

## **Update on pharmaceutical supply chain pressures imposed by the coronavirus pandemic**

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*This document will be expanded and updated as the situation evolves.*

### **In summary**

- Our pharmaceutical companies are doing everything in their power to maintain supplies to hospitals.
- Manufacturing facilities are operating very stretched workflows to ensure continuity of pharmaceutical products for French patients suffering from Covid-19 and other serious chronic diseases.
- But supply chain pressures are by no means an all-French problem. When all countries are looking for the same products at the same time, it means that manufacturing capacity is under very high pressure, not only in France, but right around the world.
- In their response to the pandemic and the sudden dramatic increase in demand for products essential for resuscitation units and the treatment of infectious diseases, pharmaceutical companies have put in place a number of measures to secure the production and supply of medicinal products of major therapeutic interest, including:
  - Ordering quota systems have been introduced to regulate product flows and ensure a fair distribution of drugs nationally as the pandemic spreads
  - Major pharmaceutical groups are drawing on international stocks
  - Employees at some manufacturing facilities have stepped in to expand teams or replace unwell team members as part of ensuring that production continues
  - Therapeutic alternatives have been identified wherever possible

## General questions

### **Shortages of drugs as a result of coronavirus: what is the general situation in France at present?**

The ANSM (French National Agency for Medicines Safety) reports that supplies of several drugs are under pressure as a direct result of the global coronavirus pandemic.

- Five molecules used to manage patients with Covid-19, particularly those in resuscitation units, are in extremely short supply. These are injectable forms of two sedatives (midazolam and propofol) and three neuromuscular blocking agents (atracurium, cisatracurium and rocuronium).
- In response to the shortages of these pharmaceuticals, the French government decided, with effect from 25 April, to centralise all orders of these five molecules and take control of their distribution.
- The first deliveries will be made on 30 April.
- A weekly stock distribution plan will be prepared by the French National Agency for Medicines Safety (ANSM) and the Regional Health Agencies (ARS). The first deliveries should arrive with the hospitals and clinics concerned by noon on Friday.
- Healthcare facilities will still be able to place orders with pharmaceutical companies until 24 April.
- The current situation is exceptionally complex, and is continually changing in response to the exponential increase in demand for hospital-administered drugs in France and around the world.
- As Prime Minister Edouard Philippe said on 31 March: *“No industry can withstand a 2,000% increase in global demand for drugs. This is a collective battle”*.
- It is by no means an all-French problem. When all countries are looking for the same products at the same time, it means that manufacturing capacity is under pressure, not only in France, but right around the world.
- We are continually monitoring this situation in the greatest detail, and remain in permanent contact with the health authorities.
- Our companies and their 100,000 employees - 43,000 of whom work in manufacturing facilities - are doing everything possible to maintain business continuity and avoid any shortage of drugs essential for inpatient and outpatient care.
- Added to which, on 31 March the French Prime Minister announced the introduction of a national pharmaceutical supply plan. The aim of this plan is to build stocks at national level, which can then be distributed on the basis of regional needs.

### **What are your solutions for avoiding shortages and stockouts?**

- The coronavirus pandemic is impacting on the rate of pharmaceutical consumption, which is increasing exponentially in resuscitation units worldwide:
  - Within a few weeks, consumption of drugs used in anaesthesia and resuscitation in French hospitals has increased by a factor of between 3 and 90, depending on the drug concerned.
  - Consumption of neuromuscular blocking agents increased by a factor of 100 in the last week of March, compared with the weekly consumption rates seen in normal times. Azithromycin (an antibiotic) by a factor of 30 and hydroxychloroquine (an antimalarial) by a factor of 90.

- On 31 March, the French Prime Minister and Minister of Health announced their intention to act on a number of levers:
  - Regional prioritisation by the ARS (regional health agencies) of those drugs essential during this period.
  - Increasing supplies through greater diversification of procurement sources in conjunction with the ANSM.
  - Regulating stocks held throughout France, as is now the case with ventilators, and distributing stocks on the basis of regional need.
  - Working with healthcare professionals and learned societies to identify alternatives for certain drugs in the event that they cease to be available in the near future, and optimising the use made of drugs normally administered in resuscitation units.
- Lastly, the French Prime Minister announced the building up of a strategic national stockpile of drugs by placing massive orders as the basis for structuring detailed regional management based on the needs expressed by healthcare facilities and general practitioners.

**Several organisations representing caregivers, patients and lawyers have requested the Council of State to ‘force’ the government into requisitioning factories to manufacture the masks, tests and drugs needed to combat the coronavirus epidemic. What is your response to that?**

- Not all production lines can be repurposed quickly.
- For several reasons, it is often impossible technically to requisition a production facility built to produce product A and repurpose it to produce product B:
  1. Each drug has its own unique manufacturing process involving the use of special equipment
  2. Transferring production in under 6 months is not feasible for a conventional drug (a chemical product with no special technical features and few manufacturing stages). Production transfers are costly and lengthy processes demanding significant levels of human and technical resources. The production process must effectively be ‘redeveloped’ to ensure that product B can be correctly produced using equipment previously used for product A. The settings of each machine must then be tested to ensure that product B is being produced to the required specifications (tablets of the right weight containing the right concentration of active ingredient, etc.). At the same time, a new quality benchmarking system has to be developed and implemented (production procedures, batch record file, analysis file, etc.), additional equipment has to be purchased and operators trained, etc. => As a result, the manufacturing lead time (including all necessary quality controls) for ampoules of the neuromuscular blocking agents essential in resuscitation units, is between six weeks and two months for companies that are already manufacturing these drugs.
- Requisitioning existing stocks of drugs and medical equipment and/or their production resources could aggravate the situation by increasing shortages:
  1. In practical terms, countries are interdependent in terms of their supplies of drugs.
  2. So responding to an emergency by requisitioning facility A, which manufactures drugs for pharmaceutical company X, could have a knock-on effect on facilities elsewhere in the world, and create shortages of other molecules if every country in Europe and in the wider world begins to requisition manufacturing resources.

3. France cannot meet its own requirement for drugs alone, and depends on supplies of drugs manufactured in third countries. So what would then happen if all other countries began requisitioning their production facilities?
- Our manufacturing facilities are already operating very stretched workflows to ensure continuity of pharmaceutical products for French patients, especially those suffering from serious chronic diseases requiring ongoing treatment.

### **What are pharmaceutical companies doing to prevent shortages of drugs?**

- Our companies are doing everything in their power to maintain supplies to hospitals.
- Despite the self-isolation measures introduced, production continues in facilities where our 43,000 people remain hard at work every day in full compliance with health safety rules to ensure that all inpatients and outpatients continue to receive full access to the drugs essential to their wellbeing.
- In their response to the Covid-19 crisis and the sudden dramatic increase in global demand, especially for products essential for resuscitation units and the treatment of infectious diseases, pharmaceutical companies have put in place a number of measures to secure the production and supply of medicinal products of major therapeutic interest:
  1. Working closely with the ANSM, they are continually monitoring situation as it evolves, and are in daily discussion with the health authorities to provide them with visibility of their stock levels and supply capacities. Responsible pharmacists belonging to pharmaceutical companies are maintaining daily contact with the ANSM.
  2. Companies themselves are considering every possible alternative to ensure continuity of drug supplies:
    - Ordering quota systems have been introduced to regulate product flows and ensure a fair distribution of pharmaceuticals nationally as the pandemic spreads.
    - Major pharmaceuticals groups are able to draw on international stocks, but they are having to do so in the context of global scarcity and countries that have imposed exports restrictions on drugs
    - Employees at some manufacturing facilities have stepped in to expand teams or replace unwell team members as part of ensuring that production continues.
- Sourcing the protective masks needed to comply with the quality and safety standards that apply to the manufacture of pharmaceuticals.
- To relieve congestion in hospitals, measures are also in place to work alongside healthcare professionals to move chemotherapy patients onto oral therapies to avoid the need for them to attend hospitals.

## **The impact of Covid-19 on production**

### **What impact is the lockdown and self-isolation measures having on production? Can you quantify the resulting loss in business terms?**

- It is impossible to give a precise figure for the loss of business the industry is now suffering.
- Some facilities have lost business in certain areas due to staff self-isolating or falling ill.
- They are having to cope with increased numbers of employees off work, largely as a result of childcare issues.
- Other facilities, which are producing round-the-clock in 3X8 shift patterns 7 days a week in response to the priority needs for Covid-19 treatment, have structured their operations to maintain or even increase production volumes.
- In order to be in a position to guarantee continuity of supply and boost production capacity, pharmaceutical companies are waiting for the industry to be recognised officially by the government as an industry essential for national security and the continuity of economic and social life. Receiving this recognition will enable them to gain exemption from the maximum and weekly periods introduced by the order of 25 March.

### **How are the lockdown and self-isolation impacting on the availability of other drugs (excluding those used to treat coronavirus)?**

- Pharmaceutical companies are continuing to meet their obligations to supply the market appropriately and continuously. They are ensuring the highest-possible level of production continuity to achieve this goal.
- Pharmaceutical companies have put in place business continuity plans and, in some cases, have had to adapt their production to prioritise the availability of medicinal products of major therapeutic interest.

## **Solutions to ensure continuity of supply**

### **What measures are being put in place to ensure a continuous supply of drugs essential for treating Coronavirus?**

- All solutions are possible:
  - Avoid wasting these drugs. Introduce guidelines for economising on products. Avoid over-prescription. SFAR (the French Society of Anesthesia & Intensive Care Medicine) has issued recommendations.
  - Identify possible reserve stocks that remain unused in some hospitals, while other healthcare facilities are struggling to meet demand.
  - Identify therapeutic alternatives wherever possible.
  - Be prepared to import wherever possible, including those drugs not initially intended for France.
  - Use veterinary drugs by adapting their formulation under the supervision of health authorities.

- There is no single solution, but many different solutions within the very realistic approach now being taken by companies on a daily basis.

### **Is it not the case that you were required by law to build up safety stocks?**

- As part of their shortage management plans, companies are already building up safety stocks to cope with possible increases in demand and prevent risk of shortages.
- The obligations to build up safety stocks have been tightened in the 2020 Social Security Finance Act, which now requires companies to build up security stocks for all their products. The duration of these stocks, which will vary from product to product, must be set out in a future decree.
- Pharmaceutical companies are complying with the legislation. They already have safety stocks in place for the drugs they manufacture, but the pandemic is imposing major strains on these stocks at global level.

### **Have you built up sufficiently large safety stocks?**

- Safety stocks are being built up for all drugs, but not in proportion to the level of demand that is being driven by this Coronavirus pandemic.
- No company had planned for the need to meet orders for certain drugs that have increased by a factor of 100, 1,000 or even 2,000 in some cases!

### **How are you working with the health authorities? What guidelines have you been given by the Ministries for Health and the Economy in terms of building up stockpiles, real-time information on stockouts, governmental orders for vital drugs, etc.?**

- Leem is in permanent contact with our health authorities, and has responded to their request for information gathered from pharmaceutical companies regarding the origins of raw materials and the risks associated with the period of quarantine imposed on production facilities around the world.
- Representatives of the healthcare industries, including Leem, took part in a status update phone conference on 18 and 27 March with Agnès Pannier-Runacher, Secretary of State to the Minister for the Economy and Finance. Very regular meetings are also being held with the health authorities (DGS (the Directorate General for Health), ANSM, etc.).
- Leem President Frédéric Collet acknowledged that our companies have a very special responsibility in the context of the crisis, given their missions to ensure the ongoing supply of drugs, develop therapeutic solutions to combat Covid-19, maintain manufacturing operations in their French production facilities (ensuring the presence of personnel and their personal protective equipment), and lastly to ensure that drugs are being used correctly and appropriately.
- He stressed the need for State support and communication to keep production facilities in operation with committed staff.

- Short-term supply pressures have been notified to the ANSM, and measures are currently being put in place in consultation with the authorities to ensure continuity of supply in the short- to medium-term
- Our members are continually monitoring their supply chains and working hard to identify risks and the measures that need to be implemented in order to ensure security of supplies throughout France.

### **Does France have a working group of public authorities, health authorities and pharmaceutical companies dedicated specifically to shortages?**

- Yes, in September 2019, the Ministry set up a steering committee on stockouts, with members representing all stakeholders: healthcare professionals, non-profit organisations, authorities and manufacturing and distribution companies.
- In the context of Covid-19, many meetings are held between the pharmaceutical companies represented and the relevant authorities.

### **Does France conduct an ongoing survey of drug shortages?**

- That function is provided by the ANSM, which carries out collective detailed monitoring of all drug supply pressures and shortages. These data are not made public.

### **What proposals does Leem have for combating shortages of drugs?**

- Leem initiated detailed work on stockouts as early as 2018, and established it as a measure of the Strategic Council for the Healthcare Industries (CSIS 2018). It has also developed an action plan shared with all manufacturers to reduce discontinuities in the supply of those drugs most essential for patients. This plan has been built around 6 operational priorities:
  1. Uprating requirements for securing medicinal products of strategic importance to health (MISS).
  2. Reviewing the mechanisms used by hospitals to invite tenders for medicinal products of strategic importance to health (MISS) and reviewing the economic operating conditions for retail pharmacies.
  3. Promoting the location in Europe of production facilities for active raw materials and medicinal products of strategic importance to health (MISS);
  4. Optimising information sharing between drug supply chain stakeholders and patients;
  5. Adapting the distribution supervision in response to supply pressures and/or shortages;
  6. Improving strategic guidance at national level and working to harmonise regulatory practices across Europe.

## **Relocation**

### **How do you plan to relocate your active ingredient production plants to France and the wider Europe? Within what timeline?**

- Relocating active ingredients is one of many solutions to be considered as part of ensuring the healthcare and strategic independence of Europe in terms of pharmaceuticals, but it is clearly impossible to relocate all production facilities.
- As a priority, our efforts must be focused on the most essential drugs, as recommended by Leem in its February 2019 action plan (<https://www.leem.org/presse/penuries-de-medicaments-le-leem-presente-son-plan-dactions-en-6-axes-pour-prevenir-et-mieux>).
- It will take several years to complete such a process, given the time needed to schedule and transfer production on an industrial scale, verify the stability of drugs produced in the new facility, and obtain authorisation to carry out such a transfer from the competent regulatory authorities.

### **Have you drawn up a list of those drugs/medicinal products where all or part of manufacture is dependent on countries outside Europe, and especially China? How many drugs does that apply to? What type of drugs are they?**

- Updating and communicating this information is under the control of ANSM and DGS.
- Also, the majority of speciality products do not depend exclusively on China, and back-up solutions have been identified or are already in place.

### **Have you drawn up a list of those drugs/medicinal products for which production should be repatriated to France as a priority?**

- It remains the responsibility of each company to identify the list of drugs for which healthcare independence should be established.
- There are no industry-wide plans to compile such a list.
- It is highly likely that this issue will be addressed by the public authorities in consultation with manufacturers once the Covid-19 crisis has passed.



## **Impact on prices**

### **Is it possible that supply pressures on ingredients manufactured outside France could increase the price of certain drugs?**

- Given the current context, it is possible that we may see price increases for certain ingredients.
- If they do become a reality, these increases would inevitably result in higher prices for the drugs concerned.

### **Could such an increase feed through into drug pricing in France?**

- In France, the price of medicines sold through retail pharmacies and the prices of innovative drugs used in hospitals are set by the State.
- The majority of drugs used in resuscitation units during the COVID-19 pandemic are mature and inexpensive products, whose prices are negotiated through hospital tendering and contracting processes.
- The supply of drugs essential to meet the needs of healthcare professionals is the primary concern for pharmaceutical companies, and remains far more important than price considerations.

## Key figures for drug manufacture in France

- 271 manufacturing facilities in France
- 32 biomanufacturing facilities in France
- 80% of French manufacturing is concentrated in chemical-based drugs
- The family of production staff includes **42,718 employees**, which equates to 43% of the total pharmaceutical industry workforce
- 22% of reimbursable drugs are produced in France
- 50% of non-reimbursable drugs are produced in France
- 30% of generics are produced in France
- 27% of vaccines are produced in France
- 17% of the main drugs used in hospitals are produced in France
- 3% of monoclonal antibodies are produced in France