AFFORDABLE MEDICINES EUROPE

WORKING IN PARALLEL FOR A BETTER DEAL

DIVERSIFICATION OF THE SUPPLY CHAIN

POSITION PAPER

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THE ISSUE: CONTEXT

Over the past years shortages of medicine have been on the rise, not only in the EU but world-wide.[1] Though the causes for medicine shortages are multiple, some main problems have become evident over the last years: among those are the concentration of the supply chain to fewer and fewer producers (and individual facilities) of API's and raw materials, increasing dependency on such producers/facilities. Hence, when problems arise at these production sites they can lead to shortages. Furthermore, since many raw materials and/or API's come from India and China[2], dependency concerns of geopolitical nature have arisen.

There are many types of problems that may arise at a production site. These include: problems with quality in the production like those witnessed in the Valsartan case[3]; natural disasters, GMP issues, such as disruption of production due to e.g. wrong temperature condition; manufacturing lag times sometimes caused by e.g. disruptions; and lack of manufacturing capacity when demand surges.[4] This can happen at all levels of production, from production of raw materials, over the production of active pharmaceutical ingredients (APIs) and excipients, to the production of the final pharmaceutical.

For decades manufacturers have streamlined their production processes – outsourcing the production of pharmaceutical raw materials, starting materials, intermediates, APIs, etc. This way the companies were able to reduce production costs and especially for generic medicines respond to increased competition and lower prices paid by healthcare systems. However, this has also led to an increasing dependency on fewer production sites. Simultaneously, more production is taking place outside Europe, and especially in China and India, adding to dependency concerns of a geopolitical nature rather than a supply chain nature.

Though the COVID-19 Pandemic exposed vulnerabilities in the supply chain and caused problems – keeping the supply chain international and globalized is still the safest approach to guarantee supply safety. This paper therefore focuses on the diversification of the supply as a solution to potential shortage of medicines. Whether a production is located in or outside Europe, from a supply continuity perspective is less important. The main factor is the diversification of supply. That means production of a given raw material, API, excipient, or finished pharmaceutical should take place in multiple production sites. To address geopolitical concerns, such production may need to also have a certain geographical spread – but not necessarily focusing on production in Europe alone.

Therefore, a central part of the solutions to shortages, is figuring out how to become less dependent on individual factories and the disruptions and/or quality problems occurring there – be that of raw materials, API's or with finished products. In this paper, we identify the vulnerability of single source supply chains and discuss how we can diversify production so as to decrease dependence on individual factories.

What's the problem? The example of the Valsartan-Case

An example that illustrates the vulnerability of the global pharmaceutical supply chain is the Valsartan case. Valsartan is a blood pressure lowering agent from the group of sartans, which is used for the treatment of high blood pressure, for heart failure and for the prevention of heart attacks.

The European Union has high standards for pharmaceutical production. These standards are administered by the European Directorate for the Quality of Medicines & HealthCare (EDQM) who publish and review these quality standards for medicines in the *European Pharmacopoeia* (Ph. Eur.). The legal basis for these standards is anchored in the Directives 2001/82/EC and 2001/83/EC. They state the legally binding

[1] *WHO, 2016: https://www.who.int/medicines/publications/druginformation/WHO_DI_30-2_Medicines.pdf?ua=1.*
[2] *European Commission, DG SANTE, note to the Pharmaceutical Committee, November 2019: https://ec.europa.eu/health/sites/health/files/files/committee/ev_20191217_788_en.pdf.*
[3] *EMA: https://www.ema.europa.eu/en/news/ema-reviewing-medicines-containing-valsartan-zhejiang-huahai-following-detection-impurity-some. Website accessed 2 May 2020.*
[4] *Stakeholder paper "Addressing the root causes of medicines shortages", 6 December 2019; https://affordablemedicines.eu/wp-content/uploads/2020/01/addressing_the_root_causes_of_medicines_shortages_-_eu_supply_chain_stakeholders_views_on_root_causes_and_solutions.pdf.*

character of European Pharmacopoeia texts for Marketing Authorisation Applications (MAA) and make sure that products are manufactured in a save way. Hence, manufacturers should guarantee the application of these rules also, when they produce medicines, active ingredients and starting materials outside the Union[5].On 5 July 2018, the European Medicines Agency (EMA) reviewed medicines containing valsartan following detection of an impurity, N-nitrosodimethylamine (NDMA), a probable human carcinogen, in medicines from Zhejiang Huahai Pharmaceutical Co Ltd, Linhai, China.

As a consequence, a world-wide recall of the badges suspected of being contaminated followed. Zhejiang Huahai **held a market share of 45% in the generics market for valsartan**.[6] In other words, almost half the market of valsartan was affected by the quality issue at Zheijang Huahei – this inevitably lead to shortages of valsartans worldwide.

In the Valsartan case, new manufacturing methods used abroad were not checked and introduced into the European *Ph. Eur.*. Had that been the case, the weaknesses of the new production method may have surfaced earlier and prevented a shortage from happening.

Vulnerabilities of production and supply chain

Production processes are now so lean that as little as two, or even one, factories produce a certain essential ingredient which cannot be replaced, if there are any difficulties in supply. While this lean supply chain is very cost effective, a lot of things can go wrong during production but also during the supply process. A total of about 60-80% of raw- and starting materials and intermediates are sourced China or India[7]. This is a fact of globalisation, but in its own, not a problem. In fact, it only becomes a problem, if there are not sufficient alternatives to compensate for that lost supply in case things go wrong.

> *"Should problems arise in these companies (technical problems, quality problems, natural disasters, strikes, etc.), the market demand can usually no longer be covered for at least several months. As a result, insufficient quotas are now available to supply the world market and thus the individual national countries, including the EU. The replacement of other (smaller) manufacturers, if they still exist, is then not possible or only possible to an insufficient extent."*[8]
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> **Austrian Federal Office for safety in Health Care**

The reasons for sometimes severe, unexpected disruptions are multiple. A few examples illustrate the variety of such reasons:

Serious accidents during production

Chemical production remains, regardless of progress made in safety procedures, a hazardous endeavour. A fire at the Aarti Drugs pharmaceutical company production site in Mumbai in 2013, for instance, claimed lives of workers and led to a sense of doubt over the reliability of safety arrangements at such plants.[9] Other accidents such as the fire of a chemical plant delivering raw materials and excipients for pharmaceutical production, have also shown the vulnerability of having concentrated suppliers irrespective of location.[10]

Such accidents lead to temporary factory closures, which again can lead to short term shortages. This is especially true if this concerns a supplier with a very large market share.

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[5] The European Pharmacopoeia, background & mission, https://www.edqm.eu/en/European-Pharmacopoeia-Background-Mission, accessed: 18.11.2020.
[6] Eric Palmer, 7.8.2018, Tainted valsartan has been on the market for 4 years, FDA discovers, https://www.fiercepharma.com/manufacturing/tainted-valsartan-has-been-market-four-years-fda-discovers, retrieved 28.10.2020.
[7] AESGP Position Paper on Medicine Shortages, https://aesgp.eu/content/uploads/2020/07/AESGP_PP_Shortages_2020.pdf, July 2020, accessed: 28.09.2020.
[8] Austrian Federal Office for safety in Health Care; https://www.basg.gv.at/en/market-surveillance/reporting/medicine-shortages#c21154, retrieved 04.11.2020.
[9] Accident Analysis, 25.04.2013, in: Express Pharma journal India, https://www.expresspharma.in/management-pharma/accident-analysis/, retrieved on 22.10.2020.
[10] Alles Europa News, https://www.alleseuropa.net/in-rouen-france-lubrizol-factory-under-an-intensive-investigation-after-fire-outrages/, retrieved on 04.11.2020.

Insufficient supply of older active substances

Some substances that have been on the market for a long time, though they never lost any importance because they are essential to the production of various products, are increasingly in the hands of a decreasing number of global manufacturers. The danger of shortages caused by this advancing global development has increased in recent years, not only in theory but also in practice[11].

Manufacturing principles

Some manufacturing problems relate to the just-in-time (JIT) principles on production adopted by many manufacturers. Such production principles lead to very low stock levels throughout the supply chain in an effort to reduce inventory costs.

Using the JIT principle, companies are buying smaller quantities of raw materials from suppliers, thus reducing the amount of materials in inventory, leading to an increased return on investment among other benefits[12]. However, this makes the production chain less resilient to even minor shocks – such a production cycle gone wrong creates a cascading effect of delays throughout the production chain. As a response to this development, some countries have started to introduce requirements to have larger stock levels readily available (already before the COVID-19 crisis the Netherlands and France introduced these).

When combining the adverse effects of JIT manufacturing practices with the issue of accidents or other manufacturing disruptions (such as risks of sight closures due to new environmental standards etc.) we get a ripple effect. The lack of supply chain resilience due to JTM will lead to worse and longer lasting shortages when unforeseen manufacturing site closures occur.

DIVERSIFICATION OF SUPPLIERS

Diversifying the global pharmaceutical supply chain is about creating resilience. European countries and the companies executing that strategy need to be in it for the long run because the process of diversification is likely to be expensive, challenging, and time-consuming[13]. Looking at the issues of medicine shortages globally, however, it is still the most feasible option. Drug manufacturing is a global process which is a necessity for companies, given that markets are global as well. In order to service patients world-wide, production and distribution networks have to be sturdy and resilient.

There are a variety of factors that companies have to consider when thinking about diversifying their supply network. The biggest advantage of a diversified supply network is obviously greater supply security and in turn, business predictability. Having a broader network of suppliers also allows for higher access to innovation and creative thinking as having more suppliers also means more exchange on manufacturing problems and brainstorming on solutions together[14].

Besides the great advantages, diversification inevitably increases transaction costs which leads to a trade-off question: Do manufacturers want better protection against disruption but higher costs, or lower costs but a greater chance for disruption[15]. For pharmaceutical manufacturing, the answer should be clear. European patients and health systems need more reliability and safe access. Hence, policy tools must address how we transit to diversification in a context where it will decrease the profitability of supplying medicines. Especially in the context of the supply of generic medicines, where prices are already fairly low.

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[11] Austrian Federal Office for safety in Health Care; https://www.basg.gv.at/en/market-surveillance/reporting/medicine-shortages#c21154, retrieved 04.11.2020.
[12] Jerry Chapman, Did COVID-19 Kill Just-In-Time Pharma Supply Chains?, Blogpost from 09.04.2020, https://govzilla.com/blog/2020/04/pharma-did-covid-19-kill-just-in-time-pharma-supply-chains/, retrieved on 22.10.2020.
[13] Sarah Hippold, Diversifying Global Supply Chains for Resilience, 02.09.2020, https://www.gartner.com/smarterwithgartner/diversifying-global-supply-chains-for-resilience/, retrieved 23.10.2020.
[14] The importance of supply chain diversity, 11.04.2017, http://gomarketwise.com/blog/importance-supply-chain-diversity/, retrieved on 23.10.2020.
[15] Supply Chain Risk: Diversification vs. Under-diversification. https://www.ideasforleaders.com/ideas/supply-chain-risk-diversification-vs-under-diversification, retrieved on 23.10.2020.

While many have suggested to move production back to the EU, this will, on its own, not be a sufficient response to this problem – and it will come at an even greater economic cost. As outlined above a lean production will always lead to vulnerabilities. It does not help to relocate certain production sites, which would have to be as great in size as the Asian ones surrendered in their place, and then have one of them experience a manufacturing disruption. The effect would be the same. Regardless of whether that factory is located in France or in India. Therefore, the EU should look into other tools at its disposal which may guarantee a more diversified supply chain. Among the possible solutions are:

Recommendation 1:

Affordable Medicines Europe recommends that marketing authorisations should require multi-sourcing down to raw material level, irrespective of the geographical location of those sources.

Recommendation 2:

Affordable Medicines Europe recommends that requirements for having diversified supply sources be incorporated in public tenders, irrespective of geographical location.

Ultimately, the strategy can be boiled down to this; Decrease the dependency on individual factories and the disruptions and/or quality problems occurring there will not have as much of a negative impact on supply. For this to be valid, the production needs to be diversified for all sub-categories of products - be that of raw materials, API's or with finished products.

CONCLUSION

Diversification is the preferential policy choice to make in order to reduce manufacturing and distribution related drug shortages in Europe. In contrast to reshoring it is more feasible from an economic perspective.

As mentioned, diversification has a number of advantages. An additional one that should not be underestimated, is that it makes for a better trade and development policy. Third countries outside the EU, such as India, have established economic ecosystems out of pharmaceutical and raw material production as well as Research and Development. Next to providing the world with high quality APIs and medicines, the production ecosystems created there are keeping people employed while creating more good jobs in other sectors as well because of economic spill-over effects. This helps whole regions to alleviate poverty and improve peoples' quality of live. By strengthening these ties, both can contribute and profit at the same time by promoting EU-standards for labour, environmental protection, and good manufacturing practice on a global scale.

While reshoring is currently on top of the political agenda, Europe should be careful not to resort to what correspond to protectionist measures. In the case of drug manufacturing, protectionism only localises the risk while the system remains vulnerable. Furthermore, protectionism reduces the diversity of potential external suppliers and diminishes the pressure of competition, economies of scale and, finally, affordability. All of which is self-defeating.

The overall objective of the European response to address the problem of medicine shortages has to remain securing a well-functioning global supply chain of pharmaceuticals. To accomplish that goal the EU should maintain and expand its diverse global supply chains. In turn, it can serve as a driver for Europe's welfare and engine for the post-Covid-19 recovery and build on it by diversifying suppliers and setting higher standards for supply security. At the same time there must be an active debate involving all stakeholders: manufacturers, distributors, policy makers, doctors and patients to investigate how the issue of strategic resilience of the supply chains should be addressed and which legislation and incentives are affordable and appropriate in doing so.

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Affordable Medicines Europe represents Europe's licensed parallel distribution industry, an integral part of the European pharmaceutical market that adds value to society by introducing price competition for patented medicines and a supplementary layer of product safety. We represent 125 companies in 23 EU/EEA Member States. These members account for approximately 85% of the total parallel import market volume in the EU/EEA. Membership in Affordable Medicines Europe is exclusive to companies holding a wholesale (GDP) license (export and import). All importing members furthermore are GMP licensed.

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