API SUPPLY CHAIN RESILIENCE BY DESIGN

The Budapest site is the main source of EuroAPI's prostaglandin manufacture

Didier Combis of EuroAPI looks at why considering the API value chain can strengthen the global medicine supply chain

For ducades, pharmaceutical companies have globalised their drug substance supply chains, looking for cost-optimisation. In parallel, now chemical entities INCEs) produced by chemical synthesis, including peptides and oligonucleotides, have been characterised by a steadily growing complexity accelerating. the creation of sophisticated transnational supply lines,

These supply lines Inok today li Jigsaws where China and India are gradually integrating larger pieces year after year. According to Indian statistics data base, one can easily see that the large Indian API producers were importing their chemical intermediates overwhelmingly from China in 2024 while also relying on China for nearly 70% of its APIs whereas Europe and the US are now importing off-patert APIs predominantly from China and India.[1]

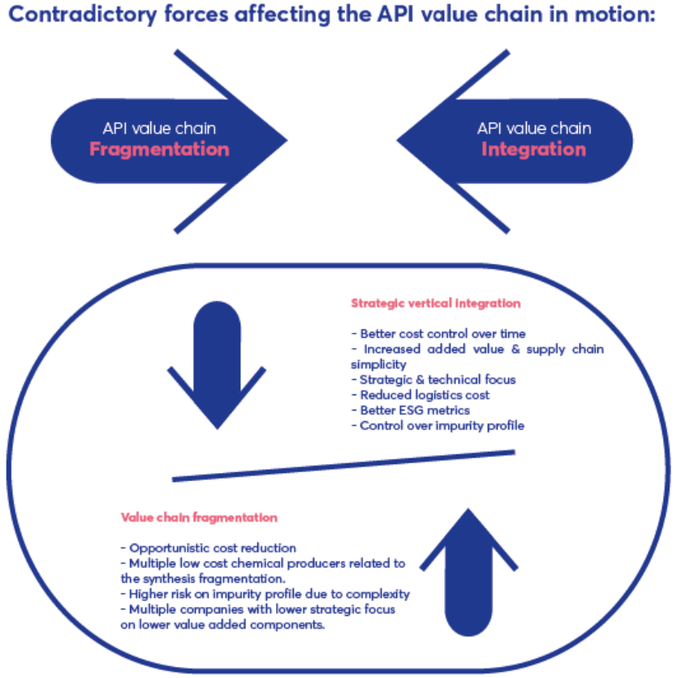

Figure [1] - Contradictory forces affecting the API value chain

The COVID-15 pandemic in 2020 was in some ways a wake-up call, triggering tensions over critical APis and knocking some companies off balance. It became apparent that building reliable and secure supply chains for key medicines should be one of the industry's top priorities. Close collaboration with drug substance companies capable of ensuring arobust supply at every stage of the API lifecycle emerged as a critical factor in de-risking.
swing.

2024 may have been another tipping point where the pharmaceutical industry's over-reliance on APIs and intermediates from China turned into a major issue in building stable supply Ines. Last year also saw the awakening of a strong political will, with a slightly different focus on the two sides of the Atlantic.

The EU has tackled the problem with the main objective of preventing shortages of commercial critical medicines. Meanwhile, mounting geopolitical tensions between the USA and China are triggering a dramatic shift on how NCE supply chains will be designed.

This is exemplified by how the Biosecure Act targeted the Chinese CDMOs Wuxi AppTec and Wuxi Biologics. This passed through the US House of Representatives on 16 December 2024, but has yet to make it through the Senate. If passed, the law would prevent US companies from outsourcing to certain Chinese providers.

Depending on China

Whether it becomes law or not in 2025, this text is already an effective call to relocate significant parts of the western new APIs supply chains. Indeed, as per a New York Times article on 31 December 2024, any such war would mean that "Washington would also have to work with allies on a crash reshoring of critical products from China on which America has become heavily dependent, including APIs and drones".2

Even so, 80% of global medicines by volume depend upon China, directly for the API or indirectly through key chemical intermediates or raw materials. This figure is 90% in some (possibly exaggerated) reports. The reshoring pressure applied on the development and production of NCEs is now triggering effective actions to rebalance drug substance supply, the game is still very different further away in the API lifecycle.

Generic medicines comprise around 80% of each major therapy area by volume and, except in oncology, their share has been slowly increasing over recent years. Right now, generics are dealing with extreme economic pressure. Laboratories have to deal with the contradictory forces of regionalising the supply base and the need to reduce costs by all means for short-term financial results.

So, doing the maths, roughly 60-80% of established medicines out now depend on Chinese supply.3 The Critical Medicines Alliance for Europe is seeking "to identify the best measures to address and avoid shortages [and] to come forward with a strategic plan which the Alliance will consider and endorse", as per its first meeting in April 2024.4 However, implementation will take time and

will focus on a limited number of substances, mainly for hospitals.

Derisking the chain

The pharmaceutical industry needs to create value chains with long-term resilience. This requires holistic approaches to managing API supply lines and protecting against future disruptions.

Experts and consultancy firms such as Bain & Company or EY provide good insights and path forward through a typical process of thorough risks assessment and control strategies, resulting in the implementation of capacity buffers, dual sourcing across regions, flexible partnerships and predictive IT tools for better visibility.5,6.

However, these proposed measures to derisk the drug substance supply chain, while pertinent and full of common sense, are often quite general and do not capture the root causes of a disruption at the manufacturer level. When going in beyond the accidental disruptions or geopolitical risks, it is important to understand the core strength of a company in producing an API.

In other words, we recommend emphasising the value chain perspective. The question to ask is 'In assessing my strategic API supply, is my supplier truly robust in making this molecule for me ?'

Supply chain resilience by design

EuroAPI, a major player in drug substance production created in 2022 from former Sanofi API operations, is rapidly developing its custom services activities for NCEs alongside being one of the largest global producers of commercial small molecule and 'tide' APIs. After two years of strategic review and adaptation, the company has solid financing for a growth strategy where customers will benefit from a unique level of supply chain integration.

Since EuroAPI achieved its independence, a large-scale real-life exercise has been conducted over 200 commercially produced APIs across its three main technology platforms of small molecule synthesis, microbial fermentation and 'tides', in order to assess its intrinsic strengths. This exercise is now over.

The review has resulted in a streamlined value-added portfolio focused on highly differentiated APIs. About 10% of the portfolio molecules were discarded. The survivors are characterised by fundamental strengths to enable long-term, globally competitive positions: a competitive route of synthesis deserving appropriate R&D investment but also a very high level of vertical integration.

The vast majority of EuroAPI's molecule value chains are, by design, deeply integrated. This feature, which might have seemed corporate weakness before COVID, when the disadvantages of increasingly fragmented supply chains were not yet evident, is now a solid base for long-term robustness and is now starting to bear fruit.

All of the key products in our small molecules business show a high degree of integration, either through a key RSM associated with an innovative process, such as fexofenadine, produced at the Frankfurt site, or by the belonging to a structured 'product tree'.

Euroapi Fermentation process at Elbeuf

Key product trees

For example, EuroAPI is the world's largest producer of prostaglandins with 16 commercial molecules, such as bimatoprost (for glaucoma) or treprostinil (pulmonary arterial hypertension), which require on average around 15 chemical steps. The main production site in Budapest is supported by a back-up facility in France synthesising early intermediates for contingency and capacity purposes.

Vertolaye's integration was critical during the COVID crisis

It is a similar story in the Corticosteroids & Hormones product line, where the APIs require 15-25 chemical steps on average. These are made at Vertolaye, France – unusually, because advanced intermediates are mostly sourced from China. This integration was critical during the COVID crisis since Vertolaye was producing dexamethasone, among the first COVID medicines to be successfully used.

Integration is even more striking for the Opiates & Derivatives product lines. It starts with some 1,000 farmers making the crude alkaloids precursors, which are then transformed using advanced synthesis into highly complex molecules to fight addictions and other serious conditions. These include naltrexone and buprenorphine forto treat long-term addiction, while naloxone is the reference overdose reversal medication against synthetic opioids like fentanyl.

EuroAPI's Microbial Fermentation business makes highly sophisticated small molecules using fermenters up to 300 m3, while the company is fully integrated from cell banking to downstream processing (DSP) and final drug substance production. This integration starts from critical raw material sourcing like vegetal biomass. For example, the Vitamin B12 (cyanocobalamin) precursor is sourced from farmers located within a 300 km radius aroundin Normandy.

Finally, the Oligonucleotides & Peptides business is also integrated along the value chain, where precursors and critical side chains such as Galnac could be produced, and in addition along the API lifecycle with capabilities from early clinical support to launch and commercial manufacturing.

Contradictory pressures

Pharmaceutical companies face contradictory forces for off-patent medicines. That said, other than for NCEs, finding the trade-off between sourcing from the lowest spot available price and a longer-term perspective is not an easy task.

The cost pressure for standard generic medicines has reached a tipping point, where any weakness in the supply chain may turn what could have been a short-term disruption into a deeper crisis. Most Western countries are now suffering from chronic shortages of mature medicines, which are caused by multiple factors often embedded into an overall cost reduction process.

National health agencies are now employing dedicated teams to track and follow medicine shortages, with the option of significant fines. In September 2024, France's ANSM fined 11 French pharmaceutical laboratories €8 million in total over this.7 Consequently, procurement and strategic sourcing in most pharma companies need to reach a fine balance between the multiple factors they need to consider in their API sourcing and supply chain resilience.

Figure 1 shows the forces affecting the API industry. These are now clearly in favour of integration when long-term cost control, strategic fit and environmental aspects are truly considered. Perhaps the most important factor is 'economic value added fragmentation' associated with multiple actors in the API synthesis. This decreases supply chain robustness under strong economic pressure, creating the temptation to quit manufacturing towards a more profitable product.

Conclusion

The increasing fragmentation of manufacturing processes, which was seen ten years ago as a never-ending search for cost reduction, specialisation and leveraging on low-cost intermediates produced in China is now turning a major weakness.

Where the strategy of buying each chemical at the lowest possible cost, anywhere in the world, can effectively reduce costs in the short term, the consequential supply chain weakness is a dangerous strategy in the long term for many established APIs. The disadvantages are now growing: higher logistical costs, an environmental impact which cannot be hidden where the carbon atoms have travelled several times around the global prior to reaching the drug substance stage and inherent fragility.

Strategic sourcing and procurement teams should therefore take a value chain perspective and consider the integration level among their supplier as a key long-term driver for value creation and supply line robustness.

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