A warning signal about breaks in supplies of drugs!

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Background

95%[1] of the drugs sold through pharmacies are available on the same day in France, thanks to the quality and efficiency of the drug manufacturing and supply chain.

Nevertheless, the results of a Leem survey conducted by IPSOS earlier this year amongst 1,000 French people (the survey report can be downloaded from www.leem.org) highlight the concerns French people have about breaks in supply.

What French people think about this issue

Nearly a third of the French people interviewed by IPSOS in February this year as part of the Observatoire Sociétal du Médicament (French Societal Drug Observatory) survey published on 10 April identified breaks in supply at pharmacies as a threat to their health, after drug counterfeiting (83%), online sales of drugs (66%) and the geographic relocation of drug production (50%). 55% of those surveyed said that they had encountered supply problems in their pharmacy. However, this figure does not distinguish between a true break in supply and a simple late delivery to the pharmacy.

This perception is consistent with the latest reports[2] prepared by the ANSM (French National Agency for Medicines Safety) highlighting the consistently rising trend in actual and potential breaks in supply for vital products in recent years: 44 in 2008, 173 in 2012, and more than 200 in 2013.
A total of 324 stockouts and 103 potential breaks in the supply of vital and less vital drugs were recorded by the ANSM between September 2012 and October 2013.

To gain a clearer understanding of the extent of this issue, Leem conducted a survey between September 2012 and October 2013 amongst 90 pharmaceutical laboratories (originators, generics, vaccines, etc.) that had reported at least one break in supply to the ANSM. 51% of those laboratories responded, together representing 71% of breaks in supply.

This survey, which covered 180 of the 324 breaks in supply identified by the ANSM, revealed that:

- breaks in supply can vary between 0[3] and 398 days (13 months)
- the average break in supply is 94 days

[1] Académie nationale de pharmacie. 20 March 2013 meeting.
[2] Figures published by the ANSM. These figures refer to breaks in supply of a given drug. If we use the number of cases opened by the ANSM as the indicator, the number of breaks in supply rises to 467, since multiple cases can be opened for the same drug.
[3] 0 days where the laboratory concerned was able to anticipate the situation and manage residual stocks effectively until new stocks were supplied

This situation is difficult for patients, doctors and pharmacists to accept, because **any interruption to treatment, no matter how short, may have serious implications for patient health.**

Are these concerns justified? Will breaks in supply and 'shortages' become more commonplace? Who is responsible? Have solutions been implemented?

Here are some explanations to provide a clearer understanding of this issue.

Breaks in supply: what are we actually talking about?

If a particular drug is not available from the pharmacy, there is a ' break in supply'. But what exactly does that mean?

Breaks in supply are largely the result of global economic factors that lead

- either to a break in the availability of drugs at the manufacturer, which is referred to as **a stockout**
- or to a break in the supply chain, making it impossible for pharmacists to provide their patients with a particular drug at a particular time, which is referred to as **a break in supply**

In both cases, the consequence for the patient is the same: the prescribed drug is not **immediately** available.

A stockout occurs **upstream** in the drug manufacturing chain: either the drug cannot be manufactured, or the drug is manufactured, but has not complied fully with the required quality standards. It will not therefore be permitted to enter the supply chain.

A break in supply occurs **downstream** in the same chain: a manufactured drug cannot be supplied via all pharmacies.

Drug shortages, to adopt the term currently used to describe the non-availability of a drug, are the result both of stockouts upstream and breaks in supply downstream. In order to complete this overview, it should also be added that cessation of manufacture will inevitably cause a 'shortage' of a given drug, since it will no longer be manufactured. However, such cessations are planned in advance and organised in consultation with health authorities.

Why do stockouts occur?

Stockouts have many causes, nearly all of which are financial, beginning with the mass outsourcing of pharmaceutical raw materials production. Estimates suggest that between 60% and 80% of these raw materials[4] are now manufactured outside the European Union. 30 years ago, this proportion was 20%. According to EMA (the European Medicines Agency), China produces 52.9% of active pharmaceutical ingredients, followed by India (22.2%) and Israel (17.7%.)

[4] IGAS report. September 2013.

Proliferation and geographical remoteness of various production facilities extracting active ingredients, manufacturing or processing drugs and packaging products add considerable complexity to the process of controlling every link in the production chain, and inevitably accentuate the risks posed to the entire chain, which can be immobilised by a temporary problem in any one of these different facilities.

So the more fragmented the chain becomes, the greater the risk. And the slightest weakness in one of these many links is all it takes to bring the entire supply chain to a halt. In this way, a break in the supply of a single excipient can bring the entire production chain to a halt.

And nature can also get in the way!

Following the March 2011 earthquake and the Fukushima disaster, a hospital drug used to treat certain types of haemorrhage ran out. The reason was that it was produced using an active substance extracted from the eggs of salmon caught off the island of Honshu. The laboratory then had to find an alternative source of supply very quickly…

It is important to add that other factors can also have a negative impact on the entire production chain: increasing global demand for pharmaceutical products from emerging countries (which puts raw materials suppliers under pressure), production stoppages for financial reasons, and the concentration of drug production in just a few manufacturing facilities, and sometimes in only one.

Why are there breaks in supply?

"A break in the supply of a drug[5] *is defined as the inability of a dispensing pharmacy or a pharmacy internal to a healthcare facility or nursing home to dispense a drug to a patient within 72 hours*".

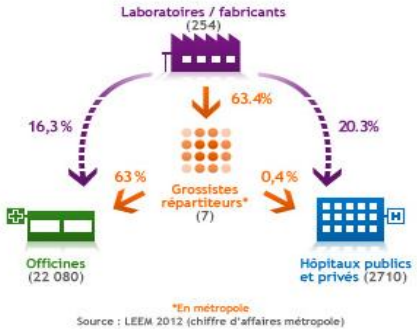
With 22,100 pharmacies and 224 manufacturing facilities, France could reasonably think itself immune from breaks in the supply of drugs. Five or six years ago, a break in supply was still a very marginal event, whether in dispensing pharmacies or hospital pharmacies.

A break in supplies is the result of a failure in one or more links of the supply chain, whether amongst drugs manufacturers, pharmaceutical warehousing, wholesale distributors or drug purchasing centres

According to statistics[6] published by the French health ministry, public and private hospitals purchase 95% of their drugs direct from manufacturers or their pharmaceutical warehouses on the basis of a tendering procedure governed by the public contracting code. The dispensing pharmacy supply chain is largely dependent on the wholesale distributors from which these pharmacies buy 80% of the drugs they dispense, as shown in the following diagram, which also gives a breakdown of sales made by the 254 manufacturers or laboratories located in France.

[5] This definition is taken from the decree of 28 September 2012 on breaks in supply.

[6] Figures available at http://www.sante.gouv.fr/rupture-d-approvisionnement-d-un-medicament.html



Laboratoires / fabricants	Laboratories / Manufacturers
Grossistes / répartiteurs	Wholesale distributors
Officines	Dispensing pharmacies
Hôpitaux publics et privés	Public and private hospitals
*En métropole	*In mainland France
Source : Leem 2012 (chiffre d'affaires métropole)	Source: Leem 2012 (sales figures from mainland France)

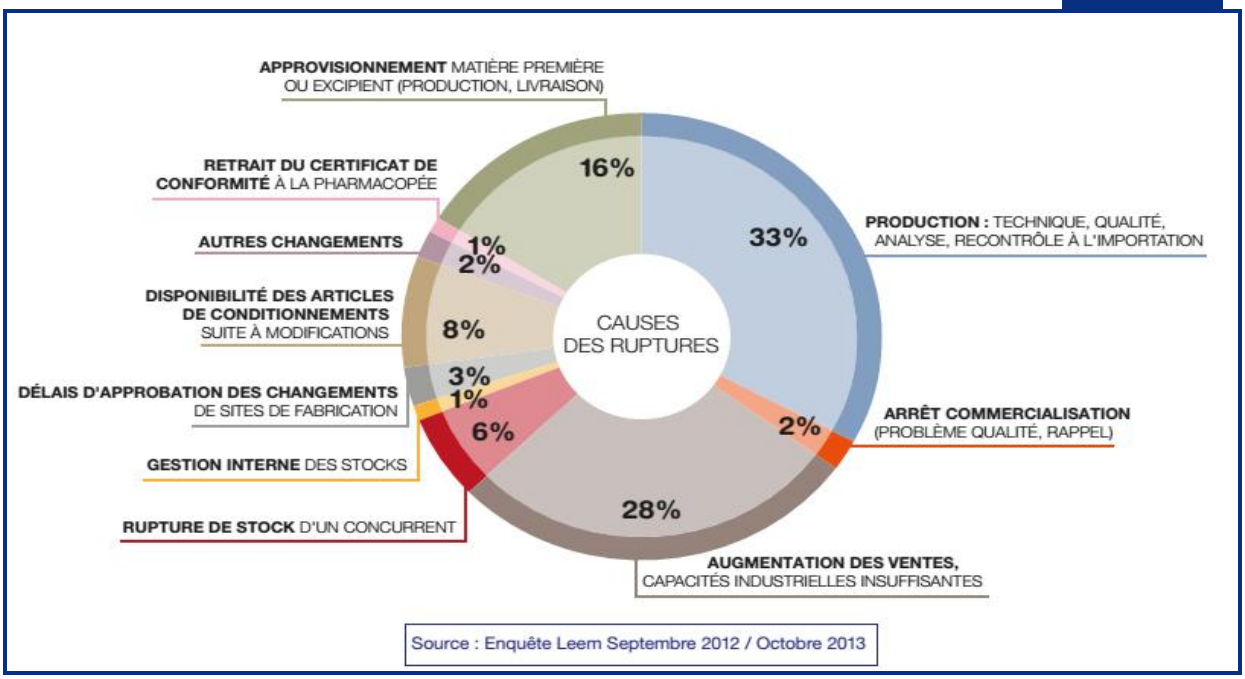
Wholesale distributors are legally required to maintain 15 days of stocks. Nevertheless, a scheduling error originating in one or more of their 181 centres throughout France may cause a break in a supply for a dispensing pharmacy. Breaks in supply can also be caused by parallel exports of drugs to countries where they are sold at a higher price.

The fact remains that patients have been used to a very French market for drugs in which they receive the treatment they need immediately. There is therefore a strong tendency for these patients to regard a simple late delivery or pharmacy ordering error as a break in supply.

What are the main causes of breaks in supply?

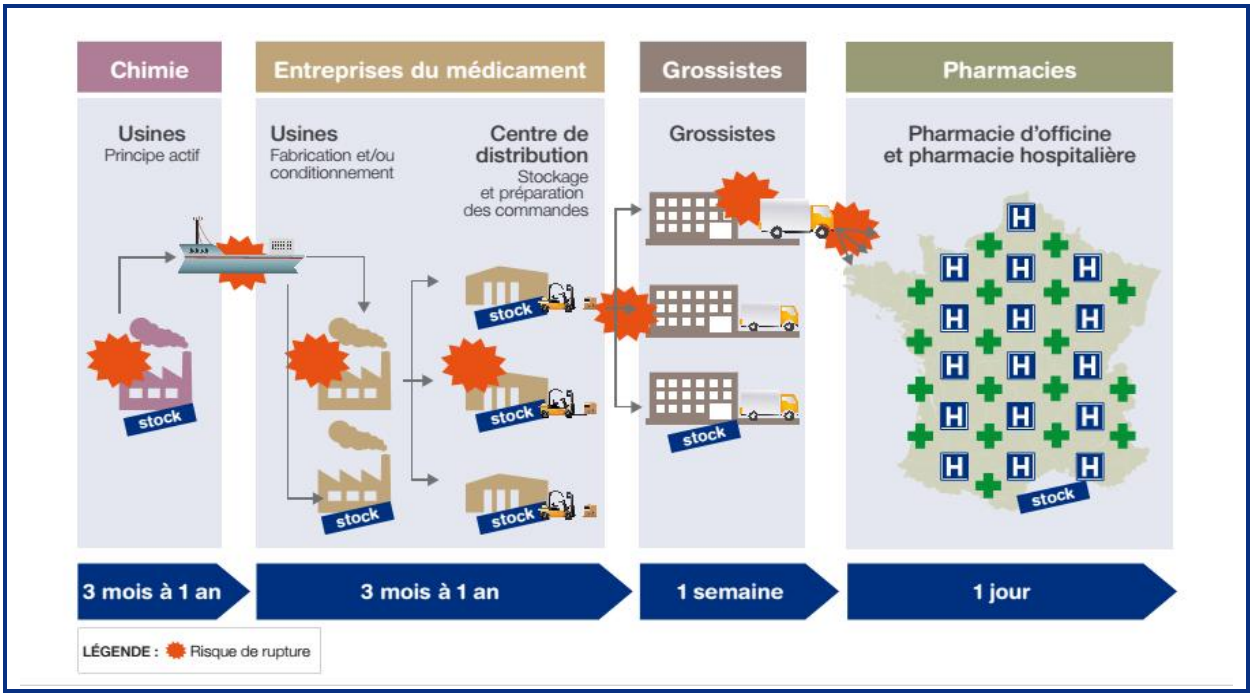
The Leem survey breaks down the causes of breaks in supply, creating a picture that confirms their multiplicity and heterogeneity.

Percentage breakdown of the causes for breaks in the supply of drugs.



APPROVISIONNEMENT EN MATIERE PREMIERE OU EXCIPIENT (PRODUCTION, LIVRAISON)	SUPPLY OF A RAW MATERIAL OR EXCIPIENT (PRODUCTION OR DELIVERY)
RETRAIT DU CERTIFICAT DE CONFORMITE A LA PHARMACOPEE	WITHDRAWAL OF A CERTIFICATE OF COMPLIANCE WITH THE PHARMACOPOEIA
AUTRES CHANGEMENTS	OTHER CHANGES
DISPONIBILITE DES ARTICLES DE CONDITIONNEMENT SUITE A MODIFICATIONS	PACKAGING AVAILABILITY FOLLOWING CHANGES
DELAIS D'APPROBATION DES CHANGEMENTS DE SITES DE FABRICATION	DELAYS IN APPROVING CHANGES OF MANUFACTURING LOCATION
GESTION INTERNE DES STOCKS	INTERNAL INVENTORY MANAGEMENT
RUPTURE DE STOCK D'UN CONCURRENT	COMPETITOR STOCKOUT
CAUSES DES RUPTURES	CAUSES OF BREAKS IN SUPPLY
PRODUCTION : TECHNIQUE, QUALITE, ANALYSE, RECONTROLE A L'IMPORTATION	PRODUCTION: TECHNICAL, QUALITY, ANALYSIS, IMPORT RE-INSPECTION
ARRET COMMERCIALISATION (PROBLEME QUALITE, RAPPEL)	SUSPENSION OF SALES (QUALITY ISSUES, RECALLS, ETC.)
AUGMENTATION DES VENTES, CAPACITES INDUSTRIELLES INSUFFISANTES	INCREASED SALES, INSUFFICIENT MANUFACTURING CAPACITY, ETC.
Source : Enquête Leem Septembre 2012 / octobre 2013	Source: Leem survey September 2012 / October 2013

The points in the chain where breaks in supply occur



Chimie	Chemicals
Entreprises du médicament	Pharamaceutical companies
Grossistes	Wholesalers
Pharmacies	Pharmacies
Usines	Production plants
Principe actif	Active ingredient
Fabrication et/ou conditionnement	Manufacture and/or packaging
Centre de distribution	Distribution centre
Stockage et préparation des commandes	Storage and order preparation
Grossistes	Wholesalers
Pharmacie d'officine et pharmacie hospitalière	Dispensing and hospital pharmacies
stock	stock
3 mois à 1 an	3 months to 1 year
1 semaine	1 week
1 jour	1 day
LEGENDE	LEGEND
Risque de rupture	Risk of break in supply

For stockouts:

- **Stockout point: active ingredient:**
  Raw materials are sometimes difficult to obtain for a variety of reasons:

  - ✓ production has failed temporarily
  - ✓ the materials available do not meet European quality standards

- ✓ the producing countries (chiefly China and India) are experiencing political, weather, financial or other difficulties preventing them from delivering the production volume required within the expected lead time
- ✓ There has been an unexpected increase in orders

- **Stockout point: drug manufacture**
  There is insufficient manufacturing capacity of the drug concerned:

  - ✓ The specialisation and globalisation of pharmaceutical production facilities may compromise continuity of supply in the market when manufacturing facilities fail to perform
  - ✓ Technical issues, quality failures, analysis delays, re-inspection at the point of import or the rejection of manufactured batches as a result of compliance failures have halted the manufacture, and therefore availability, of the drugs concerned
  - ✓ A smaller number of companies manufacturing the drug concerned (following company mergers, for example)
  - ✓ Some companies have ceased production of a product following a failure to comply with the quality requirements of regulatory authorities or for financial reasons

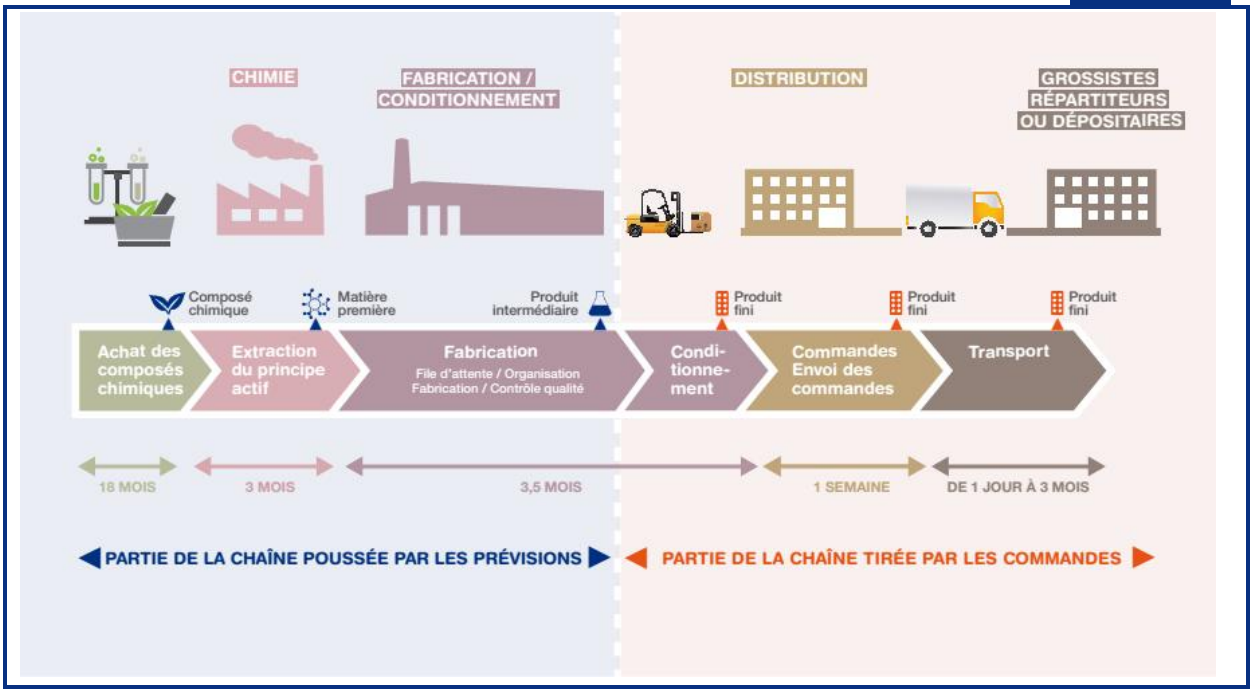
For breaks in supply:

- **Break in supply point: distribution**
  Some business practices have the potential to cause breaks in supply:

  - ✓ Limitations on the stock held by distributors with the aim of boosting efficiency through just-in-time management
  - ✓ Building up of safety stocks following the announcement of a potential break in supply or product price increase
  - ✓ Preferential distribution availability for destinations where prices are higher

  The increasing level of production complexity and the diversity of supply chain players increase the risk of breaks in supply and the likelihood of destabilisation in the supply chain as it is currently structured.

  To these factors should be added the **'zero fault'** requirement that governs the drugs supply chain. A quality failure in one batch out of hundreds of thousands of packs may paralyse the drug production chain, given the lengthy response periods dictated by manufacturing processes. Sudden dramatic changes in consumption cannot always be covered by safety stocks. High-quality forecasting remains the key factor in drugs supply chain scheduling.



CHIMIE	CHEMICALS
FABRICATION / CONDITIONNEMENT	MANUFACTURE / PACKAGING
DISTRIBUTION	DISTRIBUTION
GROSSISTES REPARTITEURS OU DEPOSITAIRES	WHOLESALE DISTRIBUTORS OR PHARMACEUTICAL WAREHOUSES
Composé chimique	Chemical compound
Matière première	Raw material
Produit intermédiaire	Intermediate product
Produit fini	Finished product
Achat des composés chimiques	Chemical compound purchasing
Extraction du principe actif	Active ingredient extraction
Fabrication	Manufacture
File d'attente / Organisation / Fabrication / Contrôle qualité	Queue / Organisation / Manufacture / Quality control
Conditionnement	Packaging
Commandes	Orders
Envoi des commandes	Order shipping
Transport	Transport
18 MOIS	18 MONTHS
3 MOIS	3 MONTHS
3,5 MOIS	3.5 MONTHS
1 SEMAINE	1 WEEK
DE 1 JOUR A 3 MOIS	1 DAY - 3 MONTHS
PARTIE DE LA CHAINE POUSSEE PAR LES PREVISIONS	FORECAST-DRIVEN PART OF THE CHAIN
PARTIE DE LA CHAINE TIREE PAR LES COMMANDES	ORDER-DRIVEN PART OF THE CHAIN

What regulatory provisions apply in the event of breaks in supply?

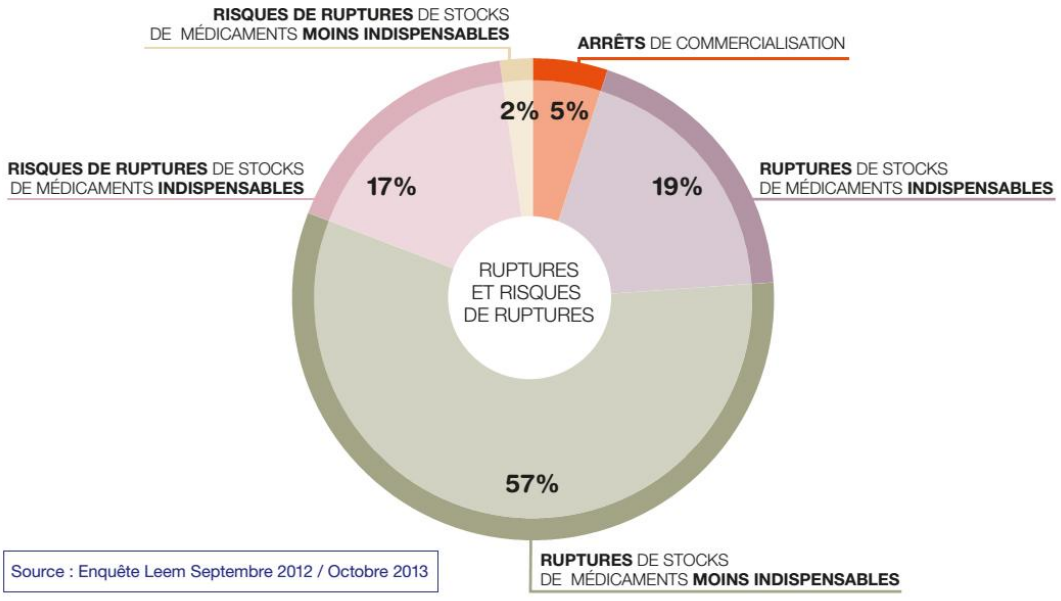
The decree governing the provision of drugs for human use published in the French Official Journal on 28 September 2012 recognises and strengthens the measures already put in place by pharmaceutical companies to manage actual or potential breaks in supply, such as:

- the introduction of an emergency call centre for dispensing pharmacists, hospital pharmacists and wholesale distribution managers
- the obligation to inform the ANSM of a potential break in supply or to remedy an actual break in supply
- emergency response

All these practices have helped to secure the drug supply chain, especially for those drugs delivering major therapeutic benefits.

Which drugs have been affected by breaks in supply in France?

The Leem survey shows that 28% of the breaks in supply reported to the ANSM related to 'vital' drugs, whilst 72% related to less vital drugs, i.e. those whose temporary suspension is unlikely to pose a threat to life.



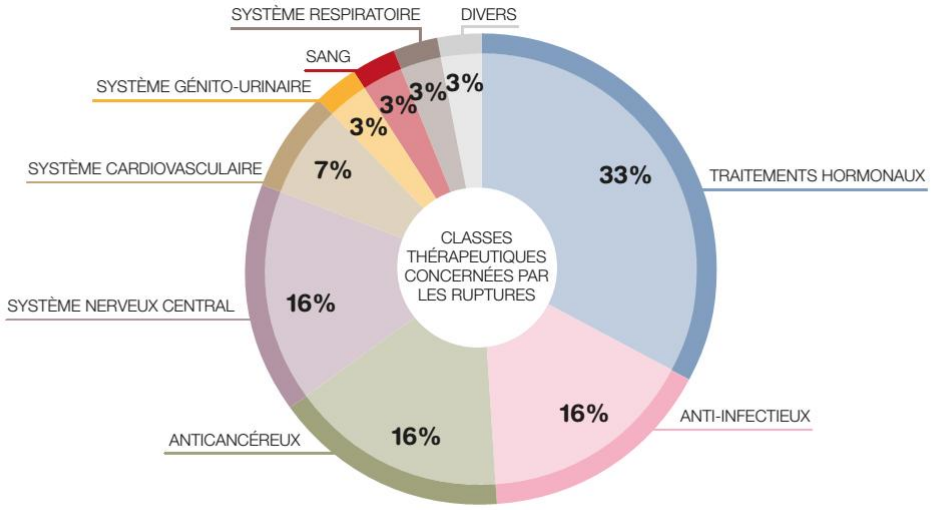
RISQUES DE RUPTURES DE STOCKS DE MEDICAMENTS MOINS INDISPENSABLES	RISKS OF STOCKOUTS FOR LESS VITAL DRUGS
RISQUES DE RUPTURES DE STOCKS DE MEDICAMENTS INDISPENSABLES	RISKS OF STOCKOUTS FOR VITAL DRUGS
ARRETS DE COMMERCIALISATION	SUSPENSION OF SALES
RUPTURES DE STOCKS DE MEDICAMENTS INDISPENSABLES	STOCKOUTS OF VITAL DRUGS
RUPTURES DE STOCKS DE MEDICAMENTS MOINS INDISPENSABLES	STOCKOUTS OF LESS VITAL DRUGS
RUPTURES ET RISQUES DE RUPTURES	ACTUAL AND POTENTIAL BREAKS IN SUPPLY
Source : Enquête Leem Septembre 2012 / octobre 2013	Source: Leem survey September 2012 / October 2013

What is a vital or essential drug?

In France, pharmaceutical companies maintain a list of drugs they consider to be vital, and that list is available to the authorities. Nevertheless, the government is currently working on a list of drugs described as having major therapeutic relevance.
This is actually more than a list, since it sets out the risk analysis criteria to be applied (seriousness of the illness concerned, evaluation of loss of chance for the patient, alternative treatment, target patient group, pharmaceutical form, etc.), all of which are important in the monitoring of drugs.

Are some therapeutic classes more affected than others?

The Leem survey reveals that all classes of drugs are potentially affected. Those administered orally or injected are most frequently at risk of breaks in supply, but these are also the most common drugs in the therapeutic arsenal for the treatment of the most serious illnesses.

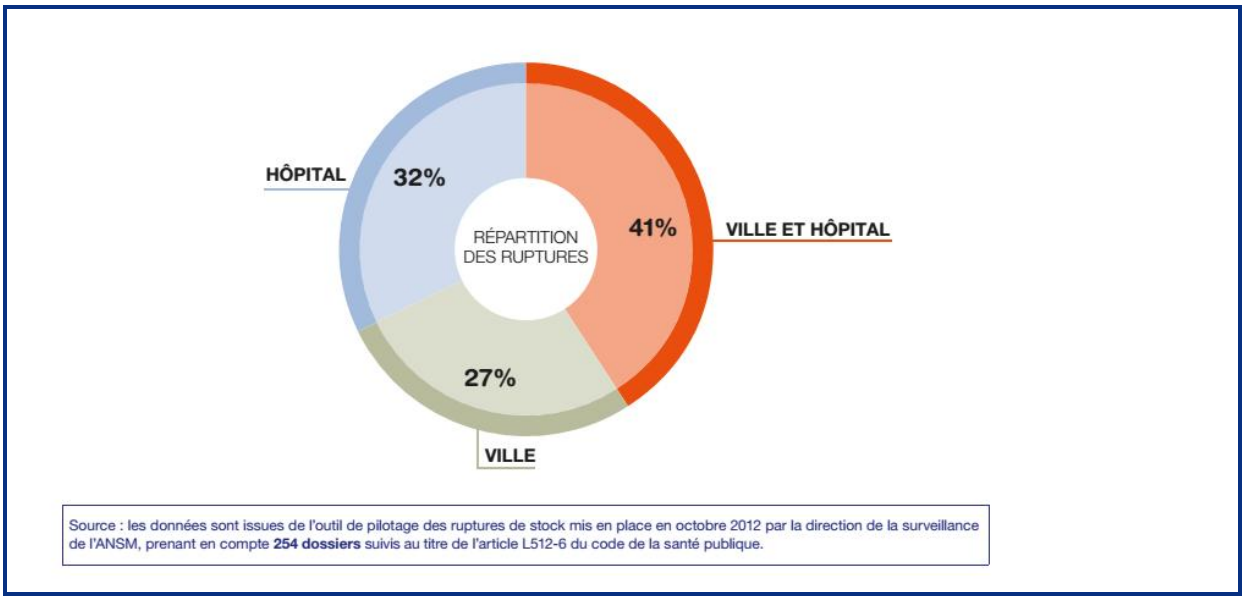


Source : Enquête Leem Septembre 2012 / Octobre 2013 portant sur les classes thérapeutiques des médicaments jugés comme indispensables par les laboratoires et ayant été en rupture de stock (148 déclarations).

SYSTEME RESPIRATOIRE	RESPIRATORY SYSTEM
SANG	BLOOD
SYSTEME GENITO URINAIRE	GENITO URINARY SYSTEM
SYSTEME CARDIOVASCULAIRE	CARDIOVASCULAR SYSTEM
SYSTEME NERVEUX CENTRAL	CENTRAL NERVOUS SYSTEM
ANTICANCEREUX	ANTI-CANCER
DIVERS	OTHER
TRAITEMENTS HORMONAUX	HORMONAL TREATMENTS
ANTI INFECTIEUX	ANTI-INFECTIVE
CLASSES THERAPEUTIQUES CONCERNEES PAR LES RUPTURES	THERAPEUTIC CLASSES AFFECTED BY BREAKS IN SUPPLY
Source : Enquête Leem Septembre 2012 / octobre 2013 portant sur les classes thérapeutiques des médicaments jugés comme indispensables par les laboratoires et ayant été en rupture de stock (148 déclarations)	Source: Leem survey September 2012 / October 2013 into the therapeutic classes of drugs deemed vital by laboratories and subject to breaks in supply (148 reports)

Are these problems worse for drugs dispensed in hospitals or those dispensed in local pharmacies?

According to the figures provided by the ANSM, breaks in supply affect drugs dispensed in hospitals (32%) slightly more than those dispensed through local dispensing pharmacies (27%). Naturally, breaks in supply can affect both types of pharmacy at the same time.



HOPITAL	HOSPITAL PHARMACIES
REPARTITION DES RUPTURES	BREAKDOWN OF BREAKS IN SUPPLY
VILLE ET HOPITAL	DISPENSING AND HOSPITAL PHARMACIES
VILLE	DISPENSING PHARMACIES
Source : les données sont issues de l'outil de pilotage des ruptures de stock mis en place en octobre 2012 par la direction de la surveillance de l'ANSM, prenant en compte 254 dossiers suivis au titre de l'article L512-6 du code de la santé publique	Source: these data originate in the stockout management system introduced in October 2012 by the ANSM monitoring department, and relate to 254 cases monitored in accordance with article L512-6 of the public health code

What is happening in other countries?

Breaks in supply occur worldwide, and all countries are affected.

Breaks in the supply of certain anti-cancer drugs are not confined to French centres: a survey whose results were presented to the American Society of Clinical Oncologists (ASCO) conference, and was conducted amongst 250 American oncologists and haematologists, showed that 80% of these doctors had experienced breaks in supply between March and September 2012.

In North America:

- The FDA[7] has compiled a list of 250 drugs that experienced breaks in supply during 2011: the resulting list showed an increase of 40% over the previous year. In addition to the increasing number of breaks in supply, it is the length of these breaks that is becoming a concern for healthcare professionals and patients on the other side of the Atlantic. The FDA estimates that the average break in supply for vital drugs is 105 days: more than 3 months.
- Even more of a concern is the fact that those drugs affected by breaks in supply are increasingly those identified as essential: according to one FDA survey, of 127 non-predictable breaks in supply between January 2010 and August 2011, 93% involved essential drugs, and 41% were both essential and came from a single source

[7] FDA: A review of FDA's approach in medical product shortages. October 2011

- Lastly, in 2008, the FDA indicated that 35% of all breaks in supply affected sterile injectable drugs. In 2009, this proportion had grown to 46%. In 2010, it was 74%.

In Europe:

The disparities in price between European Union countries may result in significant breaks in the drugs supply chain.

Front line management of breaks in supply

Christophe Ettviller, Chairman of the Leem Distribution Group

The supply of raw materials is a Chinese puzzle!

"Having organised, adapted, improved and monitored the drugs supply chain for decades, pharmaceutical companies now live in fear of stockouts. Today, this supply chain is being disrupted by external factors independent of the drug manufacturing chain and its structure, and affecting every stage, from raw material to production of the active ingredient, its packaging and its delivery to storage and distribution centres.

Over the last 10 years, the raw materials market has been restructured and is now concentrated mainly in Asia. Supplier quality controls are more difficult to apply, although the Chinese authorities make their own inspections. They have the power to close a production facility overnight. This is reassuring from the quality point of view, since the controls applied are rigorous and effective, but this type of problem is impossible to foresee and can disrupt the drug production chain.
These identified risks are accompanied by scheduling uncertainties that can lead to errors and consumption of safety stocks.

Pharmaceutical companies are aware of these risks, and have implemented measures that specifically target these 'weak' links. They accumulate strategic stocks of essential raw materials and chemicals. Wherever possible, they ensure that they have two sources of supply, with one production facility as a backup source to be called on in the event of problems".

Nathalie Le Meur, Chair of the Leem Stockout Group

How pharmaceutical companies manage complexity!

"Pharmaceutical companies have always had to deal with stockouts, as opposed to breaks in supply, which are specific to players in the drugs supply chain.
The issue has risen to a new level of importance in recent years, as the drugs production chain has become more complex, and multiple external factors have come into play (rising demand, competitor stockouts, etc.).

The fact of the matter is that drugs are high-technology products whose manufacture is controlled by many legal obligations and a series of safety checks at every stage. Some products, like injectables and anticancer drugs, for example, are particularly complex to manufacture, requiring sophisticated technologies and stringent sterile conditions The more complex the manufacturing process becomes, the more difficult it is to predict and anticipate all the problems inherent in the production chain, which nevertheless must operate continually. It only takes one link in the chain to fail, and the operation of the entire chain is compromised.

We work in an industry where ZERO FAULTS is non-negotiable

Given the multiplicity of potential causes of failure throughout the manufacturing chain (industrial incidents, natural disasters, seasonal demand, competitor incidents, etc..), every pharmaceutical company has implemented a shortage management plan based on an analysis of the risks faced by its drugs portfolio and

giving precedence to essential drugs, like anti-cancer treatments, rather than cough mixtures, (where the market often offers dozens of treatment alternatives).

This risk analysis is based on a series of criteria:

- *the severity of the illness*
- *an evaluation of short term loss of chance for the patient*
- *the way the drug is used*
- *a list of alternative therapies*
- *the specific pharmaceutical form: some forms for children will be given priority over adult forms*
- *the feasibility of switching to an alternative therapy with no negative implications for the patient. In practice, some patients with well-balanced treatment may have great difficulty in changing to an alternative equivalent treatment. This is particularly true of patients with epilepsy, schizophrenia and some types of heart disease.*

Other criteria may intervene to add complexity to the analysis:

- *the length of the drug production cycle, which can vary from three weeks to several months*
- *transfers of manufacturing facility*
- *fluctuation in demand*
- *the number of manufacturing facilities involved*

Specific analysis of all criteria and their subsequent cross-referencing form the basis of an action plan to ensure security of supply and transparent quality controls applied in full cooperation with health authorities. Pharmaceutical companies also have plans in place for structured communication with healthcare professionals and patients.
Until now, these shortage management plans have made it possible to prevent those breaks in supply that have major impacts, and to maintain the life chances of patients receiving treatment".

The daily experience of Laurence Escalup, hospital pharmacist in the pharmacy department of the Institut Curie. Paris and Saint-Cloud sites:

"We've been juggling with breaks in supply of some anti-cancer drugs for around five years now. The breaks in supply that we've had to cope with have been caused essentially by problems with a raw material manufacturer and the sale of some products to markets prepared to pay a higher price, although that reason is less frequent.

We invite tenders from suppliers every two years, depending on our needs at the time. We select our supplier not only on the basis of price, but also of raw material quality and security of supply.

Initially, we handled the first breaks in supply by calling on other cancer treatment centres, but since then, we've developed our own procedures. We negotiate the quantities we need on the basis of a contract that includes a clause stating that if there is a break in supply of a particular drug, it is our supplier's responsibility to provide us with the quantities ordered, even if the supplier has to pay more for them. We've also been able to work with the laboratory concerned to forecast breaks in supply of essential drugs as a result of problems with a raw material manufacturer. A medical unit has been set up with the laboratory to provide monthly monitoring of the quantities required, and manage available stocks in conjunction with other cancer treatment centres. We also hold one month of safety stocks for sensitive products".

Solutions and proposals from pharmaceutical companies

Breaks in supply pose a strategic challenge for which pharmaceutical companies are identifying cooperative solutions.

The fact that the causes behind breaks in supply are multiple and often unpredictable, makes it all the more difficult to implement solutions. There are many players in the drug supply chain, and in a way, they bear joint responsibility for breaks in supply.

- Pharmaceutical companies may have to cope with production issues at raw materials manufacturers, problems with their own production facilities, natural disasters, transport problems, logistics issues, etc.
- Stocks of drugs may be exported to more lucrative markets, triggering shortages in the French market
- There may also be poor forward planning of local needs by wholesalers, and therefore an unsatisfactory allocation of drugs between regions, even where the volumes available are sufficient nationally
- Regulation may also be a factor, as a result of administrative delays in evaluating formulation change requests, suspension of production in a raw materials production facility following an inspection, etc.

Responding to this body of causes requires a body of measures applying individually to each player in the supply chain within its own field of responsibility, and to the entire chain in terms of its operation. It is therefore necessary to introduce monitoring of the entire chain.

Each of its links has a role to play in reducing the number of breaks in supply and ensuring that patients suffer as little as possible where such breaks in supply are inevitable.

What pharmaceutical companies are doing:

Pharmaceutical companies understand the significance and extent of these breaks in supply, and are putting in place the resources required to prevent them and address them:

- All have set up an emergency call centre that healthcare professionals and patients can use to contact them at any time. They also recommend that patients should not wait until the last day to collect repeat prescriptions in order to avoid being affected by micro-breaks in supply at dispensary level
- They update drug inventory status on a daily basis so that they can react as quickly as possible if a potential break in supply is identified, rather than wait for the actual break in supply to occur. Breaks in supply are costly financially and in terms of manpower, demand complicated emergency solutions, and must therefore be prevented wherever possible
- They identify inevitable breaks in supply at the earliest-possible opportunity, and implement quotas for remaining stocks as quickly as possible when the break is identified.

- They work in coordination and agreement with the National Agency for Medicines Safety (ANSM) to agree the conditions for replacing a drug where supplies have failed: with another form or alternative dose of the same drug, with a packaging initially intended for another market, or with an identical (often generic) drug from another laboratory

- They maintain contact with healthcare professionals to avoid new prescriptions being issued to new patients
- They organise emergency measures to address urgent needs

Illustration:

Management of problems in the supply of Levothyrox between June and October 2013.

The facts: Levothyrox, the drug used to treat hypothyroidism, is manufactured by Merck Serono in its Darmstadt plant in Germany. Demand for this drug has increased very significantly. It is offered in 8 different dosages, and Merck Serono encountered serious difficulties in meeting demand for a few months of 2013, particularly during the summer, when several dosages were affected at the same time.

How the break in supply was managed: When it became clear that Merck Serono stocks in France were fast approaching exhaustion, the company reacted extremely quickly and proactively:
- By reserving safety stocks as soon as issues were identified in the manufacturing facility
- By cooperating fully with the ANSM to import additional stock of an equivalent specialty from Italy in June, as and when required to meet demand (although this proved hardly necessary in the event)
- By ensuring continuity of supply to pharmacies through the introduction of a toll free number to obtain direct deliveries from safety stocks where wholesalers were unable to supply
- By significantly boosting its production capacity very quickly in order to solve the problem

This case was very widely reported in the media, largely because there are around 3 million patients using this drug in France.

The outcomes of this management method for patients: Throughout the period of supply issues, dispensing pharmacies were able to obtain emergency stocks to meet the needs of their patients, even where this occasionally demanded a combination of several tablets to obtain the usual dosage, involving a delay of a few days. Ultimately, during the 4 peak months of supply issues (July to October), Merck Serono supplied a total number of packs per month that exceeded the normal requirement for patients in France; only 2% of those supplies were made through the emergency system provided for pharmacists, with the remaining 98% being made through the normal wholesale distribution channel).

Over and above the plans in place to manage every type of stockout, pharmaceutical companies have put in place additional measures to protect certain drugs where a lack of availability could pose a risk to public health. These measures include:

- building up of safety stocks
- identifying alternative suppliers of the active raw materials concerned
- introducing backup drugs production sites wherever possible. The manufacture of some biological products may prove particularly difficult to transfer

In the majority of circumstances, all these solutions are implemented in parallel.

Shortage Management Plans (PGP) may be introduced by public health legislation to provide a formal framework for the measures already planned and organised by laboratories.

Stockouts pose a real threat to companies, their operation, their finances and their image. Currently, 95% of drugs are available to patients on a daily basis. Pharmaceutical companies are prepared and ready to work with other players in the pharmaceutical supply chain and with public authorities in order to implement every possible solution with the aim of further increasing this percentage for the ultimate benefit of patients.