

Impact of COVID-19 on active ingredient and medicines manufacturing and supplies in Europe

18 February 2020

Mr. Fergus Sweeney
European Medicines Agency

cc. Mr. A. Rys, European Commission

Dear Mr Sweeney,

In response to your request, Medicines for Europe shared your letter reminding manufacturers of the requirement to monitor and inform the authorities of developments which could affect the supply of medicines to patients and has consulted on the potential impact of COVID-19 on medicines manufacturing and supplies in Europe.

China is a major producer of pharmaceutical inputs – notably of key starting materials, intermediate materials and active pharmaceutical ingredients. There are several hundred factories located in the regions most affected by the viral outbreak (Hubei & Zhejiang provinces host over 100 production sites) and the control over the movement of people from those provinces could also affect production in the other provinces. An extended shut down of Chinese production or block on Chinese exports would certainly affect global pharmaceutical production and likely materially affect global production costs.

Based on media reports and data collected by the Indian pharmaceutical ministry, we know that China is by far the leading supplier of API or key intermediates (i.e. in a near global monopoly situation) for certain essential medicines such as pain killers or anti-infectives. In addition, Chinese manufacturers are large producers of ingredients for almost all medicines so a major production blockage could impact global production across most therapeutic areas.

Based on the information we have received, there is limited immediate risk to production or supplies in Europe resulting from this situation. This is because companies typically maintain certain stocks in Europe for their manufacturing networks. In addition, it is likely that some additional stock would be available with chemical traders or due to stockpiling for the recent Lunar New Year holiday period where production shuts down temporarily in China. The uncertainty will naturally affect future shipments and will increase the cost of available stocks with traders. Our members (which produce both active ingredients and medicines) are continuously monitoring their supply chain to assess stock levels and potential impacts on manufacturing and supplies in Europe.

It is not currently possible to evaluate the specific risks caused by the temporary disruption of supplies from the affected areas in China. This will depend on the resumption of production and shipments from factories including how many workers will return to those sites (as there are many restrictions of person movement in China to control the outbreak). This will also depend on the impact this could have on exports from China to key active

ingredient and pharmaceutical production centres in Europe and India. Please note that we do not believe the virus can be transmitted via trade in goods but there could be bottlenecks in the logistics at Chinese ports. Travel restrictions (official or corporate) for personnel from Europe to the affected regions could also have an impact on supplies. We will communicate this information to you as and when we receive updates.

Manufacturers are aware of their legal obligations and are working to avoid potential drug shortages. To facilitate this, manufacturers and regulators should maintain an open dialogue to adapt rapidly to the risk of a production shortfall if production or export problems continue in China. Manufacturers will need authorisation from regulators to prevent further disruptions in the supply chain and to maintain medicines supplies. We advise that the Commission and regulatory agencies consider Medicines for Europe's recommendations to address potential shortages – notably the possibility for emergency variation procedures and accelerated regulatory reviews for both active ingredients and for finished products (see annex). In addition, it would be important to ensure pan-European coordination as national measures could have spill over effects on the rest of the EU.

If the situation continues, we cannot exclude an important impact on supplies due to the potential market effects of the crisis. The scarcity generated by the interruption of Chinese ingredient production and exports could hypothetically impact the price of those ingredients with a knock-on effect on the cost of goods of pharmaceutical production globally. As most European countries apply some form of regulated pricing policy, often combined with price control policies such as maximum ceiling prices for tenders, there could potentially be an unsustainable market situation in the months ahead. This would affect not only manufacturers but also the distribution chain for medicines. Considering this, it would be important to address the potential market problems that could arise from a worsening of the situation, including a sudden increase in supply chain costs, such as:

- Manufacturers could experience difficulties in meeting delivery deadlines in procurement contracts due to *force majeure*.
- Under certain circumstances, manufacturers cannot legally sell products at a loss (i.e. EU procurement law forbids "abnormally low bids").
- Distributors could hoard supplies to comply with public service obligations or due to different incentives in the market leading to a suboptimal distribution to patients.
- Hospitals and pharmacists are often reimbursed according to a reference price. They could struggle to supply patients if the reference price would become negative, below their costs or substantially lower than their past returns.

Medicines for Europe will continue to monitor this situation with manufacturers. We are also prepared to work with regulators and the Commission on the above-mentioned policy matters that could also impact manufacturing and supply in Europe in a worst-case scenario.

Yours respectfully,



Adrian van den Hoven
Director General

Annex: Recap of measures

Reducing time and cost associated with alternative API or ingredient supplier:

- For DCP/MRP/National products: Timelines of variations in the guideline should be respected in all countries for validation time, the start of the variation procedure and for national finalisation.
- For CP products: Timelines of EMA for variations are mostly in accordance with legislation. Shorter timelines should be considered in case of urgency to supply the market.
- Registering an alternative source of API can take up to 12 months. Any alternative source of APIs should be preferably registered before the Marketing Authorisation of the medicines. However, maintaining several API suppliers in the dossier without actual purchasing APIs for production creates challenges for MAHs in view of the workload, API production oversight, audits and regulatory maintenance effort. Some policy measures should be put in place to encourage companies to look for alternative suppliers:
 - o Incentives to reward manufacturers sourcing a second API supply as this is considerably more expensive than a single supply. For example, tender criteria should reward multiple API sources as part of security of supply (which is currently not recognised by any payers in the EU in any material way).
 - o Information that is GMP related should be kept out of the Regulatory dossier and should be secured in a centralised GMP system to reduce the regulatory maintenance burden.
 - o In urgent cases of adding a new API supplier, the procedure should be simplified and quicker.

Temporary imports: To balance the difficulties and costs of temporary Imports due to a shortage, Health Authorities should provide:

- Clear timelines and guarantees that committed import quantities are purchased, even if a competitor returns to the market. Otherwise alternative manufacturers face a financial risk for supplying a shortage.
- Flexibility in accepting products from another market without repackaging with a translated patient information leaflet. The Commission should accelerate work on electronic patient information to permanently solve this issue.
- Flexibility for import licenses: In emergencies, we should allow medicines approved outside the EU (in highly regulated markets).

Repackaging:

- Allow secondary repackaging on a case by case approval by the NCA without adding the repackaging site to the regulatory dossier.
- Non-serialised products should be allowed on an exceptional basis (e.g. small volume, critical hospital products).
- Acceptance and implementation of an e-leaflet instead of a paper base leaflet, for example in hospitals where they do not use paper leaflets in any case.

Alternative Dossier/ alternative medicinal product:

- If a product is already approved in another European market, a zero day repeat use procedure (RUP) should be the basis to register the dossier in the MS where the shortage occurs.
- An extended use of article 126a should be considered in cases when the MAH is not able to use the standard MA procedure.