"Medicinal products: Stock-outs and supply disruptions"
A multi-faceted problem which has various causes and multiple solutions

Recommendations

For several years, medicinal product shortages and supply disruptions have been on the rise, and the phenomenon seems to be increasing at different stages of the “supply chain”, both in France and in the rest of the world.

- 14%\(^1\) of medicinal product stock-outs are caused by supply problems concerning raw materials for pharmaceutical use;
- 60-80%\(^2\) of active pharmaceutical substances are manufactured in countries outside the European Union, mainly in India and Asia, compared with 20% thirty years ago.
- Europe's almost complete loss of independence in terms of sources of supply of active pharmaceutical substances will lead to an eventual loss of corresponding industrial know-how.

The stock-outs are largely caused by world economic factors, leading to either the medicinal products being unavailable from the manufacturer (stock-out) or a disruption in the supply chain, making it temporarily impossible for the community or hospital pharmacist to obtain the product and dispense it to the patient (supply disruption).

On a daily basis, all of the players in the medicinal product chain pursue the short-term goal of making the medicinal product available to the pharmacist again as soon as possible. In the case of a prolonged stock-out, or if it is absolutely necessary for a patient to have the medicinal product, the public authorities take the appropriate measures to limit the consequences of this shortage of the medicinal product, including providing advice on similar medicinal products which could be used as a substitute. However, given the scale of the phenomenon, in order to mitigate the effects of these shortages, stock-outs and supply disruptions, appropriate responses should be collectively sought.

\(^{1}\) A review of FDA’s approach to medical product shortages, October 2011.
To this end, it is firstly important to identify the various causes and to consider appropriate solutions for each cause, even if in some cases they are multiple:

- shortages or discontinued production of certain active substances which are still used in public health and stock-outs and supply disruptions due to quality defects of the imported raw materials;
- medicinal product shortages due to the discontinued production of certain pharmaceutical formulations with low profitability;
- medicinal product stock-outs due to manufacturing quality defects, to the manufacturing policy in particular for certain medicinal product formulations or to the management policy of industrial stocks;
- supply disruptions associated with the distribution network;
- difficulties associated with the public procurement system (hospitals);
- shortages of specific medicinal products (orphan, paediatric, radiopharmaceutical medicinal products);
- specific difficulties encountered at community pharmacy level.

This is a major public health issue.

The French National Academy of Pharmacy [Académie nationale de pharmacie], was first to raise awareness of the quality of pharmaceutical raw materials* in June 2011. It has analysed all of these factors in order to make proposals, according to each of the problems identified, which are likely to provide practical solutions both in the short and long term, in France and across Europe.


1- ACTIVE PHARMACEUTICAL SUBSTANCES

STOCK-OUTS AND SUPPLY DISRUPTIONS DUE TO SHORTAGES OR DISCONTINUED PRODUCTION OF CERTAIN ACTIVE SUBSTANCES

In the long term, the production cost differential between third countries and Europe will reduce, given the social aspirations of third country citizens, the progression of their standard of living and the development of ecological values in these countries, as they follow the example of Europe. However, there is still an industrial base for fine chemicals for pharmaceuticals in Europe, although the industry is struggling, as it has to deal with environmental standards which are incommensurate with those imposed on third country operators. Nevertheless, although this industrial base, which is the outcome of the gradual sale by major European pharmaceutical companies of their fine chemicals industry, is highly fragmented due to the rising number of SMEs on the market, European SMEs could regain their competitiveness, even if their fixed costs, mainly because of the impact of social and environmental regulations (e.g. REACH, DREAL), are currently higher than those of firms operating in third countries. **There is an urgent need to undertake a proactive policy to relocate the manufacturing of active pharmaceutical substances which are considered to be strategic in the public health protection plan.**
STOCK-OUTS AND SUPPLY DISRUPTIONS DUE TO QUALITY DEFECTS OF THE IMPORTED RAW MATERIALS

In order to guarantee the quality of raw materials imported into the European Union, Directive 2011/62/EU\(^3\) delegates to the Authorities of the exporting countries, as of July 2013, the responsibility of drawing up a written confirmation confirming that each substance imported into the European Union conforms to European quality standards and that each manufacturing site is regularly inspected by these Authorities, unless the substance is imported from a country on the European Commission’s "white list", whose manufacturing standards are recognised as being at least equivalent to those of the European Union. For these Authorities, this delegation includes, in particular, being fully assured of the feasibility of meeting these commitments, in view of the associated costs for these States, bearing in mind that this includes for China alone more than 5000\(^4\) sites, without counting sub-contractors of specific synthesis stages, and that local export subsidies are granted in different forms by certain regions of third countries in order to promote their local industry, especially in India.

The production risks arising from false written confirmations or corruption when drawing up or distributing false written confirmations in order to facilitate import into the European Union should not be underestimated. The US federal authorities were aware of the inability, without additional means, of coping with controlling the considerable increase of suppliers from Asia, India or other third countries, and adopted a pragmatic solution within the framework of the “Generic Drug User Fee Act, GDUFA” − FDA/USA. This legislation came into effect on 1 October 2012 and focuses on three main objectives: safety, accessibility and transparency, with the aim of both protecting the quality of the active substances and making the sources of supply of raw materials used in generic medicinal products more reliable. It requires companies which manufacture active pharmaceutical substances which are already in the public domain to submit a declaration for importing active substances manufactured in a third country and to pay an annual fee in an amount which allows for regular inspection of their manufacturing site by agents of the Food and Drug Administration (FDA). The payment of a fee for filing a US DMF application relating to these active substances is also covered by the GDUFA. Products and raw materials which are considered to be falsely labelled or for which a declaration has not been submitted (from a manufacturing site or an inspection site) are denied entry into the USA.

RAW MATERIALS: The French National Academy of Pharmacy recommends:

1. creating a list of active substances already in the public domain, the shortage of which could cause public health problems, by focussing specifically on active substances from therapeutic classes such as antibiotics, anti-cancer drugs, anaesthetics, anticoagulants, immunoglobulins, and on active substances which are essential for emergency treatment (e.g. antidotes, heparins);

\(^3\) Directive 2011/62/EU of the European Parliament and of the Council imposes an obligation to declare, from the 2 July 2013, the importation of active pharmaceutical substances from third countries.

\(^4\) Chamber of commerce for import and export of medicine and health products, source reworked by the French General Inspectorate of Social Affairs (IGAS) (report RM2012-115 P annex 2 on raw materials for pharmaceutical use).
2. getting the French National Authority for Health (HAS) and the National Agency for the Safety of Medicine and Health Products (ANSM) involved in producing a list of active substances which are essential to public health and which should be closely monitored in order to ensure their availability;

3. in accordance with these lists, drawing up an inventory of risks and opportunities, with the fine chemicals manufacturers and the relevant pharmaceutical companies, in order to define a long term relocation policy, specifically for those active substances for which a single global manufacturer has been identified;

4. following an investigation carried out by the MHRA on behalf of the group of European Agency leaders, institutionalising the creation of a European data directory, shared by the relevant European Authorities, listing all of the sites where active substances for pharmaceutical use are manufactured, as well as the inspection sites, including a history of events (supply disruptions and a description of the causes, type of inspection carried out and the Inspection Authorities, certificates obtained) by making it compulsory for site declarations to be kept up-to-date by the marketing authorisation holders, and in France, by the pharmaceutical distribution companies;

5. for active substances which are already in the public domain, making it possible for European marketing authorisation holders to access part of this directory so that they can verify the credibility of the source of supply;

6. establishing, at the level of European Authorities, in conjunction with interested parties, periodic reports on the risks of shortages and relocation requirements by identifying the economic measures which makes these relocations viable for obtaining sources in close proximity, taking into account, in the economic estimates, the full energy savings in terms of a sustainable economy;

7. establishing, at European level, legislation similar to that imposed by the the US Generic Drug User Fee Act in order to allow the Supervisory Authorities (EMA and the network of Member State Supervisory Agencies) to provide sufficient means so that the inspection bodies can carry out inspections of the manufacturing sites for active substances which are declared as imports into Europe, in the same way as they would for those sites which are located in Europe.

2. MEDICINAL PRODUCTS:

Certain pharmaceutical formulations have been discontinued due to low profitability

There are no European provisions relating to product withdrawal, comparable to the provisions of Article L.5124-6 of the French Public Health Code, for centrally authorised medicinal products, and the European Medicines Agency (EMA), in its reflection paper on medicinal product supply shortages caused by compliance problems only mentions maintaining a public catalogue of medicinal product shortages where marketing authorisation holders report "temporary" shortages caused by quality defects on a voluntary basis. Similarly, there are no provisions for cases where

---

production of certain expensive pharmaceutical formulations, such as injectable formulations which are essential in hospitals (e.g. some types of antibiotics or anti-cancer drugs) is stopped. Moreover, the current regulatory framework does not make it easy to reactively add a new source of supply for active pharmaceutical substances or an alternative medicinal product manufacturing site to the marketing authorisation dossier if there is a sudden failure on the part of the distributor. Finally, a number of medicinal products require the use, when being administered to a patient, of autonomous, non-standard medical devices (captive market), which prevents other therapeutic alternatives being used when these fail.

**Legislation on the distribution network needs to be adapted**

French pharmaceutical distribution involves major domestic and multi-regional players and dozens of micro-companies which are generally located at a single-site. The operating rules for this sector remain as those defined in the framework of a 1962 decree, which has only been updated on a very small scale on three occasions, with obligations to achieve specific results which no longer correspond to current requirements. In fact, there is a whole variety of health products nowadays (generic, biotechnological medicinal products, medicinal products with short-term stability). Products available on the domestic market are "just-in-time", and European supply is still lucrative and can determine the economic viability of certain operators. **The sector accounts for over 70% of supply to pharmacies in terms of volume, and just 1% of supply to health care establishments.** The number of product references to manage (more than 30,000, of which 10,000 are medicinal products) has increased significantly with the development of generic medicinal products. Even if the intervention of distributors enables them to divide by three the number of stock-outs and supply disruptions they suffer, their contribution to solving the problem should be optimised.

**MEDICINAL PRODUCTS:** The French National Academy of Pharmacy recommends:

1. establishing **European provisions comparable to the provisions of Article L.5124-6 of the French Public Health Code** for centrally authorised medicinal products which are freely marketed in France;

2. leaving it up to national authorities to define **the sensitivity for public health prior to any cessation** of the marketing of a medicinal product or a pharmaceutical form of a given medicinal product;

3. when the cessation of marketing has been assessed by the national authorities, **considering revaluing the price**, or, if the cessation of marketing is unavoidable, developing and raising awareness of a system which facilitates transfers to those industrial players for whom a formulation or a medicinal product, with its full range of products, would still remain **profitable**; organising in France, regardless of profitability, the transfer of production to a public pharmaceutical company (pharmaceutical business) such as the French General Agency for Health Products and Equipment (AGEPS);

4. **questioning the usefulness of requiring that from now on, wholesale distributors have to own**
all stocks;

5. reconsidering, with the wholesale distributors and all other players in the distribution chain, without exception, the current obligations defined in article R.5124-59 of the French Public Health Code “to satisfy at all times the consumption of regular customers, during a period of at least two weeks” in order to verify the relevance by type of medicinal product;

6. establishing for wholesale distributors, instead of the current best effort obligations, obligations to achieve specific results according to the service categories to be established by type of medicinal product (e.g.: cold medicinal products requiring a short, protected distribution network, seasonal medicinal products, medicinal products for rare diseases, whose patients are geographically widely dispersed etc.);

7. applying these obligations to achieve specific results to all distributors, without exception;

8. prohibiting the parallel exporting of a stock of medicinal products at regulated prices which matches the stock needed for national requirements for medicinal products which don't have therapeutic equivalents, by considering this stock as pre-empted by the authorities in charge of public health and the paying agencies, for the benefit of patients and insured parties.

THESE SPECIFIC

STOCK-OUTS AND SUPPLY DISRUPTIONS ASSOCIATED WITH THE PUBLIC PROCUREMENT SYSTEM (Hospital, Army, national anti-epidemic plans and other plans, Health Emergency Preparedness and Response Agency (EPRUS))

The progressive increase in the size of the public procurement market, due to the emergence of procurement operations spanning several French hospitals, has resulted in increasingly higher levels of orders, and with it, increasingly higher risk levels in terms of failure on the part of the distributor. This phenomenon has repercussions on the reliability of the market, notwithstanding the fact that, in this crisis period, the grouping together of these hospitals aims to lower prices and costs and to obtain attractive prices for the hospitals. These levels of public procurement can therefore cause market disruption by causing a sudden increase or decrease in the volumes manufactured and sold which is incompatible with the industrial processes, as they can only take a long-term view and require transparency in order to ensure fluid supply.

PUBLIC PROCUREMENT: The French National Academy of Pharmacy recommends:

1. reflection at public authority level in order to avoid an outbreak of extremely large public procurements, which could lead to market disruption and serious supply disruptions for public health;

2. including, in the analysis criteria for public procurement, the security of supply, by requiring that the candidate provides a description of the means they have adopted in order to reduce the risks of stock-outs and disruptions, and take this into account when evaluating the tenders;

3. including clauses on total quality in the public procurement criteria (including the
economic, social and environmental conditions of the countries producing the active pharmaceutical substances;

4. **encouraging marketing authorisation holders to be proactive**, *vis-à-vis* hospital buyers and hospital co-ordinators, in order to facilitate transparency regarding dates or periods when normality will be resumed in terms of deliveries;

5. **promoting the creation of a French National Agency for the Safety of Medicine and Health Products database** which hospital buyers can easily access and consult, according to criteria to be defined with the buyers and including more comprehensive information than that which is currently on the public site; facilitating contact with pharmaceutical companies which can swiftly compensate for the failure of a marketing authorisation holder.

**HOSPITAL SUPPLY DISRUPTIONS**

Regardless of the situations described above, which mainly affect hospital facilities, the hospital is required to treat many paediatric or orphan diseases requiring medicinal products whose active substances are consequently orphans themselves. The treatment of these orphan diseases or dosage adjustments, for example in the case of paediatrics, may quite regularly require compound and hospital pharmacy preparations, for which it is often difficult to obtain the required pharmaceutical-grade raw materials. It is also important to note the specific problem associated with the supply of raw radio-pharmaceutical materials whose production at national, European and global level, occurs through nuclear reactors, and poses increasingly worrying problems in the context of calling nuclear power into question.

**HOSPITAL: The French National Academy of Pharmacy recommends:**

1. **specific reflection on dealing with orphan diseases** requiring pharmaceutical-grade active substances;

2. **encouraging domestic and European production** of these active substances even within the framework of the niche market of orphan diseases;

3. **facilitating the provision to hospital pharmacies of pharmaceutical-grade raw materials** required for preparations which are prepared there, in particular, by encouraging pharmaceutical industries to provide them with the active substances which are available to them or by promoting public structures that can ensure the supply of pharmaceutical-grade active substances;

4. **facilitating the access of hospital pharmacies, on behalf of manufacturers, to data on the quality and stability of active substances** so that they can ensure the quality of hospital preparations which include these active substances; considering, along with nuclear medicine specialists and radiopharmacists, the future of the production of radioisotopes for medical purposes.

**MEDICINAL PRODUCTS MISSING FROM COMMUNITY PHARMACIES**

Managing medicinal product shortages and supply disruptions is a daily reality for community pharmacists. They are the final link in the pharmaceuticals chain and they know that any break in treatment, even if it is only for a very short time, can have serious effects on the health of patients.

- **80% of community pharmacy medicinal products are purchased through wholesale**
• Each day, 5% of medicinal products which are ordered are out of stock.
• 50% of stock-outs exceed the authorised four day limit.

These stock-outs combine all the causes, manufacturer stock-outs or market stress (including parallel exporting) in the distribution chain. However, the community pharmacist has to deal with a lack of information since only manufacturer/distributor of medicinal product stock-outs which do not have a therapeutic alternative are the object of a declaration and information on the website of the French National Agency for the Safety of Medicine and Health Products.

Yet, the community pharmacist cannot modify the dispensing of a medicinal product given that it is often difficult, or impossible, to contact the prescriber, depending on the day and time, or the hospital wards. An exceptional import system for redressing the shortages is authorised, but it is not only unfamiliar, or even unknown to community pharmacies and even hospital pharmacists, but moreover, the system of funding through social insurance does not allow the outpatient's usual community pharmacist to dispense the medicinal product, which means that often the patient has to go to the hospital pharmacy himself, as the medicinal product can only be obtained and dispensed by it (imported medicinal products are included on the list of medicinal products which can be dispensed directly to outpatients) during the entire stock-out period.

This is why, if stock-outs occur, Quebec in particular has just granted, in relation to medicinal products, the right to substitute treatments within therapeutic classes, under the control of professional guides, in order to respond to legitimate demand in terms of patient compliance.

COMMUNITY PHARMACY: The French National Academy of Pharmacy recommends:

1. For supply disruptions linked to local market stresses:
   • ensuring better visibility for pharmaceutical laboratory emergency telephone numbers to provide emergency solutions when the community pharmacist has been assured by the distribution agencies in the region that the medicinal product is unavailable;
   • promoting the implementation of a platform for exchanging information within pharmaceutical distribution and giving community pharmacists access to this platform so that they can identify which stocks are available.

2. For manufacturer stock-outs:
   • making available on the website of the French National Agency for the Safety of Medicine and Health Products, information that it is more easily accessible to prescribers and pharmacists;
   • establishing local exchange structures for doctors/pharmacists/health insurance providers to facilitate the flow of information to community doctors and pharmacists, to allow them to share the most appropriate alternative therapeutic solutions, for the benefit of patients, and also to encourage their further medical treatment in optimal quality conditions, without causing unnecessary expenditure in terms of health insurance;
• considering a dispensing model based on the Quebec model, with controlled back-up protocols for adapting medical treatments when stock-outs and supply disruptions occur;

• establishing an import and support system which allows community pharmacists to ensure the dispensing of medicinal products which are exceptionally and temporarily imported to compensate for shortages, with patient service in mind and continuity of care for patients treated as out-patients;

• organising the distribution network for medicinal products which are exceptionally and temporarily imported to compensate for a shortage in order to facilitate direct supply to the community pharmacist.