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# BRINGING ACTIVE INGREDIENT PRODUCTION BACK 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 for the return of active ingredient production to Europe. How can, should companies react in a meaningful way? A commentary by Dr Konrad Schaefer, Head of Consulting and Operational Expert at VTU Engineering.

Dr Konrad Schäfer, Head of Consulting and Operational Expert at VTU Engineering, advocates a sense of proportion.

Over the course of the last few years, situations have repeatedly arisen in which essential medicines were not available to the extent intended. Often the cause was in the area of supply chains outside Europe and led to the public perception that the industry had accepted disproportionate risks here and should now re-establish production in Europe. In fact, India and China together have more than four times as many active ingredient production sites as Europe and the USA combined, so around 80 per cent of all active ingredients and 40 per cent of all finished forms worldwide come from these two Asian countries. How did this development come about and where do we really stand today?

## Development over the last decades

Following in the footsteps of other industrial sectors, the fine chemicals industry and subsequently the pharmaceutical industry underwent massive relocations of production in the 1980s and 1990s, starting with simple, early and patent-free manufacturing steps towards the East. The undisputed progress of the Far Eastern countries in competence and quality then allowed the gradual shift along the value chain to the active ingredient or even further to the finished form. The decisions to do so were not based exclusively on immediate pecuniary considerations, but were in many cases more complex.

In the early stages of relocation, the focus was often on the different legal frameworks, an aspect that has fortunately become obsolete due to the globalisation of norms and ethical standards. However, there were also entirely different motives, let us think, for example, of the patent law situation for generic producers in Europe, which did not allow timely preparation for a patent expiry from Europe until after the turn of the millennium.

Every crisis in recent years, whether triggered by quality issues such as the so-called heparin scandal, by political decisions such as the closure of numerous companies to improve air quality prior to the 2008 Olympics, by natural events such as the eruption of Eyjafjallayökull or by the recent blockade of the Suez Canal, drastically exposed weak points in the supply chains and made the call for own production loud again.

## Where do we stand today?

Parallel to the relocations, the pharmaceutical companies' landscape changed significantly: consolidation through merges, portfolio fine tuning through split-offs, spin-offs and reintegrating of generic activities, etc., making knowledge and expertise no longer available.

In most cases any accompanying development work was also discontinued even before the relocations, resulting in outdated processes without underlying process knowledge at best. Registrations are no longer legit and the old dossiers are insufficient according to today's criteria. And last but not least, the production facilities are being used for other purposes or have been shut down – all in all, not the best conditions to restart production.

## Thoughts before a new start

It is therefore essential to make a neutral assessment of the status quo from a business perspective. The starting point for this must be the target molecule and the process. Which active ingredient has a weak manufacturing chain? What are the essential intermediates or what are the crucial process steps? What is the raw material situation? It is important to remember that it is not necessarily complex side chains or intermediates that need to be scrutinized critically. They are often simple chemicals such as acids, alkalis or solvents.

Several years ago, for example, there was a shortage of acetonitrile, which led to problems not only in production itself, but also in analytical laboratories. Or they are tying products that are influenced by other industries. For example, declines in the plastics sector can have an impact on chlorine production, which in turn is linked to caustic soda; and caustic soda is a basic chemical for processes and cleaning. A holistic view, including sourcing options and logistics requirements, is therefore essential to ensure that the focus is on the right material at the right stage.

However, the economic and strategic consideration is just as important. How does the product fit into the portfolio, do the conditions exist for a sensible production volume, does the market perhaps need to be segmented? The more blurred the positions are here, the more risky the decisions are with regard to a sustainable business case. Regular production with corresponding development support is inevitable to build up and maintain the absolutely essential process knowledge. Keeping production capacities free on demand for possible products is no more successful than short-term reallocation when necessary and therefore does not usually make sense. And for all the justification of a short-term opportunistic approach, there must be no contradiction with the long-term strategy.

Finally, the financial support usually offered in this context must also be critically examined. Short-term measures such as investment subsidies are easy to integrate into a profitability analysis, but long-term models such as tax breaks or import barriers pose a risk to any payback calculation that should not be underestimated. In addition, all kinds of subsidies are usually associated with obligations that can restrict entrepreneurial freedom in the long term and prevent necessary decisions from being made in the future.

## … so no future? – yes, of course!

Even if the previous considerations do not paint a very optimistic picture, this definitely does not mean that the production of active ingredients in the EU has no future per se. Rather it shows that bringing back previously relocated large-volume molecules such as paracetamol or penicillin is not feasible from a private-sector perspective. However, work can be done to safeguard existing production and to spare new, innovative products this fate in the future. However, long-term competitiveness beyond patent expiry means constant further development of processes, increasing automation and exploiting the possibilities of data acquisition and analysis to increase yield, process stability and product quality.

An examination of longer production chains may also be useful for the profitability analysis, as the influence of quality defects or supply interruptions at later stages is not sufficiently taken into account when optimising individual stages. The effect of an intermediate's or active ingredient's cost difference on the finished medicinal product may well be negligible in an overall consideration, although it is significant when analysing the individual stage in isolation.

And even if a mere logistical safeguarding of supply is the right decision for many substances, it is to be hoped that recent experience will lead to more whole production chains remaining in Europe in the future and guarantee more security in the face of a crisis