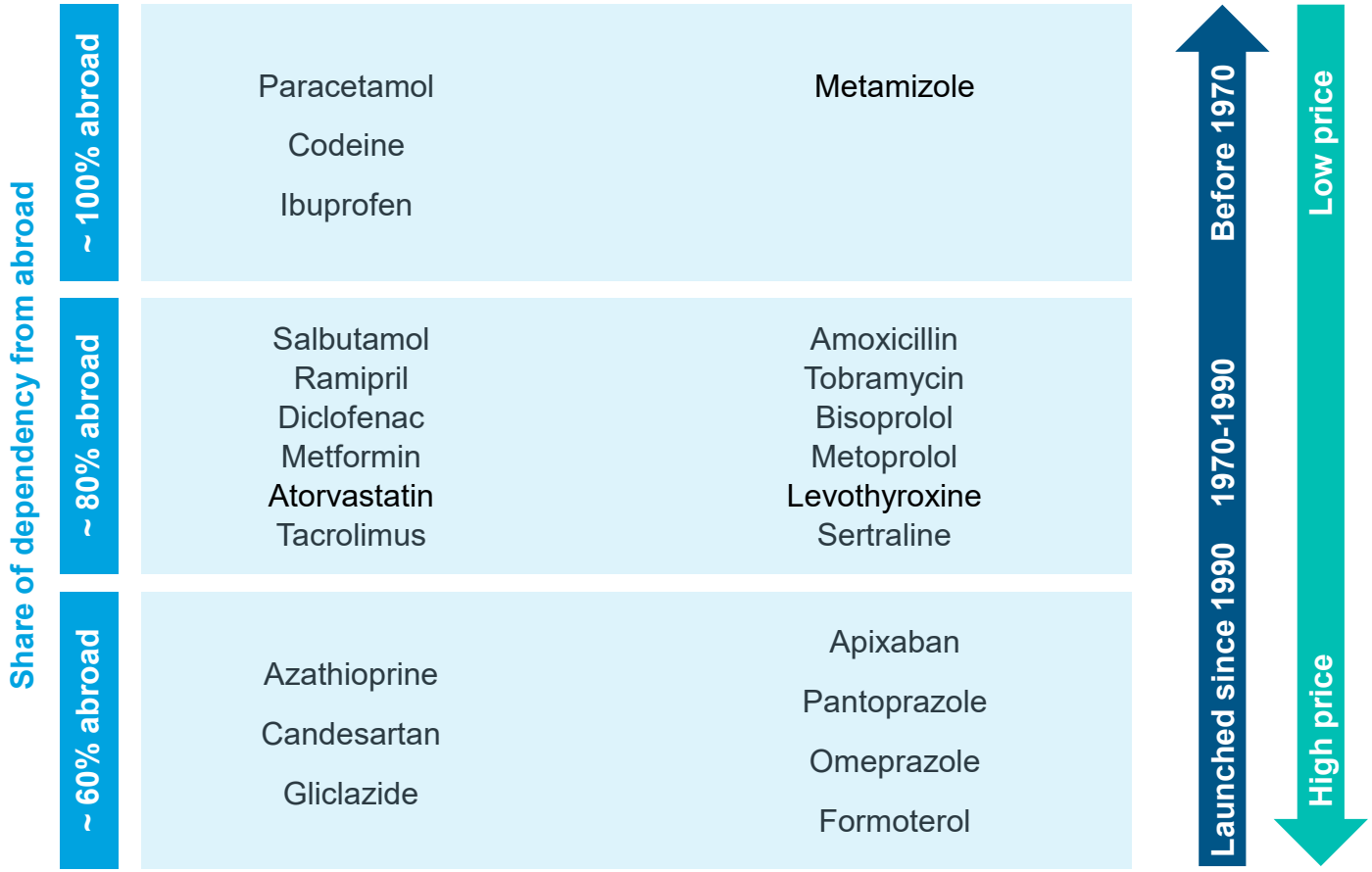
Top areas from survey EFCG

- Pain
- Asthma and COPD
- Cardio (renin-angiotensin antagonists)
- Gastro
- Anti-rheumatics
- Psycholeptics
- Diabetes
- Oncology
- Immunology
- Anti-coagulants
- Antibiotics
- Cardio (Beta-blockers)
- Antidepressants

Top therapeutic areas represent ~ 150 Bn SU, corresponding to ~ 40% of total EU5 market in volumes

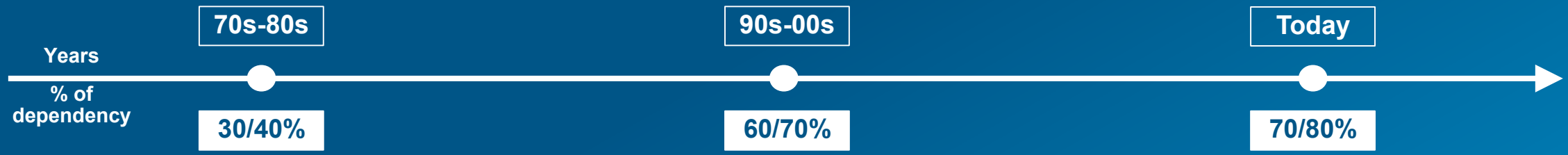
Top APIs

Top APIs among identified therapeutic areas have been assessed to map most relevant APIs for European Union based on foreign dependency



Source: IQVIA Databases and PMR qualitative and quantitative

Percentage of European dependency from foreign countries for APIs and precursors



> ***"The origin of APIs and intermediates was Europe, especially Italy, also Spain and Portugal, in the 60s, 70s, 80s the market was growing 10% per year, but now it has been overtaken by India, and mostly China."***
>
> *EU Industry Stakeholder*

China leverages several advantage factors to attract Global manufacturing

China's key advantage factors[1]

Cheaper Labor cost
The cost benefit depends on how labor-intensive the manufacturing process is. Savings **range from 20% to 50% of the labor cost** by manufacturing in China

Economies of scale
China's massive manufacturing sector is highly competitive and **offers huge economies of scale**, which translates to world-beating prices

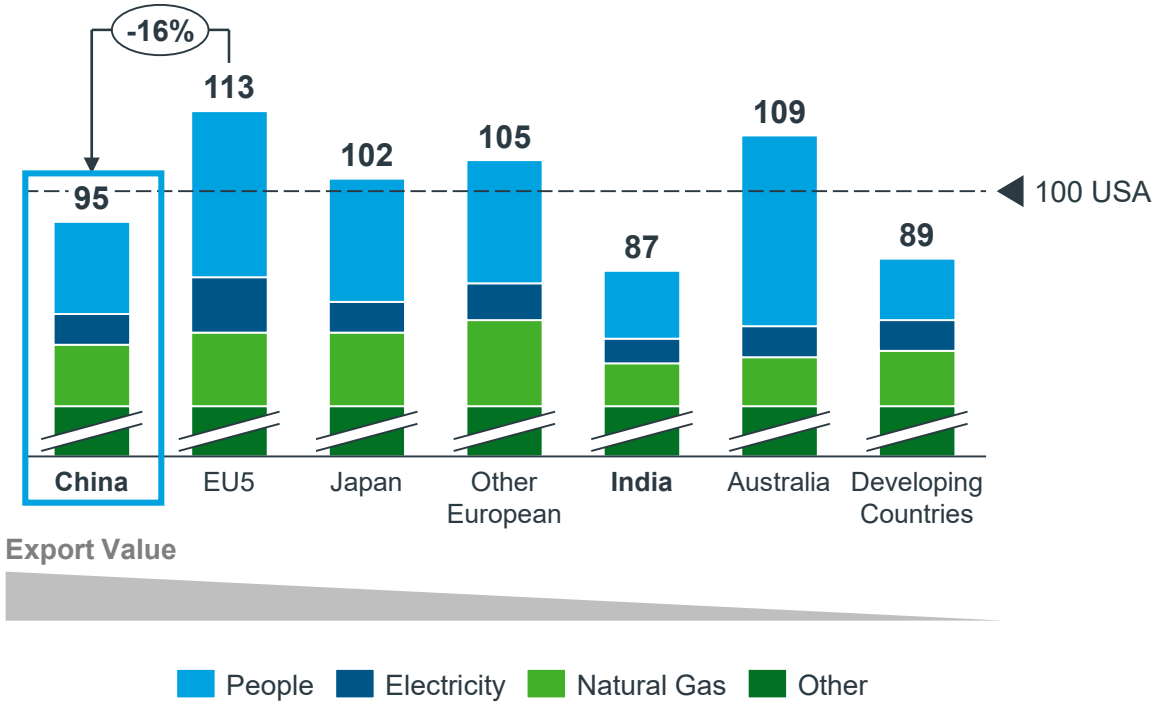
Established supply chains
Globalization have created deep-set supply chains across East Asia that provided **access to every kind of raw material** – this can deliver significant savings

Tax benefits
Goods made for export are **exempt from taxation** and the Chinese government refunds the VAT for products exported from the country

Currency manipulation
China undervalues their currency by an estimated 30%-40%, which makes every product that China **ships out 30-40% cheaper** than those of a foreign competitor

Low environmental control
Although China has its own environmental protection agency, the environmental protection laws are **ignored and not enforced**, generating savings for firms

Global Manufacturing Cost-Competitiveness Index, 2019[2]



- The index develops **competitiveness scores based on four direct costs**, with no difference assumed for "other". **The cost structure is calculated as a weighted average across all industries**. The US serves as a benchmark, with a score of 100.
- The Export Value line ranges countries from the largest exporter to the smallest exporter.

Source: [1] IQVIA Elaboration based on Industry Week report
[2] IQVIA Elaboration of BCG Global Manufacturing Cost-Competitiveness Index, 2019

Thanks to key advantage factors, India is among the most attractive Countries for manufacturing

India's key advantage factors[1]

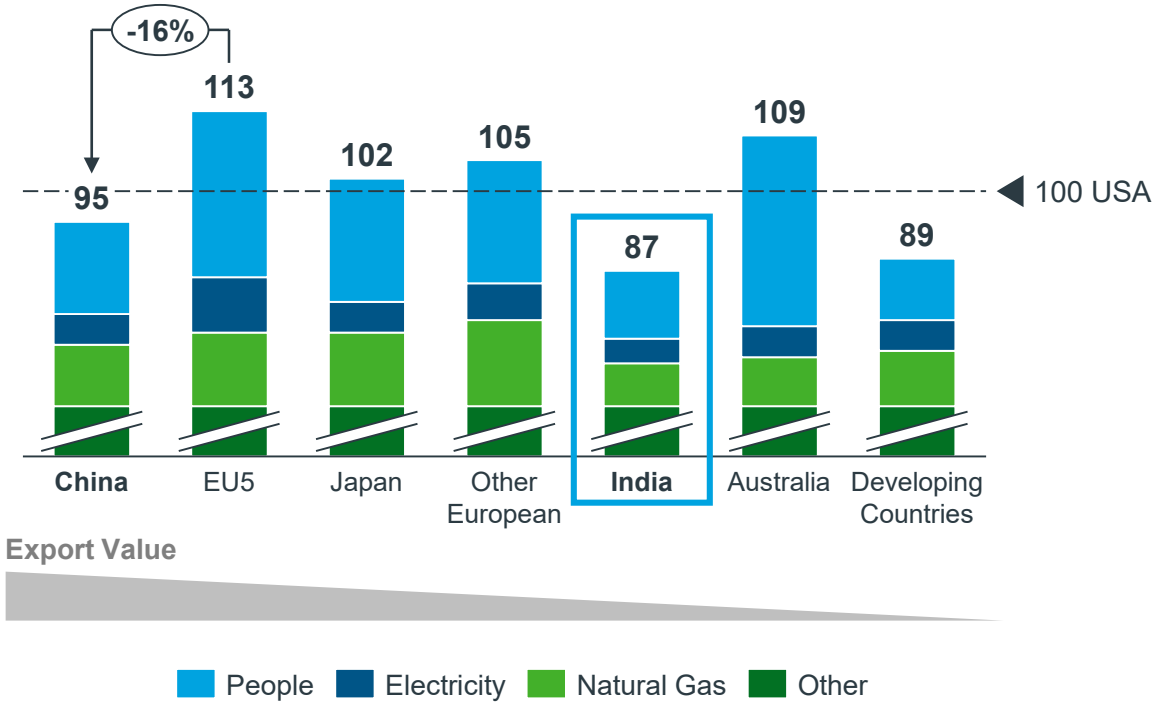
Cheaper Labor cost
India's manufacturing wages are among the lowest worldwide, averaging 1,5 US$ per hour

Currency
The rupee's falling value against the dollar makes India exports increasingly competitive

Infrastructure Investment plans
Indian Government plans to invest US$ 1trillion in infrastructures in the next years to lower logistics and supply chain costs

Low environmental control
Although India is facing serious issues related to environmental situation, the environmental protection laws are **ignored and not enforced**, generating savings for firms

Global Manufacturing Cost-Competitiveness Index, 2019[2]



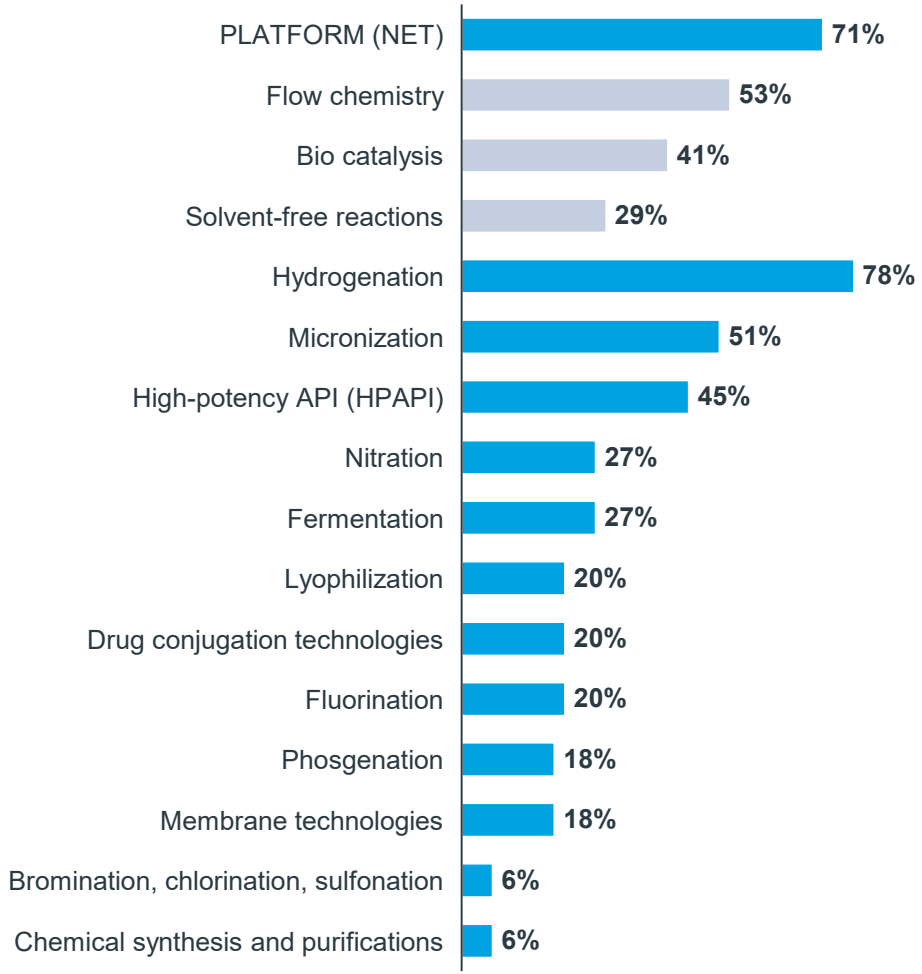
- The index develops **competitiveness scores based on four direct costs**, with no difference assumed for "other". **The cost structure is calculated as a weighted average across all industries**. The US serves as a benchmark, with a score of 100.
- The Export Value line ranges countries from the largest exporter to the smallest exporter.

Source: [1] IQVIA Elaboration based on East West article, 2020
https://news.ewmfg.com/blog/7-advantages-to-india-manufacturing

Among the consequences, key technologies have been totally/partially outsourced from Europe

CURRENTLY USED TECHNOLOGIES in EU

8. What are the main technologies that your company uses or can use for APIs or Intermediates production?



Totally lost in Europe

Fermentation in segregated plants

(must avoid cross-contamination) to produce penicillins

Because the **European industry has invested in multipurpose flexible plants, to increase production efficiency**

Partially lost in Europe

Fermentation

Because of

- **price of key ingredients and high energy costs**
- **environmental impact -** cooling cost and water consumption during the fermentation process.

Fluorination

"Finding manufacturers with GMP fluorination capabilities is a challenge."

Reagents' application to API/intermediates' synthesis has been limited, for **handling problems**, **safety**, costs, **environmental issues**.

Chlorination

Wastes and **environmental issues**

Still present, but critical

Nitration

*"Almost 65% of **APIs** requires at least one **nitration** step in the whole process."*

All nitration reactions are **potentially hazardous** because of the explosive nature of the products and the strong oxidizing tendency, characteristic of the nitrating agent.

If additional issues emerge, dependency could become vulnerability

Dependency

The EU is **increasingly dependent on non-EU countries** - mainly India and China - when it comes to the production of APIs and precursors

70/80% of API precursors are sourced from India and China

Starting from early 2000s, **large outsourcing and off-shoring initiatives took place** – with discontinuation of production in Europe for the benefit of production / contracting in Asia

Example

- Last paracetamol plant in Europe **closed down in 2008**; production has been outsourced to India and China[1]

Additional issues

In addition to such a strong dependence, several factors could have **a further significant impact on EU dependency**

- **Geographical concentration of suppliers** in certain critical parts of the supply chain
- **Lack of liability** of the contractual framework and uncertainty about regulations enforcement
- **Lack of visibility and control on Asian production / producers**, which makes lose track of the supply network
- **Externalization of core activities** which should be performed internally

Vulnerability

Such a context of strong outsourcing/off-shoring and potential additional issues could generate **vulnerability problems to firms**

Out Sourcing - Off Shoring + **Addit. issues** ⟩ In case of **supply chain disruption** (due to adverse political conditions, pandemics, etc.) **delays or shortages could be generated**

Source: [1] The Conversation.com, 2020; [2] The Pharmaletter.com

Pricing pressure, safety regulations and difficulties in approval path contributed to EU vulnerability

Heavy pricing pressure from Asian suppliers

Stringent environmental and safety regulations

EU REACH legislation (2006) concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), has encouraged the supply of Asian precursors and APIs and the relocation of production to Asia

Delayed or difficulties in approval path for off-patent drugs, and regulatory barriers, varying from country to country
(AIFA regulatory extremely binding in Italy)

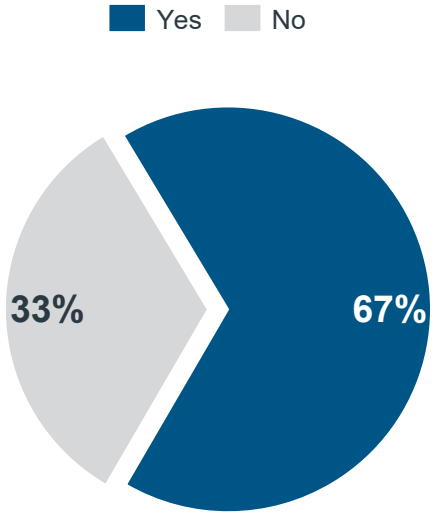
- *"in the US you could get ready to have an approval before the patent expiring. While in EU you could not prepare in advance, could not make one single lab experiment, no bioequivalence studies before the patent had expired. So, EU producers had to go out of EU to get bioequivalence data, to Iceland, Turkey, South Africa.* ***As a result, EU does not have a large generic company****"* (EU Industry Stakeholder)
- *"If I just change a solvent, I have to apply to AIFA to change the DMF (Drug Master File) and it costs a lot of money. But not only that, my client also has to change the DMF and pay money. Then it doesn't suit me! For the time spent and the risk that AIFA will not approve, and the risk that my client will not change the DMF"* (EU Industry Stakeholder)

EU VULNERABILITY AND RISK OF SHORTAGE LONG THE SUPPLY CHAIN

67% of survey respondents state to have experienced shortages in the past years

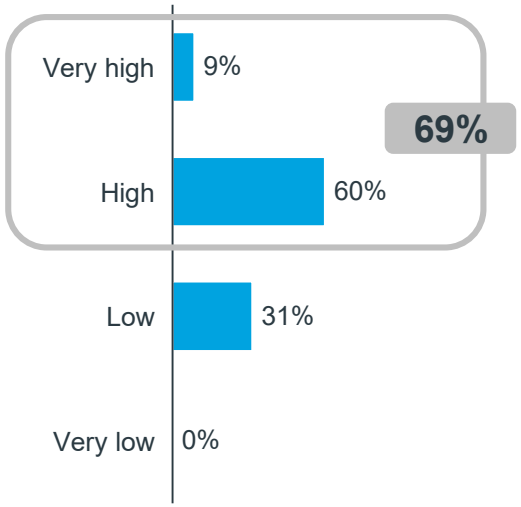
EXPERIENCED SHORTAGES?

10. Have you / your company experienced historical shortages of purchased raw materials and/or intermediate?



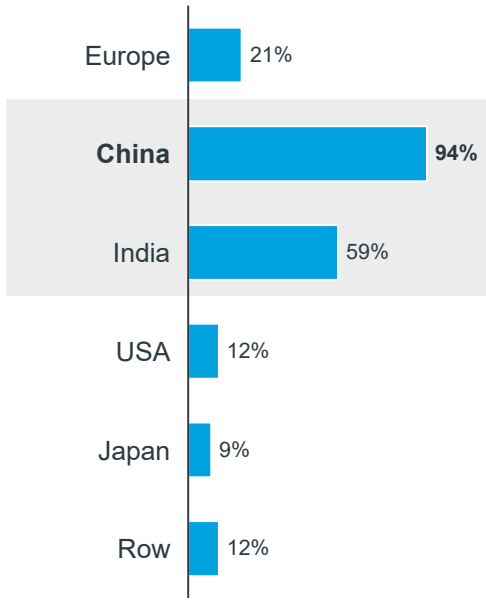
LEVEL OF IMPACT

12.What level of impact did this shortage have on your business continuity?



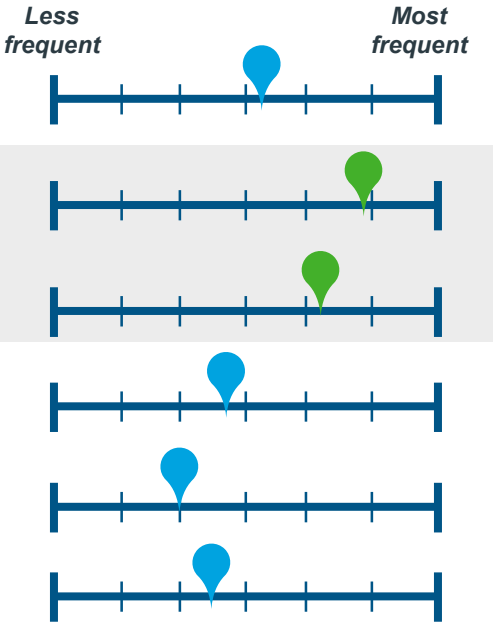
AREAS OF SHORTAGE

11. From which geographical areas of purchase have you experienced this raw material and/or intermediate shortage?



FREQUENCY

11.1 Can you please rank by shortage frequency the indicated geographical areas?



Bases: 52 respondents

While antibiotics are impacted by general shortages, Covid-19 has exacerbated shortage of anesthetics

General Shortages

Pain and Oppioids
Paracetamol, Fentanyl

Antibiotics
amoxicillin, amoxicillin clavulanic, azithromycin, rifampicin, ceftobiprole, cefuroxime, flucoxacillin, piperacillin tazobactam

Vaccines
anti-influenza, hepatitis A, hepatitis B, pneumococcus, HPV

Immunoglobulin

Shortages exacerbated by the COVID-19 emergency, concerning APIs and their supply chain

Anesthetics
midazolam, propofol, lidocaine prilocaine

Muscle Relaxants
(used for hospital procedures such as intubation):

mivacurium chloride, atracurium, cisatracurium

Tocilizumab, Hydroxychloroquine
(off label for Covid-19 patients, no longer available for patients with rheumatoid arthritis, lupus)

Antivirals
(off label for Covid-19 patients)

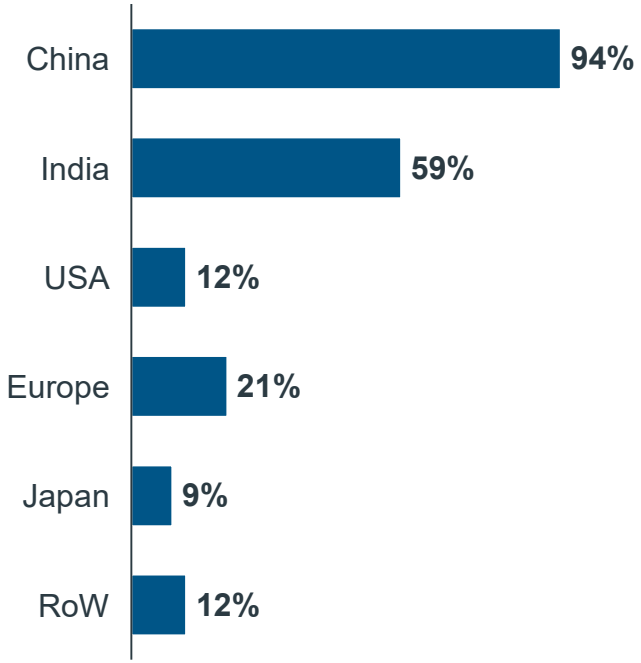
Remdesivir, Darunavir, Favipiravir

Source: Desk research and qualitative interviews to EFCG members and IQVIA experts

China and India have been identified as the areas with the highest shortage probability in the future

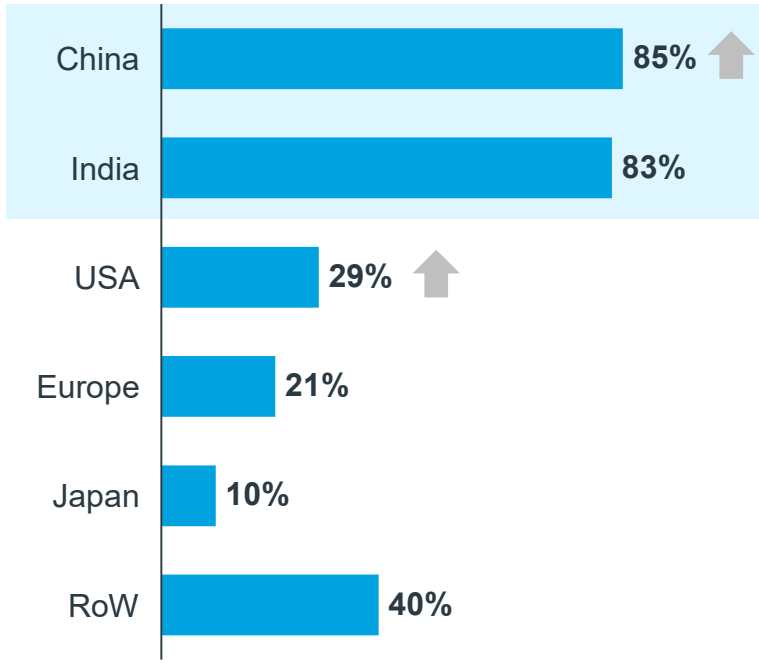
HISTORICAL AREAS OF SHORTAGE

11. From which geographical areas of purchase have you experienced this raw material and/or intermediate shortage?



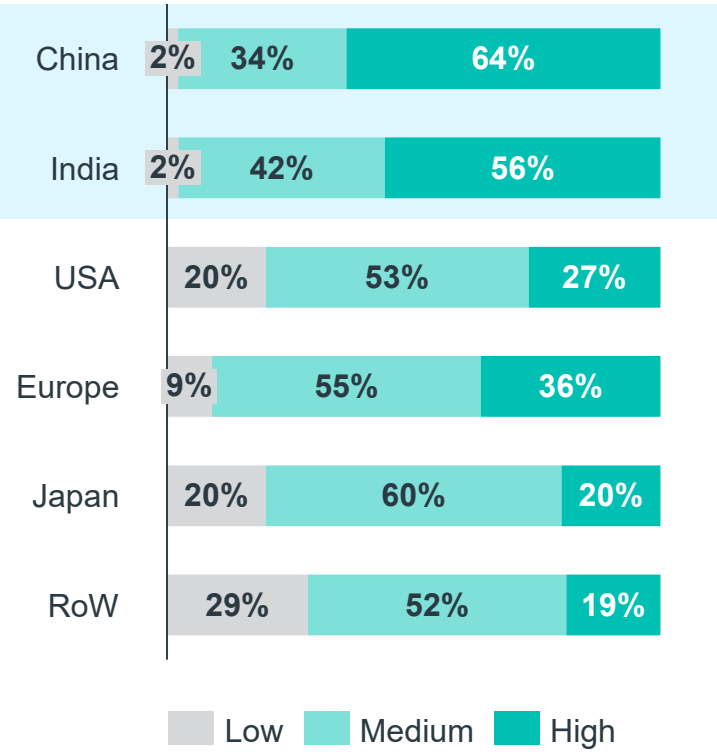
FUTURE AREAS OF SHORTAGE

14.With regards to the future, in your view, which of the following geographical areas raise concerns about future shortages?



PROBABILITY OF SHORTAGES IN THE FUTURE

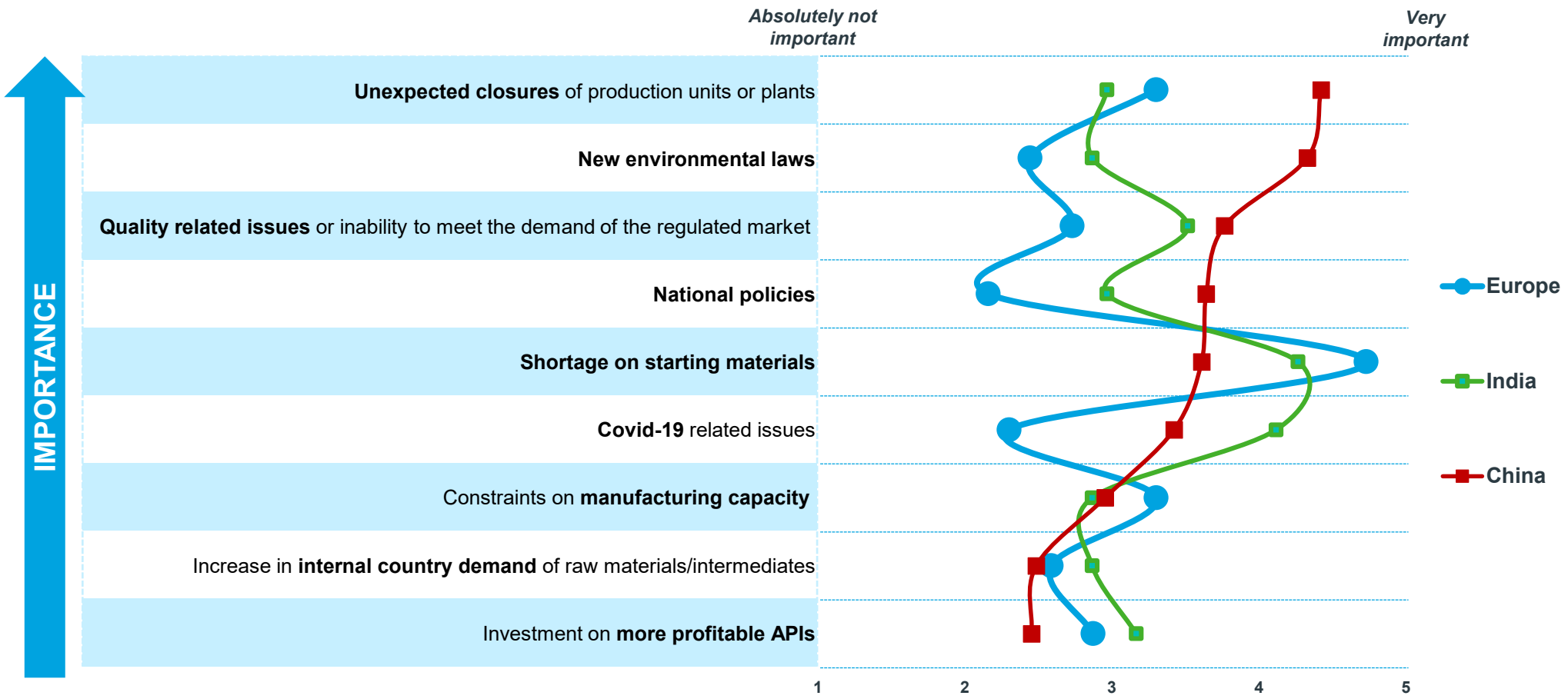
14a. How are these shortages likely to happen in the next 3-5 years?



Bases: 52 respondents

Unexpected closures, new environmental laws, quality issues and shortage of precursors are key risks for shortage from Asia

REASONS FOR RISK OF SHORTAGE



13. You are going to see a series of statements regarding the possible reasons for these historical shortages of raw materials and/or intermediates. For each geographical area at relevant risk of shortage please rate each statement. (1-5 scale)

Bases: 52 respondents

Concerns for future shortages are different for every geography and span from national policies to quality related issues

Main reasons for concern about future shortages

IMPORTANCE

CHINA

New environmental laws

- Increase in **safety and environmental impact standards**, with a parallel action of **compliance enforcement**, which determine closure of plants. **But the implementation of the rules remain uneven in some provinces.**
- The **organization in industrial parks** (conglomerates of thousands of companies) **determines the closure of all the plants** in the park, even if only 1 has problems.

National policies

- **"dual circulation" strategy to cut its dependence on overseas markets and technology** in its long-term development, a shift brought on by a deepening rift with the United States.
- China **will rely mainly on "internal circulation"** - the **domestic cycle of production, distribution, and consumption** - for its development, supported by innovation and upgrades in the economy.

INDIA

Quality related issues or inability to meet the demand of regulated market

- India struggles with a 'bad quality' reputation**; regulations in US and EU can be barriers for Indian producers.**
- Industrial parks are poorly maintained**,** although entrepreneurial skill is high.

Dependency from China

India is also heavily dependent on China.

Any production disruption in China causes heavy shortages in India, therefore in the EU.

USA

National policies

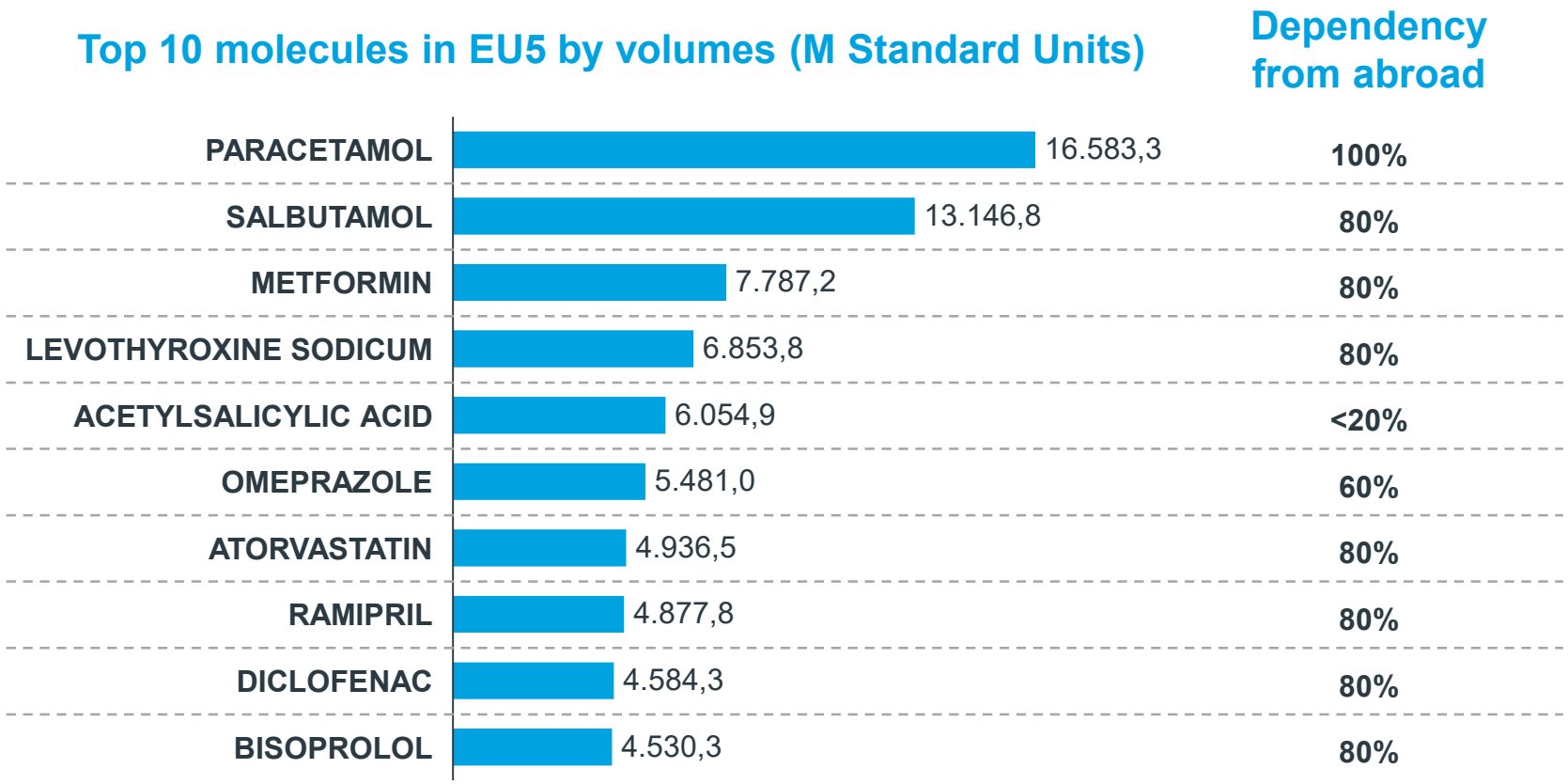
- **USA – China trade war**
- On August 2020 the Trump administration has issued an **"Executive Order on Ensuring Essential Medicines, Medical Countermeasures, and Critical Inputs Are Made in the United States".**
- Federal Government **funding for advanced manufacturing** (including "flow" chemistry and other continuous manufacturing techniques)
- **Strategic Active Pharmaceutical Ingredients Reserve (SAPIR)** with the goal of developing a long-term, national **stockpile to secure key ingredients to manufacture the most essential medicines in the U.S.**, thereby reducing the dependence of the U.S. on other nations to support its drug supply chain of **America's most essential medicines at risk of shortage**,

Bases: 52 respondents

14.1. For each country that, according to your opinion, in the future could raise concerns about future shortages, please add your comments on the reason why this could happen

In case of total shortage on top APIs in EU5 market, the impact would be dramatic

High level estimation



Total volume at risk is ~ 58 Bn SU, corresponding to 78% of total top 10 molecules volume

Top 10 molecules represent ~ 75 Bn SU, corresponding to 20% of total EU5 market in volumes

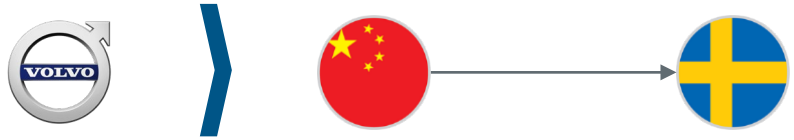
Source: IQVIA Databases and PMR qualitative and quantitative

Reshoring is the process by which companies shift away from globalisation and towards a more localized approach

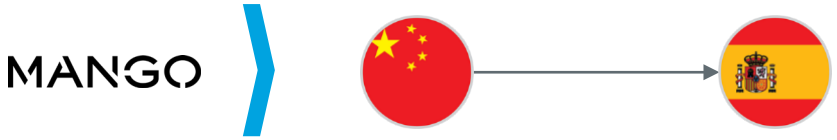
Reasons behind reshoring[1]

1. **Shorten Supply Chains** – in order not to depend too much on foreign countries and become more flexible, by reducing lead times and responding quickly to changing demand
2. **Diversification** - being able to draw on multiple suppliers, home or abroad, helps to reduce disruptions by spreading the risk
3. **Data Security and Privacy** – many concerns have been raised regarding hacking problems in China and lack of IP protection due to less developed legal systems
4. **Changing cost structure** – production costs in emerging countries have significantly increased (China recorded a 15-20% hourly wage increase per year)
5. **Digitalization in OECD Economies** – growing digitalization allows for lower-cost and high-quality production in developed economies, favoring reshoring
6. **Co-location of R&D, innovation and production** – some companies have brought manufacturing closer to their R&D as innovation may slow down if these two activities are separated

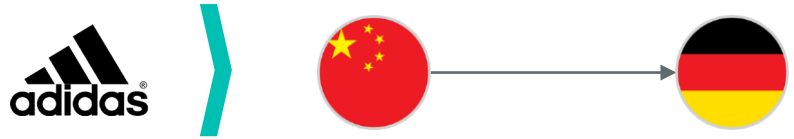
Examples in recent year[2]



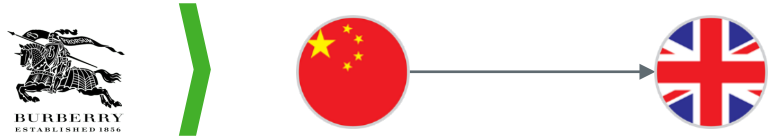
2018 – Production of Volvo XC60 for US market due to increase in tariffs after trade war China-USA



2016 – Delivery time, proximity to customers and new technologies in Europe like 3D printing and body scanner



2016 – Automation of production process, delivery time, Implementation of strategies based on product/process innovation



2015 – "Made in" effect, risk of brand counterfeiting, unattractiveness of the offshore market

Source: See next slide for details

Covid-19 undermined the "Global value chain" model and represented a key trigger to the reshoring process

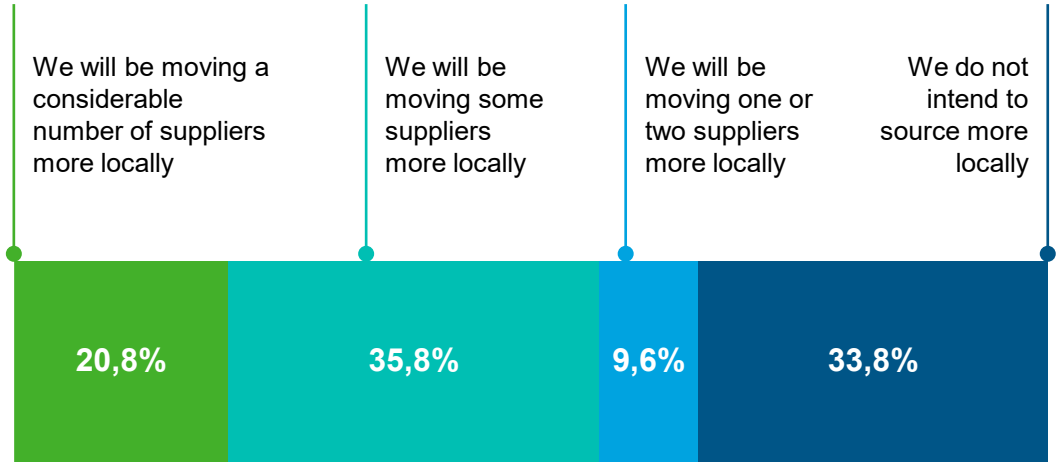
Covid-19 as a trigger[3]

The pandemic has caused 80% of global sectors to face supply chain disruptions, forcing over 75% to widen the scope of their existing re-shoring plans.

"Covid-19 has acted as a catalyst to accelerate this process of relocation; this favors a broader community of shareholders, consumers, employees and the state"

Candace Browning,
Bank of America Head of Global Research

How global supply chain professionals are planning to source suppliers post-pandemic[4]



Source: See next slide for details

Examples led by Covid-19[5]

The response to the reshoring decisions triggered by Covid-19 is led by two elements, namely the time (short term vs. long term) and the decision-maker (single firm vs. supply chain)

		Time Horizon	
		Short-term	Long-term
Decision Maker	Single Firm	Individual reactive reshoring	Individual preventive reshoring
	Supply Chain		Joint preventive reshoring

Individual reactive reshoring	**Still** – brought back the production of glass thermometers to France because of unexpected closure of its Chinese suppliers
Individual preventive reshoring	**Diasorin** – Italian company that is moving part of its production back to Italy to have a back-up production in case of disruption
Joint preventive reshoring	**Sanofi** – together with API producer Seqens, recognized need to bring back to France the production of API and the whole production of paracetamol

Several sources have been leveraged to analyse re-shoring

Sources

1. https://www.oecd-ilibrary.org/docserver/5jm56frbm38s-en.pdf?expires=1604567153&id=id&accname=guest&checksum=90CE36C26745F300AF5BB13BE26DB6C9
2. https://reshoring.eurofound.europa.eu/reshoring-cases
3. https://www.cnbc.com/2020/08/18/bofa-us-european-firms-face-1-trillion-to-relocate-china-supply-chains.html
4. https://res.cloudinary.com/yumyoshojin/image/upload/v1601393733/pdf/supply-chain-2020.pdf
5. https://link.springer.com/article/10.1007/s12063-020-00160-1#ref-CR9

Following COVID disruption, USA, China, Japan and India governments implemented reshoring measures

USA

On August 2020 the Trump administration has issued an **"Executive Order on Ensuring Essential Medicines, Medical Countermeasures, and Critical Inputs Are Made in the United States".**

Phlow, a U.S.-based, public benefit drug manufacturing corporation, has received **federal government funding** of $354 million **for advanced manufacturing (including "flow" chemistry and other continuous manufacturing techniques)** of **America's most essential medicines at risk of shortage**, including medicines for the COVID-19 pandemic response.

This project has been funded with federal funds from the Biomedical Advanced Research and Development Authority (BARDA), part of the office of Assistant Secretary for Preparedness and Response (ASPR) at the U.S. Department of Health and Human Services (DHHS). **The total contract value awarded to Phlow is up to $812**.

Phlow is also building the first **Strategic Active Pharmaceutical Ingredients Reserve (SAPIR)** in the U.S. with the goal of developing a long-term, national **stockpile to secure key ingredients to manufacture the most essential medicines in the U.S**., thereby reducing the dependence of the U.S. on other nations to support its drug supply chain.

China

China has unveiled **a "dual circulation" strategy to cut its dependence on overseas markets and technology** in its long-term development, a shift brought on by a deepening rift with the United States.

China **will rely mainly on "internal circulation"** - the **domestic cycle of production, distribution, and consumption** - for its development, supported by innovation and upgrades in the economy.

Three decades ago, former leader Deng Xiaoping adopted a "great international circulation" strategy, but **the 2008-09 global crisis exposed the vulnerability of the export-led model and prodded policymakers to rebalance growth towards domestic demand.**

India

On May 12, 2020 prime minister Modi presented a **'Self Reliant India Initiative '** that would address the needs of businesses as well as workers and would furthermore **enable India to become more self-reliant**, with **stimulus package of $260 billion** to revive the Indian economy.

The initiative plans: to Reduce its over-dependence on other countries for trade by focusing on inward manufacturing. Promote Indian products, brands and services by becoming "VOCAL FOR LOCAL"; and Continue to trade with other countries but aim to eliminate trade imbalances and, where possible, adopt a mercantilist approach to international trade.

Japan

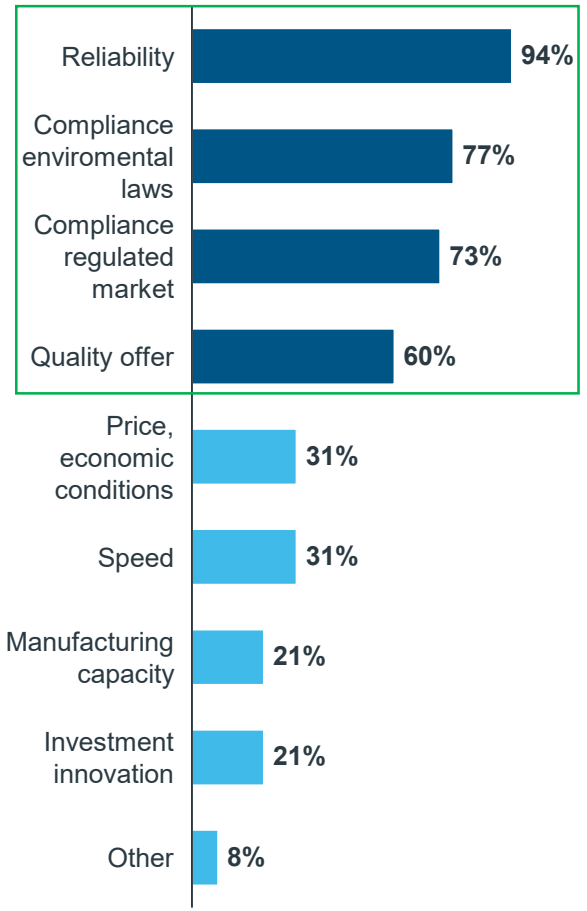
Japan has earmarked $2.2 billion of its record economic stimulus package to help its manufacturers shift production out of China as the coronavirus disrupts supply chains between the major trading partners.

The extra budget compiled to try to offset the devastating effects of the pandemic, includes 220 billion yen ($2 billion) for companies shifting production back to Japan and 23.5 billion yen for those seeking to move production to other countries.

Barriers like prices and manufacturing capacity block investments in EU, despite higher recognized quality, compliance and reliability

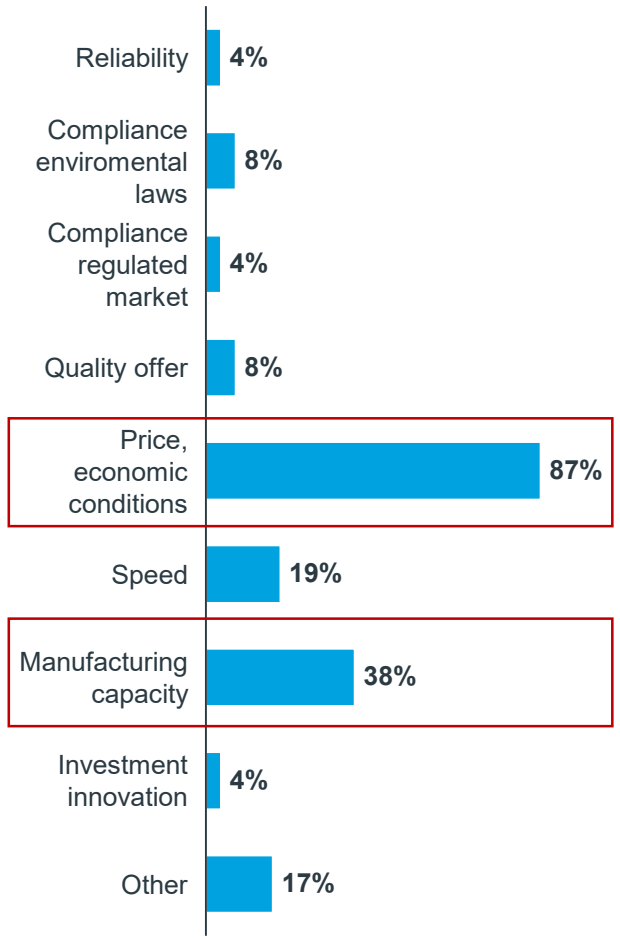
REASONS TO CHOOSE EU

19. What are the reasons you would choose a European provider for your raw materials and/or intermediates?



BARRIERS TO CHOOSE EU

20. What are the barriers to choose a European provider for your raw materials and/or intermediates?



71%

of companies are likely to invest in the API supply chain at risk of shortage if the economic barriers could be overcome.

REQUISITES TO INVEST

- Supportive European policies
- Economic incentives for innovative technologies and environmental sustainability
- Economic incentives for capacity increase
- Economic incentives for process improvement
- Regulatory: support to meet regulatory requirements

European intervention should take place in two specific areas of strategic need: Technologies and APIs

1 Technologies

Investing into new technologies: for many Industry stakeholders a priority need

- *"The only way **to keep up with Chinese price competitiveness** is to invest in new technologies, with **lower costs and higher yields**, and **less environmental impact".***
  (EU Industry Stakeholder)
- *And because: **"we don't know which fine chemicals or APIs will be significant in 30 years' time: technology know-how would allow us to react very quickly"***
  (EU Industry Stakeholder)

2 APIs

Which value chain should we invest into?

- **Considering the whole supply chain needed to manufacture and produce, to ideally get a real independence** (from fine chemicals, intermediates, excipients to APIs, up to formulation, finished)
- "Identify for critical medicines the points of fragility in the supply chain, all players in the entire value chain should be involved"
  (SICOS, France)

Agenda

+ Background, objectives and project approach
+ Sample description
+ Executive summary
+ Key detailed results
+ **Glossary**

Glossary

- **Precursors:** raw materials and intermediates used to manufacture active pharmaceutical ingredients
- **Active Pharmaceutical Ingredients (APIs):** key components in a medicine that provide therapeutic effects
- **Finished Drug:** finished pharmaceutical products, composed by active pharmaceutical ingredients and excipients, that are distributed and consumed by patients
- **Pharmaceutical Supply Chain:** means through which raw materials are transformed into finished drugs ready to be delivered to patients