CAMELOT
Management Consultants

Winds of Change in the Current Pharmaceutical Supply Chain Model

Key Challenges and Attempts Towards Resilience

White Paper

Navigating the Illusion of Reshoring

The concept of 'reshoring' is frequently discussed in connection with the current challenges of the pharmaceutical supply chain, resulting in drug shortages. It seems that the issue of “futureproofing” against supply shocks to an organization or a country against disruptions is omnipresent in the awareness of executives or healthcare authorities. But is reshoring pharmaceutical production steps closer to the end customer a tangible move or does it remain a theoretical debate?

BACKGROUND

- With its highly decentralized nature, the pharma industry is especially prone to disruptions that can lead to supply shortages.
- In recent years, developed countries such as the US and Germany faced numerous drug shortages, mainly generics.
- More frequent and more severe order backlogs due to global uncertainties push the industry into constant allocation mode.
- Currently, high pressure on governmental bodies to bring production closer to the customer and thus reduce latency and risk of stock-out can be observed.

TO ANSWER THE QUESTION ABOUT RESHORING, THREE STEPS NEED TO BE UNDERSTOOD:

1. Why do supply chain disruptions have a particular impact on the pharma industry?
2. What are the initiatives targeting the challenges of drug shortage in Europe and the US?
3. What changes are needed to incentivize reshoring?

Finally, we will point out recommendations that should be considered by key legislators in addition to initiatives by health authorities and government agencies to secure pharmaceutical deliveries.

Worldwide Pharmaceutical Supply Chain Model

Ongoing challenges, such as drug shortages or inflation, as well as disruptions like military conflicts and the pandemic situation, are well-noticed by all stakeholders of the value chain - starting from regulators (both regional ones as well as local) through industry and healthcare providers to end users, i.e., physicians and patients.

To analyze the impact of the challenges and disruptions listed above on the pharmaceutical value chain, we need to have a look at the current supply model. Unsurprisingly, the generic off-patent production of intermediaries and active pharmaceutical ingredients (APIs) has shifted to regions that offer the best price. This has led to the current consolidation of upstream manufacturing, particularly in China and India.

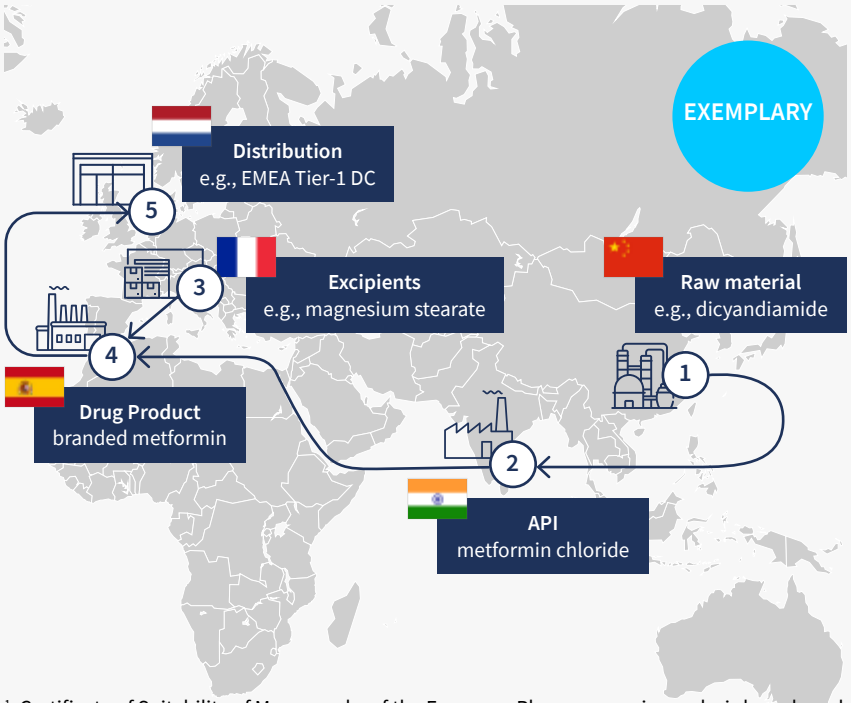
The current globalized pharmaceutical supply chain is interlinked between several geographies, with high consolidation of upstream manufacturing processes of raw materials in a few Asian provinces

STAKEHOLDERS IN PHARMA PRODUCTION (EU)

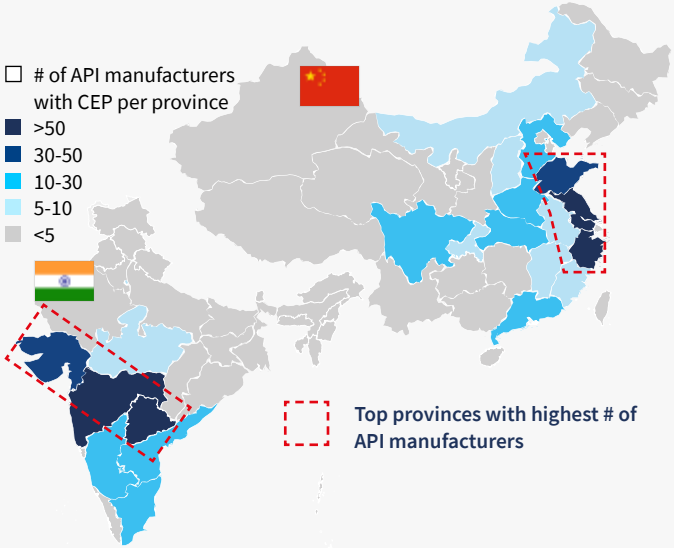
- China is a leading exporter of raw materials and excipients (>40% of antibiotic ingredients)
- Almost 60% of CEPs[1] for chemical APIs[2] come from India or China
- Drug products sites are dispersed across Europe, although according to market research reports, more than 50% of those activities are already outsourced to CMOs[3]
- 3PLs and 4PLs are used for drug distribution across the EMEA region, given the number of local market access restrictions

High pressure on governmental bodies to bring production closer to the customer and thus reduce latency and risk of stock-out!

Exemplary supply chain map for branded metformin



Deep dive on China and India API sites

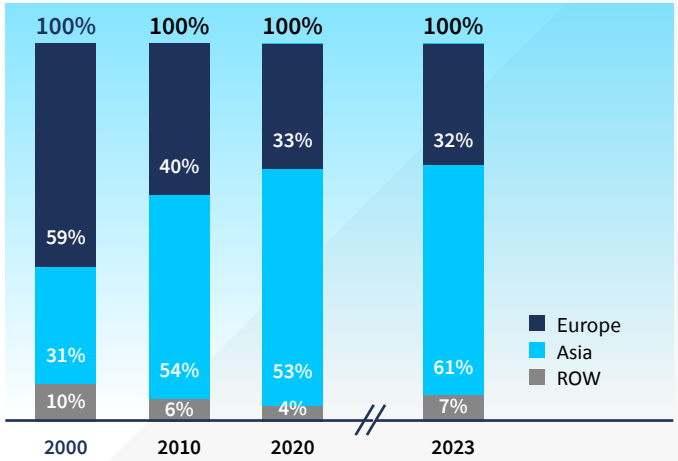


Top 3 provinces from China (Zhejiang, Jiangsu, Shantung) and India (Telangana, Maharashtra and Gurajat) **host >60% of all API manufacturers** in those countries hence increasing risk to local disruptions

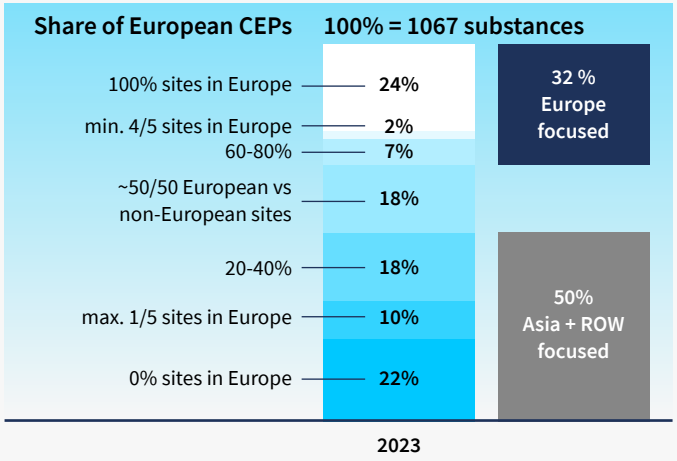
[1] Certificate of Suitability of Monographs of the European Pharmacopoeia, analysis based on chemical substances only, excl. expired and withdrawn;
[2] Active Pharmaceutical Ingredient; [3] Contract Manufacturing Organization
Source: ITC Trade Map 2023, EDQM.eu, asia.nikkei.com: The great medicines migration, April 2022

Europe lost its local APIs[1] sourcing independence over the last 20 years with the majority of CEPs[2] located in Asia and more than 20% of substances not being produced locally

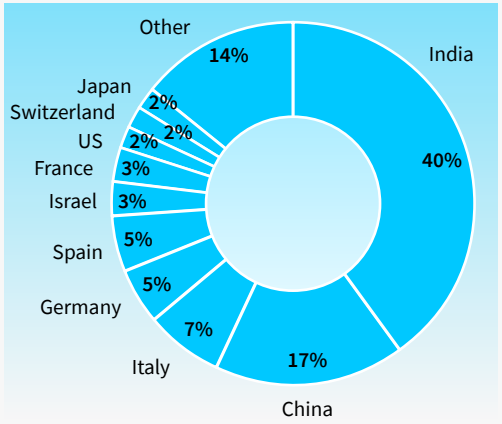
Share of issued certificates of suitability of the European Pharmacopoeia (CEP) by region, %



Localization of API production based on issued CEPs Share of APIs by Europe vs non-Europe production, %



Share of issued CEPs[1] by country, %



[1] Active Pharmaceutical Ingredient; [2] Certificate of Suitability of Monographs of the European Pharmacopoeia, analysis based on chemical substances only, excluding expired and withdrawn
Source: European Directorate for the Quality of Medicines & HealthCare, Certification of Suitability (CEP) Database 7.11.2023; Mundicare, "Where do our active pharmaceutical ingredients come from? – a World map of API production, 2020"

This notable shift in Europe's role in API production, which has been increasingly overtaken by China and India, is currently the most striking and most discussed consequence of pharmaceutical value chain globalization. On the North American market, the situation is not better: 77% of the key pharmaceutical ingredients come from overseas, again mainly from China. An analysis of the Certificate of Suitability of Monographs of the European Pharmacopoeia (CEP), which shows the number of sites allowed/certified to distribute APIs to Europe, reveals a significant reversal in Europe's share of CEPs over the last two decades, dropping from 60% in 2000 to 30% in 2023. This shift poses a challenge, as more than 20% of these substances are single-sourced with no European alternatives, and for another 30%, less than 40% of their CEPs are based in Europe. On top of this, both China and India have not diversified but rather collocated their upstream pharmaceutical operations in a few provinces. The three most important provinces when it comes to API manufacturing intensity in both China and India host more than 60% of all API manufacturers. This increases the risk of major disruptions in cases such as we have recently observed with COVID and the zero-tolerance in China which led to the closure of most of its operations in industrialized areas.

The Globalized World's Fragmenting Conflicts

There are currently numerous geopolitical conflicts around the world. Although they are all localized, they have a significant negative impact on global trade. From tariffs, sanctions, bottlenecks, and supply shortages to issues with the operation of physical infrastructure, they create an unfriendly environment for supply chains. If we look at just a few of the current conflicts, we can clearly see how disruptive they already are and how quickly they can develop into major shocks in the global pharmaceutical supply chain. The ongoing conflict between Russia and Ukraine is forcing a rethink of existing and planned logistic options e.g., the rail connection between China and Europe through Russia, Ukraine, and Belarus no longer seems to be the preferred option. This shows how conflicts can impact connections between Asia and Europe. A further escalation of tensions between China and Taiwan may further polarize Eastern and Western geopolitics, which can easily escalate into trade wars. Furthermore, API availability is a problem in any conflict. Research institutions flag potential supply issues of single-sourced substances e.g. such analyses were carried out shortly after the escalation between Israel and Palestine. A recent attack on vessels close to the Suez route by the Yemen-based Houthis has also alarmed the global industry.

Further issues such as environmental concerns are also affecting traditional distribution routes e.g., such as the blockage of the Panama Canal by ships due to historic low water in the summer of 2023. The number of ships per day has been reduced to 24 in February 2024, well below the average of 34-40 per day in 2022, with astronomic results of auctions for free slots to move through the canal reaching up to $4 million. A year ago, the average auction price was around $173,000, according to Waypoint Port Services.

However, supply is not the only cause of drug shortages these days; fluctuations in demand also require attention. A surge in bacterial infections following the lifting of pandemic restrictions in countries has led to shortages of antibiotic drugs such as penicillin and amoxicillin. A new anti-obesity indication for GLP-1 drugs caused shortages of these medicines for diabetes patients. These are just two recent examples of how unusual spikes in demand can affect global supply chains already impacted by other known disruptions.

DEEP DIVE

Russia – Ukraine

Although Russia and Ukraine are not pharmaceutical powerhouses, this war has significant implications on global trade, e.g., restrictions on Russian and Ukrainian airspace or risky use of the Black See routes. The conflict is expected to exacerbate the shortage of containers and increase their rates. With congested ports and terminals, and some becoming off-limits due to the conflict, there is a risk that freight will become stranded, contributing to higher freight prices. Russia and Ukraine collectively account for 14.5% of the world's seafarers.

Israel – Palestine

Israel is a significant producer of over 60 essential APIs, but most of these are sourced from multiple countries. Of particular importance are two substances that are only produced in Israel, such as Pegunigalsidase alfa. While no immediate disruptions have yet been reported, the situation underscores the vulnerability of global pharmaceutical supply chains, particularly for substances sourced from a single country. In addition, this conflict triggered actions by Yemen-based Houthis, who attacked cargo vessels in the Red Sea. In the first week of 2024, Maersk announced that it would divert all vessels around Africa for the foreseeable future instead of using the Red Sea to prioritize safety.

China – Taiwan

The tensions over Taiwan are contributing to the further polarization of "West vs. East" in the world. In the unfortunate scenario where this conflict escalates, trading with China might become extremely difficult. Any disruptions to trade with China can have fatal consequences for the global pharmaceutical industry.

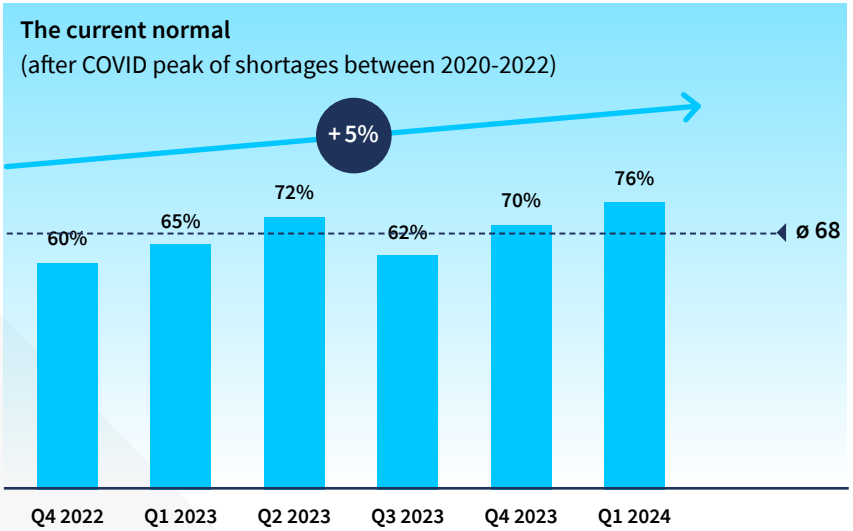
Patients Are Impacted

Recent shocks in the supply chain reinforce the message that local markets need to be protected. In 2023, the keyword “drug shortage” was entered 2-3 times more frequently on Google than in previous years. These shortages are no longer an isolated incident, but an ongoing global problem.

The UK list of medicines that cannot be exported or stockpiled from the UK averaged 68 medicines between Q4 2022 and Q1 2024. Since then, the number has grown by 5% p.a.

Since recovery from the Covid shock after Q2 2022, shortages have plateaued in the UK

Number of drugs listed or delisted for export and hoarding by the UK government



KEY TAKEAWAYS

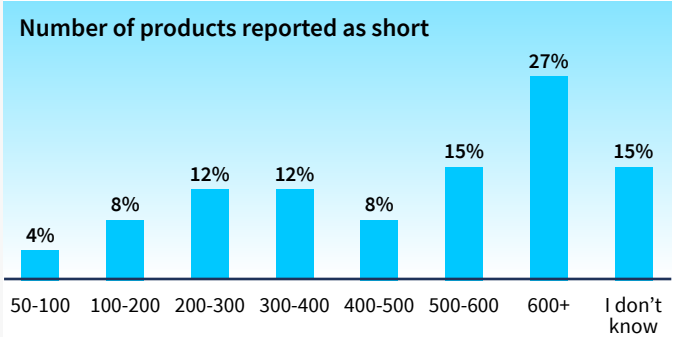
- At the peak of the Covid shock from March 2020 to Mid 2022, the drug shortages averaged ~68 drugs on the list.
- The number has increased by 5% per quarter since the end of 2022.
- More than 80% of drugs on the list are small molecules.

The same issue affects other European countries, but also the US market. IQVIA's latest report on drug shortages in the US (Nov 15, 2023) reveals that “for the currently active shortages affecting 132 molecules, 75% have been active for more than a year and 58% have been ongoing for more than two years”.

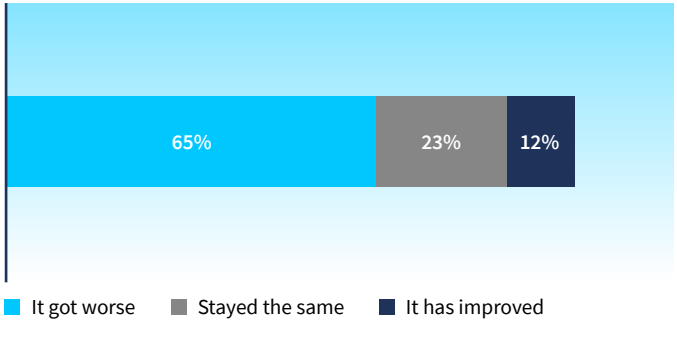
Drug shortages are omnipresent affecting less expensive drugs, without quick fixes on the horizon

EUROPE

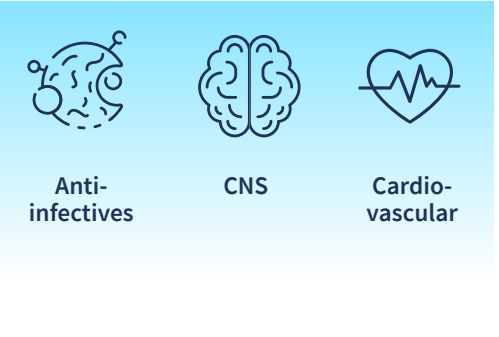
Percentage of European countries who reported medicine shortages as of 2023, by shortage size



If you have experienced shortages, **how would you compare to the situation in the previous 12 months?**

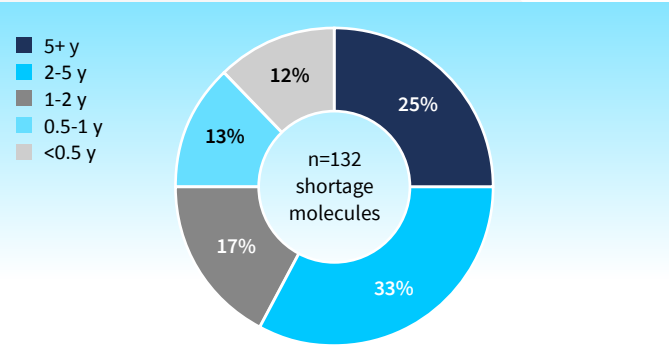


Top 3 medicines in most frequent short supply

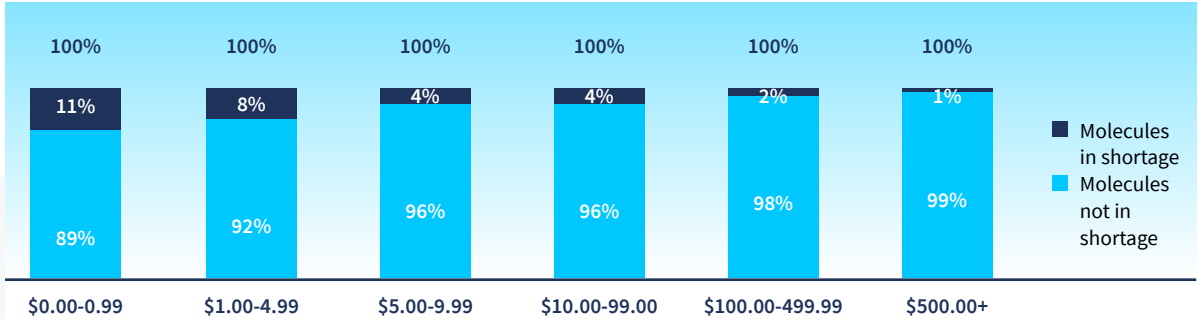


USA

Current shortages by time first posting, Jun 2023



Average invoice price per extended unit of molecules, Jan-Jun 2023, n=2026



Sources: PGEU Medicine Shortages Report, ASHP Drug Shortages Statistics, IQVIA Drug Shortages in the U.S. 2023

Another interesting observation is that medicines with low prices (below $1 per unit) are more likely to be under-supplied (11%) than expensive ones (above $500 per unit), of which just 1.3% are at risk of undersupply. This is correlated with the fact that most off-patent, low-cost medicines encounter high competition and therefore have to look for cost savings to stay competitive. This has led to offshoring intermediaries and APIs to low-cost countries in Asia. At the same time, the share of prescriptions for generics in the total number of prescriptions in the US increased from 19% in 1984 to 91% in 2022. Ongoing patent expires for blockbusters deepen the dependency on the Asian pharmaceutical manufacturing industry and as recent years have shown are becoming a real problem for patients across the globe.

Efforts to Mitigate Drug Shortages

Countries implement mechanisms to protect patients against drug shortages e.g., Public Service Obligations by introducing minimum stock levels, forcing 24-hour delivery times, or simply adding new products to the list of medicines that cannot be exported or stockpiled. However, this does not change the big picture and the current supply chain model. So, what is being done to protect the pharmaceutical industry from such shocks, and who is driving these discussions?

We have identified the main stakeholders in these trends:

- Organizations like the European Union, which publishes a set of recommendations and amendments to existing directives to secure local markets, are the most vocal. However, these actions are focused on prevention based on strict monitoring to get early signs of potential disruptions.

- Countries like the US are trying to implement local regulations that could further improve accessibility to critical drugs. On November 15, 2023, Senators Tina Smith and Tom Cotton reintroduced bipartisan legislation to reduce dependence on foreign pharmaceutical manufacturing and boost production in the US.[1] The American Made Pharmaceuticals Act would reduce dependence on foreign countries for pharmaceuticals by boosting production in the US. The legislation would create federal incentives for the onshore manufacturing of essential medicines. It should establish a demonstration program at CMS to test the provision of preferential treatment of US-manufactured generics, biosimilars, and critical medicines in at least eight states for at least seven years. In addition, eligible pharmaceutical companies should be required to provide transparency about their manufacturing locations, maintain adequate inventories and emergency reserves, and create a plan of action which links in the supply chain break down. European and US governments are showing also great interest in reshoring, nearshoring, or simply multiple sourcing of intermediate and final pharmaceutical products. Several new legislations are on the verge of changing the industry. There are also cases of localization, expansion, or new investments, e.g., the expansion of penicillin production in Kundl, Austria by Sandoz with a government subsidy of 50 million euro.

- The pharmaceutical industry tries to push authorities and highlight the problems arising from the fact that reshoring initiatives are very capital-intensive, while the prices of medicines have been constantly squeezed.

[1] https://www.smith.senate.gov/u-s-senators-tina-smith-tom-cotton-reintroduce-bipartisan-legislation-to-boost-u-s-pharmaceutical-manufacturing/

Pharmaceutical supply chain challenges evoke actions on several levels accordingly to its sphere of influence

LEVEL	REGIONAL (e.g., EU Commission, EU parliament)	COUNTRY (e.g., MoH, US FDA)	INDUSTRY OEMs (pharmaceutical, chemical companies)
ARE OF FOCUS/ INFLUENCE	**Legislation** incentivizing local footprint and increasing transparency for drug shortages/issues	**Country-level protection** mechanisms e.g., a list of drugs restricted for export or subsidies to localize pharma production	**Critical capacities expansion** investing into reshoring, nearshore programs and negotiate business incentives
EXEMPLARY ACTIONS	▸ A "Voluntary Solidarity Mechanism for medicines" (OCT 2023) ▸ The Union Civil Protection Mechanism, via ERCC[1] ▸ Union list of critical medicines (2023) ▸ The vulnerabilities in the SC of a first tranche of critical medicines on the future list (APR 2024) ▸ A new European Shortages Monitoring Platform (2025)	▸ Public Service Obligations e.g., a minimum stock of 90% of all essential Rx products with delivery time of 24 hours in Italy ▸ List of medicines that you cannot export or hoard e.g., in the UK the list comprises of ~76 critical drugs as of FEB 2024 ▸ German law to strengthen the security of supply (ALBVVG), e.g., 6 months min. stock for pharmacos ▸ Subsidies to private sector e.g., Austria investing 50 Mn EUR in Sandoz's Kundl plant expansion for antibiotics ▸ H.R.3008 bill requires manufacturers to notify the FDA if there is an increased demand that may result in a shortage ▸ Use the Defense Production Act to make more essential medicines in America	▸ Novartis unveils yet another antibiotics expansion, this time plugging $50 Mn into Sandoz's penicillin production (NOV 2022) ▸ Boehringer Ingelheim kicked off construction on a new EUR 285 Mn plant in Germany that will produce APIs and drugs for clinical trials (MAY 2023) ▸ Sanofi named its new independent API company EuroAPI in 2021 with European based footprint

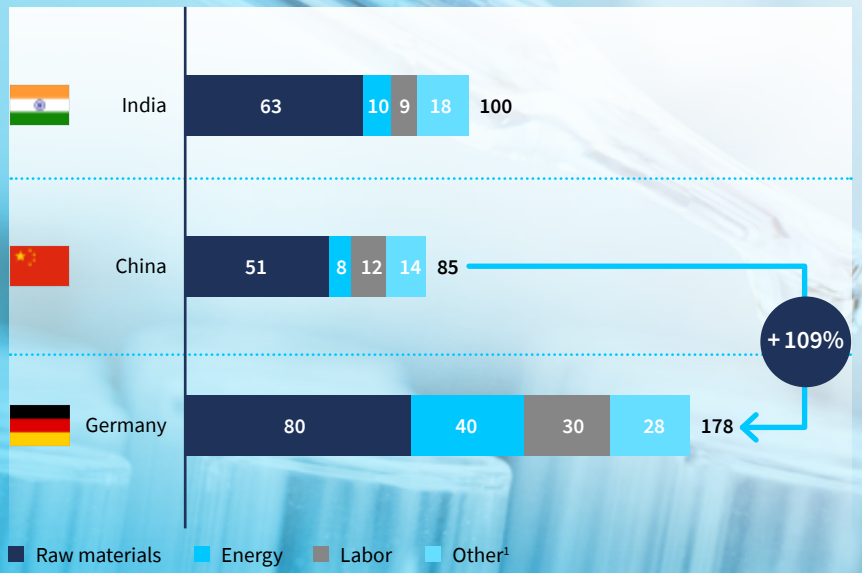
[1] European Response Coordination Centre Source: Press releases

Barriers to Reshoring

Consolidating the upstream steps of the pharmaceutical supply chain in China and India has led to a huge economies of scale effect. It may be extremely hard to compete and reshore some of these steps back to Europe to protect supply for the most critical components. The key barriers remain obvious: it is not easy to be cost-competitive and make sure that not only the API is secured locally but also all the upstream intermediaries that are required for it.

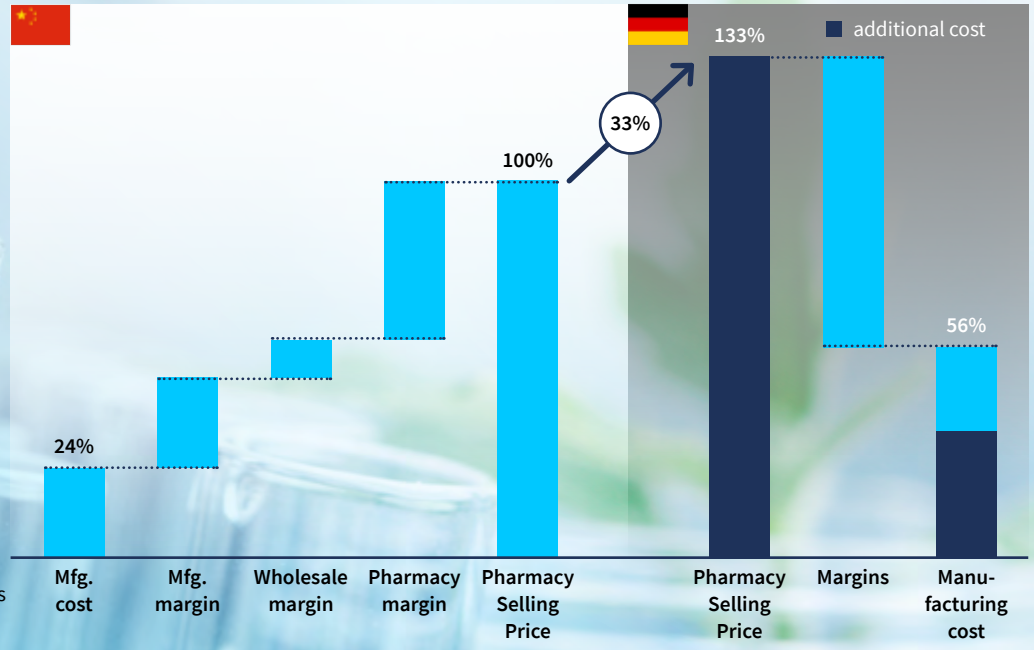
The cost gap from India or China to Germany needs to be targeted to incentivize re-shoring back to Europe as well as increase of generics price by ¬33% to keep the already declining margin of PharmaCos

Cost of API production by country, indexed
India assumed to be 100 units



¹ Other costs include maintenance, consumables, financing, logistics, production and set-up costs
Sources: STATISTA, KPMG, CII, https://reshoringinstitute.org, Camelot analysis

Gx drug cost comparison depending on manufacturing location



PRICE HIKES FOR GENERICS ARE AN OMNIPRESENT TOPIC
FOR EXAMPLE

> **Italy urged to address almost €1 billion rise in generics' production cost**
>
> Colucci, G. | Euractiv.it (2023, March 23)

> **Exclusive: Drugmakers set to raise US prices on at least 500 drugs in January**
>
> Erman, M. & Wingrove, P. (2023, December 29)

The comparison of the cost to produce API between India and China already shows the big advantage of the Chinese industry and its access to raw materials. According to KPMG and the Confederation of Indian Industry, China can produce APIs 20-30% cheaper than India. Comparing EU countries, e.g., Germany, with costs of energy being five times higher than in China ($0.44 vs. $0.09 per kWh) or with labor costs being three times higher than in China (EUR 33k vs. EUR 13.5k per respectively), there is a huge gap in price competitiveness. Without a proper collaboration between chemical and pharmaceutical industries, incentives, and some sort of protectionism on regional and country levels, it may be extremely hard to convince the industry to invest in capacity expansions, especially for low-margin, generic APIs and drug products.

Cost issues in the West can to some extent explain why, when looking at global figures and statistics, we could not find supporting facts to claim that the upstream pharmaceutical industry, causing today's supply issues, will shift towards Europe or the US. For that, we have analyzed several sources including trade maps for pharmaceutical products and components, foreign direct investments in the pharmaceutical industry, and data on API fillings and certifications by Japanese and European institutions. For example, looking at CEP share for generic APIs between Asia and the West, we can say that the dynamics have changed and the ongoing trend of increasing share in Asia has slowed down, but not reversed.

What can we expect in the next five to ten years? We believe that every new investment will be heavily discussed. Especially expansion initiatives by European or US companies will be predominantly localized in domestic markets incentivized by local authorities. This will not be a spectacular reverse of the trend but should at least stop progressing depending on the Asian industry.

We believe that there are a few additional actions that should be considered in the challenging landscape of the pharmaceutical industry, adapting to ongoing and new disruptions while maintaining efficiency and ensuring patient access to essential medications.

INCREASE OF FLEXIBILITY, COST CUTTING AND ADVANCED COLLABORATION SYSTEMS AMONG MAIN ALTERNATIVE TO RE-SHORING

Introduce shared packs for whole regions, increasing flexibility in production and scheduling as well as helping to reduce stockout risk.

Reduce cost levels of API production with shared e.g., European efforts (collaboration between chemical and pharmaceutical players will be a must to secure the E2E supply chain).

Introduce centralized warehouses in Europe for shared packs, enabling more effective balancing and management of short-term disruptions.

Implement advanced IT planning and collaboration systems to manage more complex sourcing strategies, ensuring supply security for all patients. Enhance collaboration with external suppliers using new planning options for better visibility, communication, and real-time monitoring of manufacturing operations.

We would like to thank Michał Globisz and Arkadiusz Kunc for their valuable contribution to this paper.

Camelot Management Consultants

Camelot is a leading global management and technology consulting firm focusing on value chain management. The firm's mission is to transform clients' value chains into a competitive advantage and create lasting impact where it matters most. By combining deep industry knowledge, value chain process expertise, and technology know-how, Camelot guides clients from strategy to sustainable technology adoption.

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