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# ACTIVE PHARMACEUTICAL INGREDIENT PRODUCTION IN EUROPE

## Corona bringing back API production to Europe: Which strategy makes sense?

The coronavirus pandemic has once again highlighted Europe's dependence on third countries for the supply of medicines. Almost as a reflex, politicians are calling to reinstall API production in Europe. How can and should companies respond in a meaningful way?

An analysis by Dr Konrad Schaefer, Head of Consulting and Operational Experts at VTU Engineering.

Over the last years, various essential medicines were not available on the market in Europe as needed The underlying reason was often found in the area of supply chains outside Europe and led to the public perception that the industry had accepted disproportionate risks in this respect, and should now re-establish production in Europe. In fact, India and China together have more than four times the number of sites for the production of API than Europe and the USA combined, and as a consequence, roughly 80 per cent of all active pharmaceutical ingredients and 40 per cent of all finished dosage forms worldwide originate from these two Asian countries. What caused this development and where do we stand today?

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### Changes during the last decades

Following other industrial sectors, the fine chemicals industry and subsequently the pharmaceutical industry started massive outsourcing activities in the 1980s and 1990s, beginning with simple, early and patent-free manufacturing steps into India. The obvious progress of Far Eastern countries in terms of expertise and quality subsequently allowed the stepwise outsourcing along the value chain up to the drug substance or even further to the drug product. The decisions to do so were not based on monetary considerations only, but were more complex in many cases. In the early stages of relocation, the focus was often on the different legal frameworks, an aspect that has fortunately become less significant due to the globalization of norms and ethical standards. However, there were also entirely different motives. Let us take for example the patent law situation for generic producers in Europe before the turn of the millennium, which did not allow launch preparations ahead of the patent expiry. Every crisis in recent years, whether triggered by quality issues such as the heparin adulteration, by political decisions such as the closure of numerous companies to

improve air quality prior to the 2008 Olympics, by natural phenomena such as the eruption of Eyjafjallayökull or by the last year's blockade of the Suez Canal, drastically surfaced weak points in the supply chains and triggered the strong call for more domestic production .

## Where do we stand today?

Parallel to the relocations, the landscape of the pharmaceutical companies changed significantly: consolidations by mergers, fine tunings of portfolios by spin-offs, outsourcings and reintegrations of generic activities, and so on, all that meaning that knowledge and expertise are no longer available.

Additionally, related development activities were usually discontinued even before the relocations took place and what is left are at best outdated processes without underlying process knowledge. Registrations are no longer held and maintained and the old dossiers are insufficient according to today's criteria. And last but not least, the production facilities are used for other purposes or have been shut down. All in all, not the best preconditions to restart production.

## Considerations before a new start

It is therefore essential to perform a neutral assessment of the status quo from a business perspective. The starting point must be the target molecule and the process. Which of the active ingredients have a frail manufacturing chain? What are the essential intermediates or what are the crucial process steps? What is the supply situation regarding raw materials? It is important to keep in mind that not only complex side chains or intermediates need to be scrutinized . Often simple chemicals such as acids, caustic or solvents are more critical in supply.

## Considering the entire chain

Several years ago, for example, a shortage of acetonitrile not only led to problems in the production itself, but also affected the output of analytical laboratories. Or maybe the process uses chemicals for which the availability is linked to co-products that are influenced by other industries. As an example, declines in the plastics demand can have an impact on chlorine production, which in turn is linked to caustic soda; and caustic soda is essential for processes and cleaning. A holistic view, including sourcing options and logistics requirements, is therefore crucial to focus on the right materials at the right process steps.

However, economic and strategic considerations are equally important. How does the product fit into the portfolio, do the forecasted demands allow a sustainable production volume, does the market need to be segmented? The less clearer these positions are, the riskier the decisions will be with regard to a sustainable business case. A regular production with a corresponding development support is also inevitable to build up and maintain the essential process knowledge. Keeping production capacities free for demands on short notice or  is not better than short-term reallocation of capacities when necessary , and usually both do not make sense at all. In any case, a short-term opportunistic approach must never be in conflict with the long-term strategy.

## … hence no future? – on the contrary!

Even if the previous considerations do not paint a very optimistic picture, this does not mean that the production of API has no future per se in the EU. It is evident that bringing back previously outsourced large-volume molecules such as paracetamol or penicillin is not economically feasible. However, a lot can be done to secure existing production and to safeguard new, innovative products against outsourcing in the future. Long-term competitiveness beyond an expiration of patents requires constant development of processes, increased automation, and exploiting the possibilities of data acquisition and analysis to grow yield, process stability and product quality. An examination of entire value chains may also be useful for a holistic profitability analysis, as the influence of quality defects or supply interruptions at later stages is often not sufficiently taken into account when optimizing individual steps. The effect of a cost difference of an intermediate or API on the finished drug product may be negligible in an overall view even if it is significant when analyzing a single step of the value chain. And although a mere logistical coverage of supply risks might be the right decision for many substances, the recent experiences should lead to more value chains remaining in Europe in the future, providing more supply security in case of a crisis.

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