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Complete List of Authors:	Benhabib, Amine; French Health Products Safety Agency; University of Strasbourg Faculty of Pharmacy Ioughlissen, Saïd; French Health Products Safety Agency Ratignier-Carbonneil, Christelle; French Health Products Safety Agency MAISON, Patrick; French Health Products Safety Agency; CHIC
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The French reporting system for drug shortages: description and trends from 2012 to 2018

Amine Benhabib,[1, 2] Said Ioughlissen, [1] Christelle Ratignier-Carbonneil, [1] Patrick Maison[1, 3]

[1] French National Agency for Medicines and Health Products Safety (ANSM), Saint-Denis, France

[2] Strasbourg Faculty of Pharmacy, Illkirch-Graffenstaden, France

[3] EA 7379, Paris Est Creteil University (UPEC) and CHIC Hospital, Créteil, France

Correspondance to: Patrick Maison, Agence Nationale de Sécurité des Médicaments et des Produits de Santé, 143-147 bd, Anatole France, F-93285 Saint-Denis Cedex ; Tel +331 55 87 35 23 ; Fax +331 55 87 35 23 ; Email : patrick.maison@ansm.sante.fr

Running head*:* The French reporting system for drug shortages

Keywords: Drug shortages, supply of medicines, short supply, major therapeutic interest, pharmacosurveillance, France, national reporting system

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ABSTRACT

Objectives

The aim was to provide figures for drug shortages in France and describe their characteristics, causes, and trends between 2012 and 2018.

Methods

Data from the national reporting system from the Agency of Medicine and Health Product Safety (ANSM) was analyzed. This database contains information regarding effective and predicted shortages of major therapeutic of interest (MTI) drugs (*i.e*. drugs whose shortage would be life-threatening or representing a loss of treatment opportunity for patients with a severe disease) which are mandatory reported by marketing authorization holders to the ANSM. Data are presented as numbers or percentages of pharmaceutical products (*i.e.* the product name and its formulation) reported on shortage between 2012 and 2018.

Results

There were 3530 pharmaceutical products reported on shortage during the period, including 1833 different active substances. Drugs on shortage were mostly former products (63.4%) with national marketing authorization procedures (62.8%), as well as injectable and oral forms (47.5% and 43.3%, respectively). Antiinfectives for systemic use ranked first (18%), followed by nervous and cardiovascular system drugs and by antineoplastic and immunomodulating agents (respectively 17.4%, 12.5% and 10.4%). The number of reported shortages presented a 4-fold increase between 2012 and 2018 and a sharp rise in 2017&2018, along with a rise in the number of active substances on shortage. The therapeutic classes concerned remained similar over time. Manufacturing and material supply issues were the main reported reasons for the shortage each year (30%) and there was an overall rise of pharmaceutical market reasons.

Conclusion

Drug shortages were increasingly reported in France along with a reinforced regulation. Preventive measures should specifically target the products the most on shortage, in particular former drugs, injectable, antiinfective, nervous system and cardiovascular system drugs as well as antineoplastic and immunomodulating agents.

INTRODUCTION

Drug shortages are a major public health threat worldwide occurring in all therapeutic classes.[1-7] According to the WHO, a drug shortage is defined as an insufficiency in the supply of medicines, health products and vaccines that are identified by the health system as essential to meet public health and patient need. [8] Drug shortages can have detrimental effects on patients care as they may result in delayed treatment or switches into alternative therapies, therefore leading to disease progression, increased risk of adverse effects or medication errors as well as rising healthcare costs.[9-11] Multiple reasons, such as manufacturing issues, regulatory issues or economic factors, in addition to increased global demand have been suggested to underlie drug shortages.[1 3 12 13]

In France, the management of drug shortages and short supply was first regulated in 2012 with a decree dated September 28th, 2012 on the supply of human drugs.[14] This decree requires the pharmaceutical operators commercializing drugs in France to ensure an appropriate and continuous supply of wholesalers and hospitals within 72 hours. Marketing authorization holders were thus mandated to notify the French National Agency of Medicine and Health Product Safety (*Agence Nationale de Sécurité du Médicament et des produits de santé* – ANSM) of any effective or predicted drug shortage, specifying the available stocks, the estimated period of shortage, the deadline for the availability of the product, as well as the substitute drugs. In 2016, the French health law of January 26th and its decree of July 20th targeted the shortages of drugs of major therapeutic of interest (MTI), defined as drugs for which unavailability would be life-threatening or representing a loss of treatment opportunity.[15] This decree also warrants new regulatory tools in order to reinforce the legal obligations of pharmaceutical companies and wholesalers. Marketing authorization holders and operators were required to develop shortage management plans (*Plan de Gestion des Pénuries – PGP*), and wholesalers were not allowed to export MTI drugs that are on effective or predicted shortage. Responsibilities of pharmaceutical operators were also strengthened by the implementation of administrative or financial penalties in case of non-compliance.[15 16]

According to a survey conducted in 2014, drug shortages were increasingly reported in Europe and occurred daily or weekly.[3] While the issue of drug shortages has been widely studied in the USA,[17-20] figures in Europe are scarce and national trends of drug shortages are not available.[26] The identification and surveillance of the most frequent drugs on shortage and the analysis of their causes may allow implementing targeted preventive measures in order to limit the negative impacts on patient care. The present study therefore aimed to describe the characteristics and trends of

reported shortages of MTI drugs in France using the national reporting system from the Agency of Medicine and Health Product Safety (ANSM).

METHODS

This observational retrospective study analyzed the surveillance reporting system of drug shortages from the French National Agency of Medicine and Health Product Safety (ANSM) between 2012 and 2018. Since 2012, marketing authorization holders are indeed obliged to declare any effective or predicted shortage of MTI drugs to the ANSM. The reporting database contains the information reported by the marketing authorization holders via completed declaration forms. The following data were analyzed: (1) from declaration forms: dates or report, drugs names, active substances (International Nonproprietary Names (INN)), routes of administration, setting first impacted by the shortage (community pharmacy and/or hospital), reasons for the shortages (available since 2015); (2) from the marketing authorization dossier and the summary of the product characteristics: dates and procedures of marketing authorization grants, storage conditions; and (3) ATC codes according to the WHO Collaborating Centre for Drug Statistics Methodology.[21]

Drug shortage reports were defined as both effective and predicted shortages of MTI drugs recorded by the ANSM each year.

Duration of the marketing authorization grant was defined as the difference between the years of the shortage reports and the year when the marketing authorization was granted.

Causes of shortages were categorized into: (1) manufacturing issues, including the stage of manufacturing or packaging of the final product ; (2) material issues, *i.e.,* defect in raw materials, excipients, packaging and semi-finished or bulk pharmaceuticals ; (3) pharmaceutical market, *i.e.,* related to the difficulty of the operator to purchase products, including insufficient production capacity ; (4) regulatory issues, *i.e.*, new regulation directly related to the delayed marketing ; and (5) inventory and storage practices, *i.e.,* stock errors or inappropriate management of expiry date.

Data were presented in numbers or in percentages of pharmaceutical products reported on shortage. Pharmaceutical products were defined as a combination of the International Nonproprietary Name (INN), the formulation and the packaging and are identified by the *code identifiant de spécialité* (CIS).

Patient and public involvement

No patient involved.

RESULTS

Between the years 2012 and 2018, 3530 pharmaceutical products were reported of on shortage, including 1833 different International Nonproprietary Name (INN) drugs. The overall characteristics of the pharmaceutical products reported on shortage from 2012 to 2018 are presented in **table 1**. Drugs with a marketing authorization granted more than 10 years ago (63.4%) and according to a national procedure (62.8%) were the most concerned. Generics drugs accounted for 34% of shortages overall and for 17% of former drugs (marketing authorization grant > 10 years). Community pharmacies and hospitals were similarly first impacted by shortages. Injectable and oral were the most commonly affected forms (with respectively 47.5% and 43.3%). With regards to ATC classes, antiinfectives for systemic use ranked first with 18% of total shortage reports, followed by nervous and cardiovascular system drugs as well as by antineoplastic and immunomodulating agents (with respectively 17.4%, 12.5% and 10.4) (**table 1**). Antibacterial for systemic use and vaccines accounted for 53% and 19% of antiinfectives shortages, respectively. Antiepileptic, anesthesic and analgesic products were among the most common nervous system drugs on shortage (22%, 18% and 16%, respectively).

Trends in the number of pharmaceutical products and INN drugs reported on shortage were shown in **figure 1**. There was a 4-fold increase in the total products on shortage between 2012 and 2018, to reach 917 shortages in 2018. The numbers of INN on shortage were similar in 2013 and 2017 but presented a 2-fold increase between the years 2012 and 2018, to reach a peak in 2018 (n=399) (**figure 1**).

Injectable and oral forms remained the two main pharmaceutical forms on shortage each year (from 51% to 37% and 40% to 56% between 2012 and 2018 for injectable and oral forms, respectively).

All therapeutic classes were reported on shortage each year. **Figure 2** presents the trends in proportions of shortage of pharmaceutical products by ATC classes from 2012 to 2018. The distribution of ATC classes reported on shortage was similar over time. Antiinfectives for systemic use, nervous system drugs as well as antineoplastic and immunomodulating agents ranked among the first classes on shortage until 2017. Shortages of cardiovascular system drugs were increasingly reported since 2012 and a sharp rise occurred in 2018 (n=216 reports). Cardiovascular drugs ranked

first in 2018 (24%), explained by products of valsartan accounting for half of shortages. The proportion of nervous system drugs, antiinfectives and antineoplastic and immunomodulating agents on shortage was relatively stable over the years (**figure 2**). Yet, a continuous increase of shortages was observed for nervous system drugs that ranked second in 2018 (n=181 reports) (**figure 2**). In 2018, antiepileptics accounted for the most reported class of nervous system drugs on shortage (34%), of which 13 were topiramate-based products. There was also a rise in shortages of antiinfective products in 2017 (n=122), driven in half by antibacterial drugs, in particular cephalosporins (n=23). Among antiinfectives, antibacterial drugs were the first class reported on shortage each year between 2012 and 2018, followed by vaccines (data not shown).

Figure 3 presents the trends in the proportion of shortage of pharmaceutical products by duration of marketing authorization grant from 2012 to 2018. During that period, drugs with a former marketing authorization grant (of more than 10 years) were the most reported on shortage.

Drug shortages first impacting hospital settings accounted for half of the shortages in 2017 and for a third in other years. Similar trends in the proportion of shortage were observed for settings first impacted (data not shown).

Trends in the reported causes of shortages between 2015 and 2018 are shown in **figure 4**. Manufacturing and material supply issues were the main reasons each year with approximately 30% of the shortage share. There was an overall rise of pharmaceutical market reasons.

DISCUSSION

Based on the French national reporting system, the present study described the characteristics of MTI drugs reported on shortage in France between 2012 and 2018 as mostly: former drugs, drugs with national marketing authorization procedures and injectables. Both hospital and community pharmacies were similarly affected by shortages and one third of them first occurred in hospital settings. Four therapeutic classes (antiinfectives, nervous system, cardiovascular system drugs, antineoplastics and immunomodulating agents) remained the most on shortage with the same distribution over the years. The number of pharmaceutical products reported on shortage increased by 4-fold between 2012 and 2018, along with a rise in the number of INN drugs. In 2018, the number of pharmaceutical products on shortage reached a peak, with 399 different active substances from all therapeutic classes affected by shortage. Compared with the number (n=2 800) of approved and marketed INN drugs in France in 2016,[22] there were approximately 13% of INN drugs on shortage in 2018 and 60% during the 2012-2018 period.

The present rise in drug shortages in France is consistent with overall trend observed in the USA, reflecting the international public health challenge of drug shortages. According to the University of Utah Drug Information Service (UUDIS), new drugs on shortage in the USA were found to triple between 2004 and 2018, although a decrease occurred since 2012.[23] Comparisons of figures between the two countries are yet limited by differences in definitions of drug shortage [2] as well as differences in pharmaceutical products, blister packaging being less used in the USA.

The four therapeutic classes most impacted by shortages in the present study were antiinfectives for systemic use, nervous system drugs, cardiovascular drugs and antineoplastic and immunomodulating agents, in accordance with previous results from a European review finding that these same four classes represented over 50% of reported shortage.[4] We found that antiinfectives for systemic use represented the first therapeutic class reported on shortage until 2018 (18%) among which antibacterial drugs ranked first each year. This trend is well documented across the United States. Antimicrobials were the most common drug class on shortage in critical care (2001-2016) and emergency medicine practice (2001-2014), representing respectively 20% and 24% of US shortages.[18] [19] Cephalosporins were the most common antibacterial drug class reported on shortage in our study, in accordance with findings from a US study using the UUDIS database from 2001 to 2013.[24] Shortages of antimicrobials may not have alternative production sources and may thus require the use of less effective or more toxic alternatives,[19] [24] leading to worse patient outcomes.[17] In a European survey, antiinfectives were also found to be the most common drugs on shortage in

hospital pharmacies in 2013, along with cancer drugs.[25] The burden of cancer drug shortages was previously highlighted in the United States[26 27] and more recently in a hospital paediatric hemato-oncology unit in Belgium.[7] A lack of market attractiveness and low profitability has been suggested as a cause of shortages, due to prompting the discontinuation of some long-standing or lower-priced products such as antibiotics and oncologic medicines.[1]

In the present study, cardiovascular drugs were one of the first therapeutic classes on shortage and the first in 2018 (28%). This was driven by shortages of valsartan products resulting from the detection in 2018 of impurities in the active substance of valsartan-based medicines. As a precaution, all potentially impacted batches of valsartan containing drugs were recalled in France since July 2018.[28] Shortage of cardiovascular drugs was also common in the USA.[19, 29]

In this study, shortages mostly involved injectable products each year. This finding is consistent with previous surveys in Europe and USA.[4, 19] Injectable products are at increased risk of shortage related to quality control concerns because of the complexities associated with manufacturing a sterile product.[2] Oral drugs also accounted for a large share of shortages in our study, reflecting that causes of drug shortages goes beyond pure manufacturing problems related to technical issues or quality problems.

According to our results, former drugs were the most reported on shortage during the period from year 2012 to year 2018, with 63.4% of drug shortages while there were 45% of former products on the market in 2018 in France. Age of the marketing authorization is thus likely to be a major determinant of drug shortage, in accordance with a US study finding that the age of drug was a strong risk factor for shortage in oncology.[26] According to the authors, this result suggested that policies focused predominately on promoting increases in distinct suppliers and that competition may not alleviate drug shortages.

The reasons behind drug shortages are complex and many factors may contribute simultaneously. In France, the increase in drug shortage reports may partly be linked to changes in regulations. Since 2012, marketing authorization holders are required to report shortages and otherwise subjected to financial sanctions since 2016. Yet, not all drugs were affected by shortage in our study, which goes beyond regulatory changes and is more concordant with increased needs along with inadequate production and supply issues. Raw material shortages and production issues have been considered global and as having similar impacts in European countries.[3 4 12] Manufacturing problems stem from concentration and rationalization of pharmaceutical manufacturing, as well as globalization.[3] In our study, material and manufacturing issues were the main causes of shortages each year and a rise in shortages related to pharmaceutical market was observed over the years. One explanation may be a

rise in the global use of pharmaceutical products worldwide. The structure of the pharmaceutical market was previously found to be a key determinant of drug shortages in Finland.[12] In our study, pharmaceutical market issues included hospital trade and competitive bidding tenders that may contribute to compromise the supply of MTI drugs at hospital.

Some limitations to the present study should be noted. First, the results were relating to shortage of MTI drugs from national stocks supplies, which may not allow generalization to all drugs, although MTI drugs include all therapeutic classes. Second, the data came were sourced from statement reports of marketing authorization holders and missing data cannot be ruled out. Yet, the financial penalty for non-compliance with mandatory declaration of marketing authorization holders limits the cases of under-reporting and shortages of MTI drugs would obviously be reported to the ANSM by health professionals or patients otherwise. Third, the data relating to effective and predicted drugs shortage may not reflect the effective short supplies, thus limiting the clinical interpretations of the present results.

Strengths of the present study include the analysis of a national reporting system over a 7 years period. This is the first study to analyze and describe the issue of drug shortages in France, along with a new regulatory framework. Trends of drug shortages were described according to pharmaceutical products and INN drugs, allowing a more detailed description and interpretation of drug shortages and their causes.

CONCLUSION

Shortages of major therapeutic of interest drugs are common and increasingly reported those last years in France. Preventive measures, including contingency plans, should particularly target former drugs, injectables, antiinfectives, nervous system, cardiovascular system drugs as well as antineoplastic and immunomodulating agents. The issue of drug shortages goes beyond national concerns. Many drugs reported on shortages being granted by a European marketing authorization. Even if the characteristics of drugs and reasons of shortages found in the present study are likely to be generalized to Europe, further studies are needed to address drug shortages at the European level. Reporting of drug shortages has been required to be standardized between all European member States as well as coordination of legal and organizational strategies.[3 4] A European collaboration (Task Force) set up by the European Medicine Agency is ongoing since 2016, to provide support and advice to tackle disruptions in supply of medicines and ensure their continued availability.[30]

Contributors

AB contributed to data collection and data analysis. PM designed the project. SI, CRC and PM contributed to study methods. All authors contributed to the interpretation of data and to the writing of the manuscript.

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Competing interests :

None

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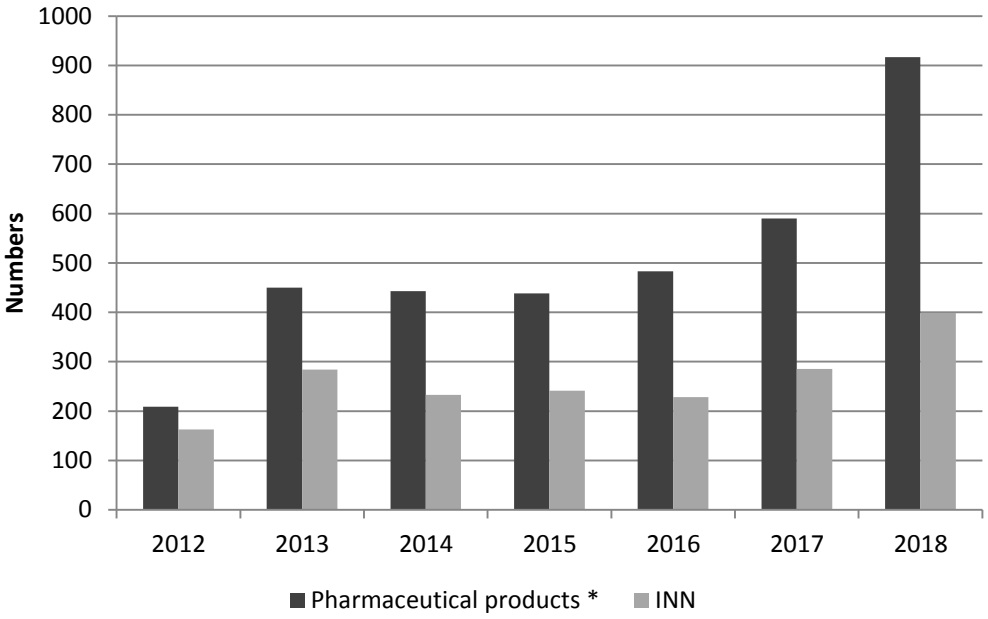
Table 1 Characteristics of pharmaceutical products reported on shortage in 2012-2018

	2012-2018 n (%)
Total	**3530 (100)**
Marketing authorization procedures	
National	2217 (62.8)
European	1249 (35.4)
Duration of marketing authorization grants	
> 10 years	2237 (63.4)
≤ 10 years	1212 (34.3)
Pharmaceutical forms	
Oral	1529 (43.3)
Injectable	1675 (47.5)
Others	326 (9.2)
Storage conditions	
Ambient temperature	2994 (85)
+2°C < Temperature < +8°C	533 (16)
ATC Classes	
Alimentary tract and metabolism	217 (6.1)
Antiinfectives for systemic use	634 (18)
Antineoplastic and immunomodulating agents	367 (10.4)
Antiparasitic products, insecticides and repellents	39 (1.1)
Blood and blood forming organs	312 (8.8)
Cardiovascular system	442 (12.5)
Dermatologicals	59 (1.6)
Genitourinary system and reproductive hormones	151 (4.3)
Musculoskeletal system	155 (4.4)
Nervous system	613 (17.4)
Respiratory system	119 (3.4)
Sensory organs	97 (2.8)
Systemic hormonal preparations	160 (4.5)
Various/others	165 (4.7)

Figure 1 Trends in shortages by numbers of pharmaceutical products and International Nonproprietary Name drugs (INN) (2012-2018)



*** Pharmaceutical products:** defined by a combination of the International Nonproprietary Name (INN), the formulation and the packaging

Figure 2 Trends in the proportion of pharmaceutical products on shortage by ATC classes (2012-2018)

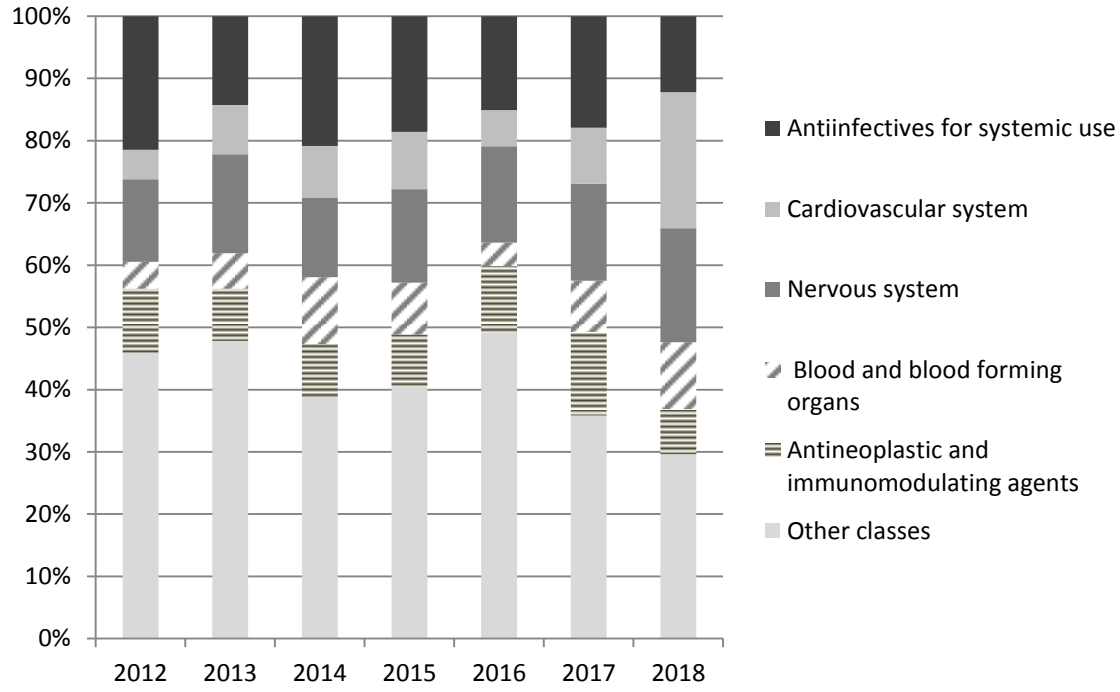


Figure 3 Trends in the proportion of pharmaceutical products on shortage by duration of marketing authorization grants (2012-2018)

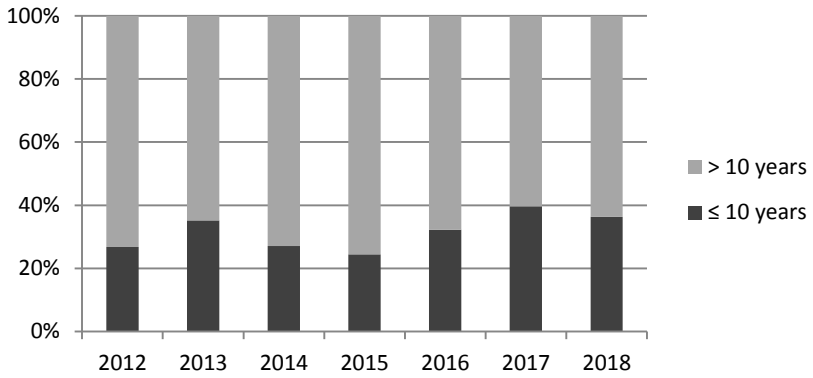
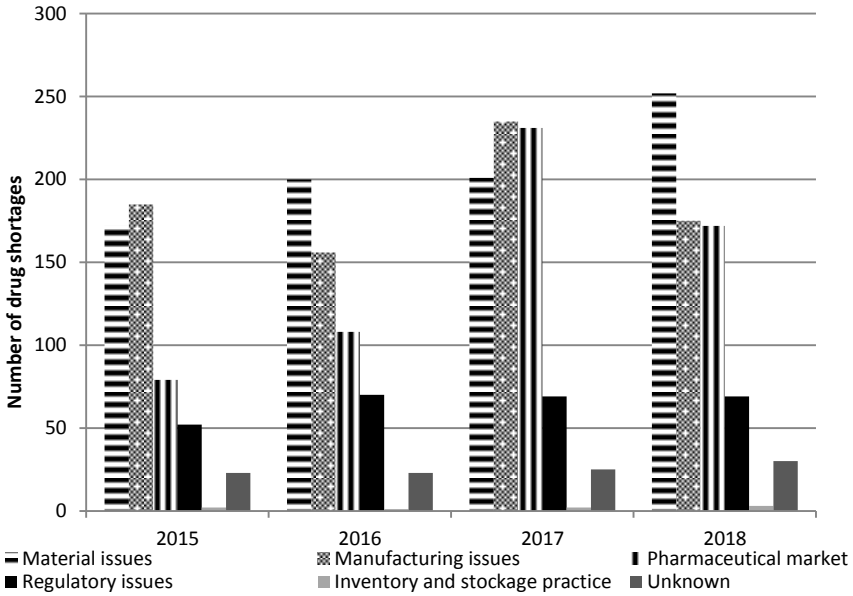


Figure 4 Trends in the causes of shortages (pharmaceutical products) (2015-2018)



STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

The French reporting system for drug shortages: description and trends from 2012 to 2018

	Item No	Recommendation		Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	OK	2 of 19
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	OK	2 of 19
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	OK	3 of 19
Objectives	3	State specific objectives, including any prespecified hypotheses	OK	3 & 4 of 19
Methods				
Study design	4	Present key elements of study design early in the paper	OK	4 of 19
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	OK	4 of 19
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection	OK	4 of 19
Variables	7	Clearly define all outcomes	OK	4 of 19
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement).	OK	4 of 19
Bias	9	Describe any efforts to address potential sources of bias	OK	4 of 19
Study size	10	Explain how the study size was arrived at	OK	4 of 19
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	OK	4 of 19
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	OK	4 of 19
		(*b*) Describe any methods used to examine subgroups and interactions	OK	4 of 19
		(*c*) Explain how missing data were addressed	OK	4 of 19
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA	NA
		(*e*) Describe any sensitivity analyses	NA	NA
Results				
Participants	13*	(a) Report numbers of products at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	OK	5 & 13 of study
		(b) Give reasons for non-participation at each stage	NA	NA
		(c) Consider use of a flow diagram	NA	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA	NA

		(b) Indicate number of products with missing data for each variable of interest	OK	5 of 19
Outcome data	15*	Report numbers of outcome events or summary measures	NA	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	OK	14 to 17 of 19
Discussion				
Key results	18	Summarise key results with reference to study objectives	OK	7 of 19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	OK	9 of 19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	OK	9 of 19
Generalisability	21	Discuss the generalisability (external validity) of the study results	OK	9 of 19
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	OK	10 of 19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The French reporting system for drug shortages: description and trends from 2012 to 2018. An observational retrospective study

Amine Benhabib,[1, 2] Said Ioughlissen, [1] Christelle Ratignier-Carbonneil, [1] Patrick Maison[1, 3]

[1] French National Agency for Medicines and Health Products Safety (ANSM), Saint-Denis, France

[2] Strasbourg Faculty of Pharmacy, Illkirch-Graffenstaden, France

[3] EA 7379, Paris Est Creteil University (UPEC) and CHIC Hospital, Créteil, France

Correspondance to: Patrick Maison, Agence Nationale de Sécurité des Médicaments et des Produits de Santé, 143-147 bd, Anatole France, F-93285 Saint-Denis Cedex ; Tel +331 55 87 35 23 ; Fax +331 55 87 35 23 ; Email : patrick.maison@ansm.sante.fr

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ABSTRACT

Objectives

The aim was to provide figures for drug shortages in France and describe their characteristics, causes, and trends between 2012 and 2018.

Methods

Data from the national reporting system from the Agency of Medicine and Health Product Safety (ANSM) was analyzed. This database contains information regarding effective and predicted shortages of major therapeutic of interest (MTI) drugs (*i.e*. drugs whose shortage would be life-threatening or representing a loss of treatment opportunity for patients with a severe disease) which are mandatory reported by marketing authorization holders to the ANSM. Data are presented as numbers or percentages of pharmaceutical products (*i.e.* the product name and its formulation) reported on shortage between 2012 and 2018.

Results

There were 3530 pharmaceutical products reported on shortage during the period, including 1833 different active substances. Drugs on shortage were mostly old products (63.4%) with national marketing authorization procedures (62.8%), as well as injectable and oral forms (47.5% and 43.3%, respectively). Antiinfectives for systemic use ranked first (18%), followed by nervous and cardiovascular system drugs and by antineoplastic and immunomodulating agents (respectively 17.4%, 12.5% and 10.4%). The number of reported shortages presented a 4-fold increase between 2012 and 2018 and a sharp rise in 2017&2018, along with a rise in the number of active substances on shortage. The therapeutic classes concerned remained similar over time. Manufacturing and material supply issues were the main reported reasons for the shortage each year (30%) and there was an overall rise of pharmaceutical market reasons.

Conclusion

Drug shortages were increasingly reported in France. Preventive measures should specifically target the products the most on shortage, in particular old drugs, injectable, antiinfective, nervous system and cardiovascular system drugs as well as antineoplastic and immunomodulating agents.

Strengths and Limitations

• Very few data quantifying drug shortages are published in the scientific literature especially in Europe.

• This is the first study to describe and analyses drug shortages in France using a national reporting system over a 7 years period.

• Trends of drug shortages were described according to both pharmaceutical products (defined as a combination of the active substance, the formulation and the packaging) and International Nonproprietary Name drugs, allowing a more detailed description and interpretation of drug shortages and their causes.

• The present study is restricted to shortages of Major Therapeutic of Interest (MTI) drugs from national stocks supplies, which may not allow generalization to all drugs.

• This study is limited to drug shortages and may not address the issue of effective short supplies, thus limiting the clinical interpretations of the present results.

INTRODUCTION

Drug shortages are a major public health threat worldwide occurring in all therapeutic classes.[1-7] According to the WHO, a drug shortage is defined as an insufficiency in the supply of medicines, health products and vaccines that are identified by the health system as essential to meet public health and patient need.[8] Drug shortages can have detrimental effects on patients care as they may result in delayed treatment or switches into alternative therapies, therefore leading to disease progression, increased risk of adverse effects or medication errors as well as rising healthcare costs.[9-11] Multiple reasons, such as manufacturing issues, regulatory issues or economic factors, in addition to increased global demand have been suggested to underlie drug shortages.[1, 3, 12, 13]

In France, the management of drug shortages and short supply was first regulated in 2012 with a decree dated September 28th, 2012 on the supply of human drugs.[14] This decree requires the pharmaceutical operators commercializing drugs in France to ensure an appropriate and continuous supply of wholesalers and hospitals within 72 hours. Marketing authorization holders were thus mandated to notify the French National Agency of Medicine and Health Product Safety (*Agence Nationale de Sécurité du Médicament et des produits de santé* – ANSM) of any effective or predicted drug shortages, specifying the available stocks, the estimated period of shortage, the deadline for the availability of the product, as well as the substitute drugs. In 2016, the French health law of January 26th and its decree of July 20th targeted the shortages of drugs of major therapeutic of interest (MTI) defined as drugs for which unavailability would be life-threatening or represent a loss of treatment opportunity.[15] The list of the therapeutic classes of MTI drugs was provided by the ministerial order of July 27th(Supplementary materials).[16] The shortage of an MTI drug has to be reported by the marketing authorization holder (MAH) to the ANSM even when another competing equivalent MTI drug is available. MAH are not aware of the productions capacities of other MAHs and thus of the availability of equivalent MIT drugs at the time of the report. The impact of a shortage in terms of public health and production is then estimated by the ANSM. The decree of July 20th also warranted new regulatory tools in order to reinforce the legal obligations of pharmaceutical companies and wholesalers. Marketing authorization holders and operators were required to develop shortage management plans (*Plan de Gestion des Pénuries – PGP*), and wholesalers were not allowed to export MTI drugs that are on effective or predicted shortage. Responsibilities of pharmaceutical operators were also strengthened by the implementation of administrative or financial penalties in case of non-compliance.[15, 17]

According to a survey conducted in 2014, drug shortages were increasingly reported in Europe and occurred daily or weekly.[3] While the issue of drug shortages has been widely studied in the USA,[18-21] figures in Europe are scarce and national trends of drug shortages are not available.[22] The identification and surveillance of the most frequent drugs on shortage and the analysis of their causes may allow implementing targeted preventive measures in order to limit the negative impacts on patient care. The present study therefore aimed to describe the characteristics and trends of reported shortages of MTI drugs in France using the national reporting system from the Agency of Medicine and Health Product Safety (ANSM).

METHODS

This observational retrospective study analyzed the surveillance reporting system of drug shortages from the French National Agency of Medicine and Health Product Safety (ANSM) between 2012 and 2018. Since 2012, marketing authorization holders are indeed obliged to declare any effective or predicted shortage of MTI drugs to the ANSM. The reporting database contains the information reported by the marketing authorization holders via completed declaration forms. The following data were analyzed: (1) from declaration forms: dates or report, drugs names, active substances (International Nonproprietary Names (INN)), routes of administration, setting first impacted by the shortage (community pharmacy and/or hospital), reasons for the shortages (available since 2015); (2) from the marketing authorization dossier and the summary of the product characteristics: dates and procedures of marketing authorization grants, storage conditions; and (3) ATC codes according to the WHO Collaborating Centre for Drug Statistics Methodology.[23]

At the time of the report of shortage, depending on the stocks, the shortage may be predictive or become effective in a few hours and vice versa. Drug shortage reports were therefore defined as both effective and predicted shortages of MTI drugs recorded by the ANSM each year.

According to the definition of drug shortage in France, short supply was not considered in present study. A drug shortage reflects the capacity of a pharmaceutical company to produce drugs in accordance to the authorities' scope whereas a short supply assesses the sanitary risk in the scope of the pharmacy practice.

Duration of the marketing authorization grant was defined as the difference between the years of the shortage reports and the year when the marketing authorization was granted.

Causes of shortages were categorized into: (1) manufacturing issues, including the stage of manufacturing or packaging of the final product ; (2) material issues, *i.e.,* defect in raw materials, excipients, packaging and semi-finished or bulk pharmaceuticals ; (3) pharmaceutical market, *i.e.,* related to the difficulty of the operator to purchase products, including insufficient production capacity ; (4) regulatory issues, *i.e.*, new regulation directly related to the delayed marketing ; and (5) inventory and storage practices, *i.e.,* stock errors or inappropriate management of expiry date.

Data were presented in numbers or in percentages of pharmaceutical products reported on shortage. Pharmaceutical products were defined as a combination of the International Nonproprietary Name (INN), the formulation and the packaging and are identified by the *code identifiant de spécialité* (CIS). Therefore, a shortage of a pharmaceutical product does not necessarily imply the shortages of all drugs with the same INN.

There were no missing data except for marketing authorization procedures and duration of marketing authorization grants.

Patient and public involvement

No patient involved

RESULTS

Between the years 2012 and 2018, 3530 pharmaceutical products were reported of on shortage, including 1833 different International Nonproprietary Name (INN) drugs. The overall characteristics of the pharmaceutical products reported on shortage from 2012 to 2018 are presented in **table 1**. Drugs with a marketing authorization granted more than 10 years ago (63.4%) and according to a national procedure (62.8%) were the most concerned. Generics drugs accounted for 34% of shortages overall and for 17% of old drugs (marketing authorization grant > 10 years). Community pharmacies and hospitals were similarly first impacted by shortages. Injectable and oral were the most commonly affected forms (with respectively 47.5% and 43.3%). With regards to ATC classes, antiinfectives for systemic use ranked first with 18% of total shortage reports, followed by nervous and cardiovascular system drugs as well as by antineoplastic and immunomodulating agents (with respectively 17.4%, 12.5% and 10.4) (**table 1**). Antibacterial for systemic use and vaccines accounted for 53% and 19% of antiinfectives shortages, respectively. Antiepileptic, anesthesic and analgesic

products were among the most common nervous system drugs on shortage (22%, 18% and 16%, respectively). Cephalosporins were the most common antibacterial drug class reported on shortage.

Trends in the number of pharmaceutical products and INN drugs reported on shortage were shown in **figure 1**. There was a 4-fold increase in the total products on shortage between 2012 and 2018, to reach 917 shortages in 2018. The numbers of INN on shortage were similar in 2013 and 2017 but presented a 2-fold increase between the years 2012 and 2018, to reach a peak in 2018 (n=399) (**figure 1**).

Injectable and oral forms remained the two main pharmaceutical forms on shortage each year (from 51% to 37% and 40% to 56% between 2012 and 2018 for injectable and oral forms, respectively).

All therapeutic classes were reported on shortage each year. **Figure 2** presents the trends in proportions of shortage of pharmaceutical products by ATC classes from 2012 to 2018. The distribution of ATC classes reported on shortage was similar over time. Antiinfectives for systemic use, nervous system drugs as well as antineoplastic and immunomodulating agents ranked among the first classes on shortage until 2017. Shortages of cardiovascular system drugs were increasingly reported since 2012 and a sharp rise occurred in 2018 (n=216 reports). Cardiovascular drugs ranked first in 2018 (24%), explained by products of valsartan accounting for half of shortages. The proportion of nervous system drugs, antiinfectives and antineoplastic and immunomodulating agents on shortage was relatively stable over the years (**figure 2**). Yet, a continuous increase of shortages was observed for nervous system drugs that ranked second in 2018 (n=181 reports) (**figure 2**). In 2018, antiepileptics accounted for the most reported class of nervous system drugs on shortage (34%), of which 13 were topiramate-based products. There was also a rise in shortages of antiinfective products in 2017 (n=122), driven in half by antibacterial drugs, in particular cephalosporins (n=23). Among antiinfectives, antibacterial drugs were the first class reported on shortage each year between 2012 and 2018, followed by vaccines (data not shown).

Figure 3 presents the trends in the proportion of shortage of pharmaceutical products by duration of marketing authorization grant from 2012 to 2018. During that period, drugs with an old marketing authorization grant (of more than 10 years) were the most reported on shortage.

Drug shortages first impacting hospital settings accounted for half of the shortages in 2017 and for a third in other years. Similar trends in the proportion of shortage were observed for settings first impacted (data not shown).

Trends in the reported causes of shortages between 2015 and 2018 are shown in **figure 4**. Manufacturing and material supply issues were the main reasons each year with approximately 30% of the shortage share. There was an overall rise of pharmaceutical market reasons.

DISCUSSION

Based on the French national reporting system, the present study described the characteristics of MTI drugs reported on shortage in France between 2012 and 2018 as mostly: old drugs, drugs with national marketing authorization procedures and injectables. Both hospital and community pharmacies were similarly affected by shortages and one third of them first occurred in hospital settings. Four therapeutic classes (antiinfectives, nervous system, cardiovascular system drugs, antineoplastics and immunomodulating agents) remained the most on shortage with the same distribution over the years. The number of pharmaceutical products reported on shortage increased by 4-fold between 2012 and 2018, along with a rise in the number of INN drugs. In 2018, the number of pharmaceutical products on shortage reached a peak, with 399 different active substances from all therapeutic classes affected by shortage. Compared with the number (n=2 800) of approved and marketed INN drugs in France in 2016,[24] there were approximately 13% of INN drugs on shortage in 2018 and 60% during the 2012-2018 period.

The present rise in drug shortages in France is consistent with overall trend observed in the USA, reflecting the international public health challenge of drug shortages. According to the University of Utah Drug Information Service (UUDIS), new drugs on shortage in the USA were found to triple between 2004 and 2018, although a decrease occurred since 2012.[25] Comparisons of figures between the two countries are yet limited by differences in definitions of drug shortage [2] as well as differences in pharmaceutical products, blister packaging being less used in the USA.

The four therapeutic classes most impacted by shortages in the present study were antiinfectives for systemic use, nervous system drugs, cardiovascular drugs and antineoplastic and immunomodulating agents, in accordance with previous results from a European review finding that these same four classes represented over 50% of reported shortage.[4] We found that antiinfectives for systemic use represented the first therapeutic class reported on shortage until 2018 (18%) among which antibacterial drugs ranked first each year. This trend is well documented across the United States. Antimicrobials were the most common drug class on shortage in critical care (2001-2016) and emergency medicine practice (2001-2014), representing respectively 20% and 24% of US shortages.[19,

[20] Cephalosporins were the most common antibacterial drug class, in accordance with findings from a US study using the UUDIS database from 2001 to 2013.[26] Shortages of antimicrobials may not have alternative production sources and may thus require the use of less effective or more toxic alternatives,[20, 26] leading to worse patient outcomes.[18] In a European survey, antiinfectives were also found to be the most common drugs on shortage in hospital pharmacies in 2013, along with cancer drugs.[22] The burden of cancer drug shortages was previously highlighted in the United States[27, 28] and more recently in a hospital paediatric hemato-oncology unit in Belgium.[7] A lack of market attractiveness and low profitability has been suggested as a cause of shortages, due to prompting the discontinuation of some long-standing or lower-priced products such as antibiotics and oncologic medicines.[1]

In the present study, cardiovascular drugs were one of the first therapeutic classes on shortage and the first in 2018 (28%). This was driven by shortages of valsartan products resulting from the detection in 2018 of impurities in the active substance of valsartan-based medicines. As a precaution, all potentially impacted batches of valsartan containing drugs were recalled in France since July 2018.[29] Shortage of cardiovascular drugs was also common in the USA.[20, 30]

In this study, shortages mostly involved injectable products each year. This finding is consistent with previous surveys in Europe and USA.[4, 20] Injectable products are at increased risk of shortage related to quality control concerns because of the complexities associated with manufacturing a sterile product.[2] Oral drugs also accounted for a large share of shortages in our study, reflecting that causes of drug shortages goes beyond pure manufacturing problems related to technical issues or quality problems.

According to our results, old drugs were the most reported on shortage during the period from year 2012 to year 2018, with 63.4% of drug shortages while there were 45% of old products on the market in 2018 in France. Age of the marketing authorization is thus likely to be a major determinant of drug shortage, in accordance with a US study finding that the age of drug was a strong risk factor for shortage in oncology.[27] According to the authors, this result suggested that policies focused predominately on promoting increases in distinct suppliers and that competition may not alleviate drug shortages.

The reasons behind drug shortages are complex and many factors may contribute simultaneously. In France, the increase in drug shortage reports may partly be linked to changes in regulations. Since 2012, marketing authorization holders are required to report shortages and otherwise subjected to financial sanctions since 2016. Yet, not all drugs were affected by shortage in our study, which goes beyond regulatory changes and is more concordant with increased needs along with inadequate

production and supply issues. Raw material shortages and production issues have been considered global and as having similar impacts in European countries.[3, 4, 12] Manufacturing problems stem from concentration and rationalization of pharmaceutical manufacturing, as well as globalization.[3] In our study, material and manufacturing issues were the main causes of shortages each year and a rise in shortages related to pharmaceutical market was observed over the years. One explanation may be a rise in the global use of pharmaceutical products worldwide. The structure of the pharmaceutical market was previously found to be a key determinant of drug shortages in Finland.[12] In our study, pharmaceutical market issues included hospital trade and competitive bidding tenders that may contribute to compromise the supply of MTI drugs at hospital.

Some limitations to the present study should be noted. First, the results were relating to shortage of MTI drugs from national stocks supplies, which may not allow generalization to all drugs, although MTI drugs include all therapeutic classes. Second, the data were sourced from statement reports of marketing authorization holders and missing data cannot be ruled out. According to the definition of drug shortages in France, short supply was not considered in the present study. The combination of data from both authorities and pharmacy practice has been suggested to improve the surveillance.[31] This requires a standardization of definition of drug shortages between European members. Yet, the financial penalty for non-compliance with mandatory declaration of marketing authorization holders limits the cases of under-reporting and shortages of MTI drugs would obviously be reported to the ANSM by health professionals or patients otherwise. Third, the data relating to effective and predicted drugs shortage may not reflect the effective short supplies, thus limiting the clinical interpretations of the present results.

Strengths of the present study include the analysis of a national reporting system over a 7 years period. This is the first study to analyze the issue of drug shortages in France. Trends of drug shortages were described according to pharmaceutical products and INN drugs, allowing a more detailed description and interpretation of drug shortages and their causes.

Reporting of drug shortages has been required to be standardized between all European member States as well as coordination of legal and organizational strategies.[3, 4] A European collaboration (Task Force) set up by the European Medicine Agency is ongoing since 2016, to provide support and advice to tackle disruptions in supply of medicines and ensure their continued availability.[32]

CONCLUSION

Shortages of major therapeutic of interest drugs are common and increasingly reported those last years in France. Preventive measures, including contingency plans, should particularly target old

drugs, injectables, antiinfectives, nervous system, cardiovascular system drugs as well as antineoplastic and immunomodulating agents. The issue of drug shortages goes beyond national concerns. Many drugs reported on shortages being granted by a European marketing authorization. Even if the characteristics of drugs and reasons of shortages found in the present study are likely to be generalized to Europe, further studies are needed to address drug shortages at the European level.

Contributors

AB contributed to data collection and data analysis. PM designed the project. SI, CRC and PM contributed to methods of the study. All authors contributed to the interpretation of data and to the writing of the manuscript.

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Data sharing

Data were reported from the pharmaceutical companies and confidential

Competing interests :

None

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Table 1 Characteristics of pharmaceutical products reported on shortage in 2012-2018

	2012-2018 n (%)
Total	**3530 (100)**
Marketing authorization procedures	
National	2217 (62.8)
European	1249 (35.4)
Unavailable data	64 (1.81)
Duration of marketing authorization grants	
> 10 years	2237 (63.4)
≤ 10 years	1212 (34.3)
Unavailable data	81 (2.30)
Pharmaceutical forms	
Oral	1529 (43.3)
Injectable	1675 (47.5)
Others	326 (9.24)
Storage conditions	
Ambient temperature	2995 (84.8)
+2°C < Temperature < +8°C	533 (16.0)
- 18°C < Temperature	2 (0.00)
ATC Classes	
Alimentary tract and metabolism	217 (6.15)
Antiinfectives for systemic use	634 (18.0)
Antineoplastic and immunomodulating agents	367 (10.4)
Antiparasitic products, insecticides and repellents	39 (1.10)
Blood and blood forming organs	312 (8.84)
Cardiovascular system	442 (12.5)
Dermatologicals	59 (1.67)
Genitourinary system and reproductive hormones	151 (4.30)
Musculoskeletal system	155 (4.40)
Nervous system	613 (17.4)
Respiratory system	119 (3.40)
Sensory organs	97 (2.80)
Systemic hormonal preparations	160 (4.53)
Various/others	165 (4.70)

Figures legends

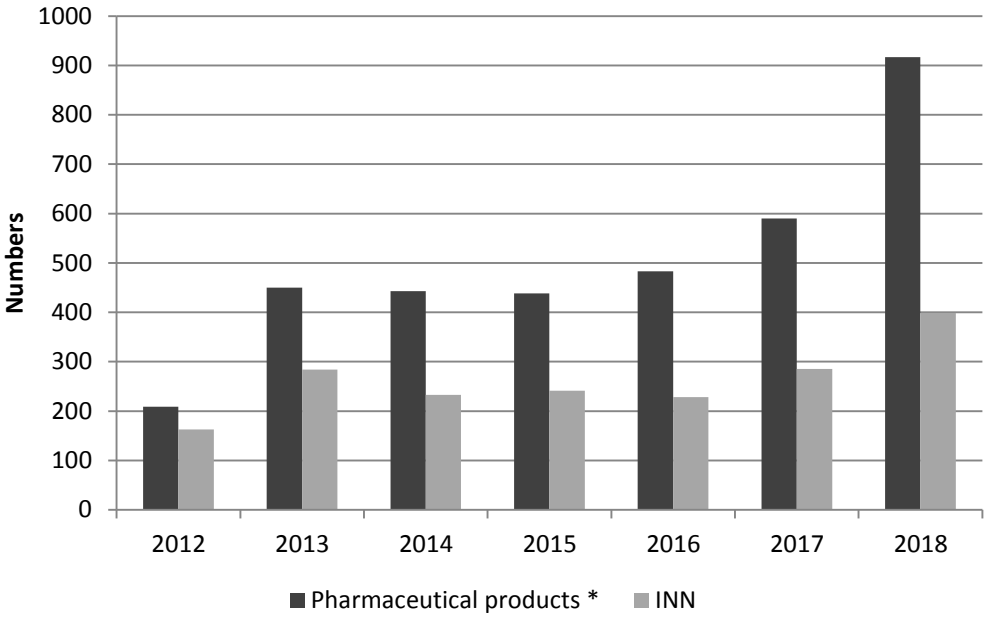
Figure 1 Trends in shortages by numbers of pharmaceutical products and International Nonproprietary Name drugs (INN) (2012-2018) in France.

Figure 2 Trends in the proportion of pharmaceutical products on shortage by ATC classes (2012-2018)

Figure 3 Trends in the proportion of pharmaceutical products on shortage by duration of marketing authorization grants

Figure 4 Trends in the causes of shortages of pharmaceutical products in 2015-2018

Figure 1 Trends in shortages by numbers of pharmaceutical products and International Nonproprietary Name drugs (INN) (2012-2018) in France.



*** Pharmaceutical products:** defined by a combination of the International Nonproprietary Name (INN), the formulation and the packaging

Figure 2 Trends in the proportion of pharmaceutical products on shortage by ATC classes (2012-2018)

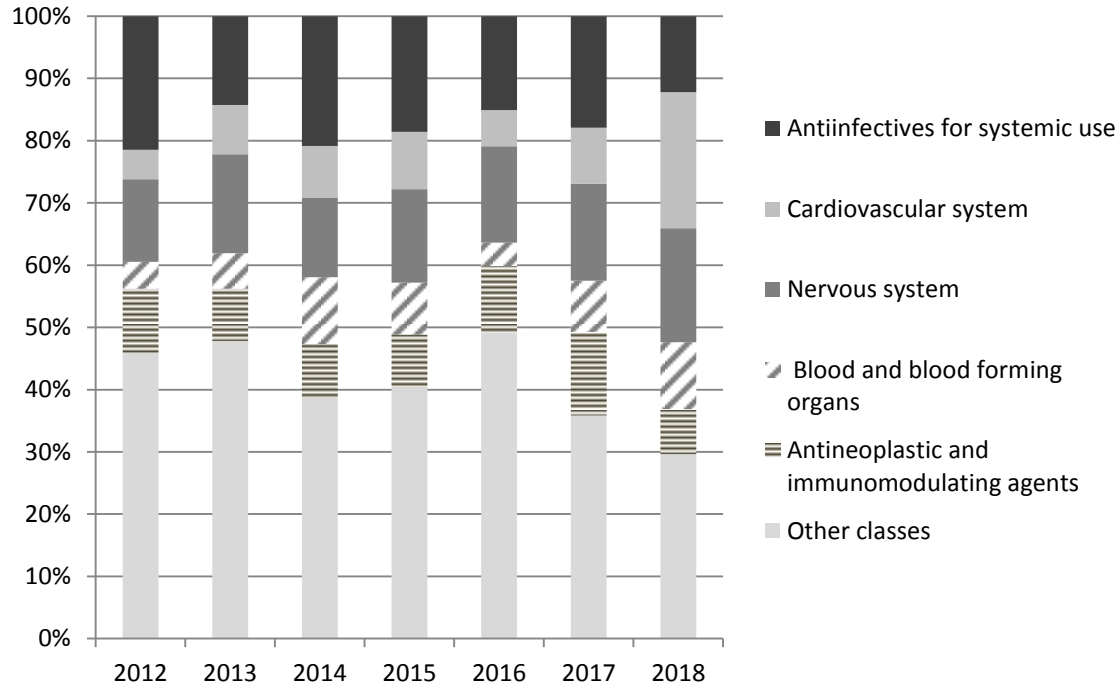


Figure 3 Trends in the proportion of pharmaceutical products on shortage by duration of marketing authorization grants (2012-2018)

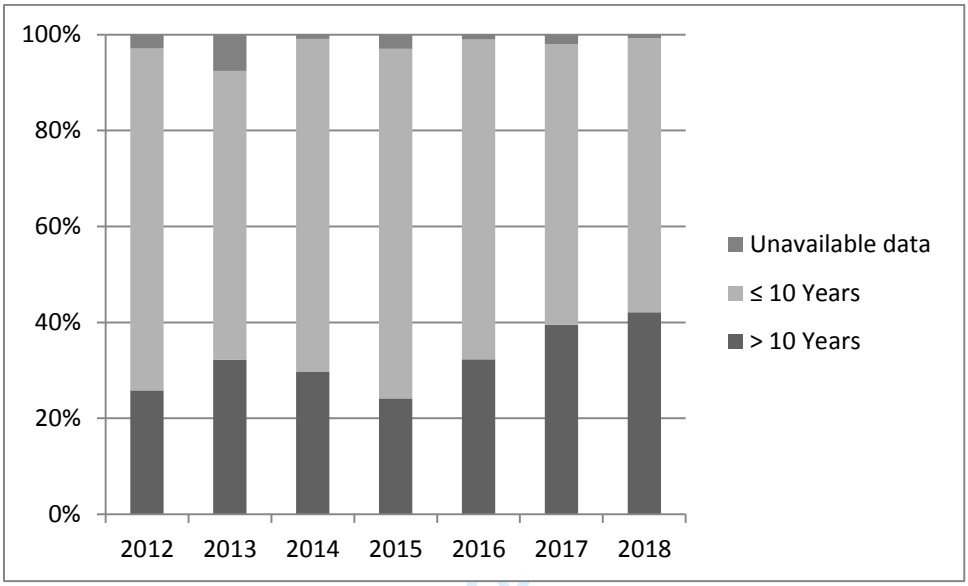
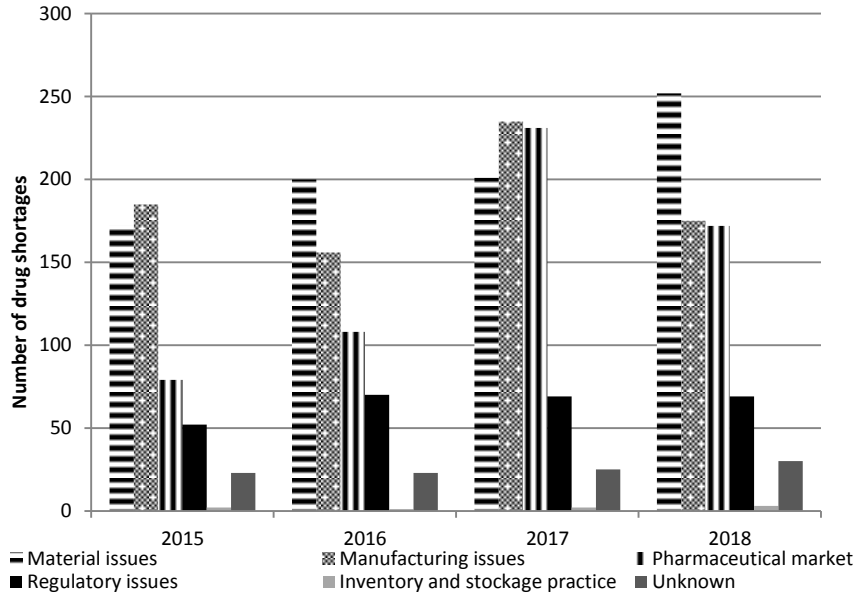


Figure 4 Trends in the causes of shortages of pharmaceutical products in 2015-2018



Order of 27 July 2016 fixing the list of therapeutic classes containing major therapeutic of interest drug mentioned in Article L. 5121-31 of the Public Health Code

A. – ALIMENTARY TRACT AND METABOLISM

A02 - DRUGS FOR ACID RELATED DISORDERS
A02B - DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)
A03 - DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS
A03B - BELLADONNA AND DERIVATIVES, PLAIN
A04 - ANTIEMETICS AND ANTINAUSEANTS
A04A - ANTIEMETICS AND ANTINAUSEANTS
A05 - BILE AND LIVER THERAPY
A05A - BILE THERAPY
A05B - LIVER THERAPY, LIPOTROPICS
A06 - DRUGS FOR CONSTIPATION
A06A - DRUGS FOR CONSTIPATION
A07 - ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ ANTIINFECTIVE AGENTS
A07A - INTESTINAL ANTIINFECTIVES
A07E - INTESTINAL ANTIINFLAMMATORY AGENTS
A10 - DRUGS USED IN DIABETES
A10A - INSULINS AND ANALOGUES
A10B - BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS
A11 - VITAMINS
A11C - VITAMIN A AND D, INCL. COMBINATIONS OF THE TWO
A11D - VITAMIN B1, PLAIN AND IN COMBINATION WITH VITAMIN B6 AND B12
A11H - OTHER PLAIN VITAMIN PREPARATIONS
A11J - OTHER VITAMIN PRODUCTS, COMBINATIONS
A12 - MINERAL SUPPLEMENTS
A12A - CALCIUM
A12B - POTASSIUM
A12C - OTHER MINERAL SUPPLEMENTS
A16 - OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS
A16A - OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS

B. – BLOOD AND BLOOD FORMING ORGANS

B01 - ANTITHROMBOTIC AGENTS
B01A - ANTITHROMBOTIC AGENTS
B02 - ANTIHEMORRHAGICS
B02A - ANTIFIBRINOLYTICS
B02B - VITAMIN K AND OTHER HEMOSTATICS
B03 - ANTIANEMIC PREPARATIONS
B03A - IRON PREPARATIONS
B03B - VITAMIN B12 AND FOLIC ACID
B03X - OTHER ANTIANEMIC PREPARATIONS
B05 - BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS
B05A - BLOOD AND RELATED PRODUCTS

B05B - I.V. SOLUTIONS
B05D - PERITONEAL DIALYTICS
B05X - I.V. SOLUTION ADDITIVES
B05Z - HEMODIALYTICS AND HEMOFILTRATES
B06 - OTHER HEMATOLOGICAL AGENTS
B06A - OTHER HEMATOLOGICAL AGENTS

C. – CARDIOVASCULAR SYSTEM

C01 - CARDIAC THERAPY
C01A - CARDIAC GLYCOSIDES
C01B - ANTIARRHYTHMICS, CLASS I AND III
C01C - CARDIAC STIMULANTS EXCL. CARDIAC GLYCOSIDES
C01D - VASODILATORS USED IN CARDIAC DISEASES
C01E - OTHER CARDIAC PREPARATIONS
C02 - ANTIHYPERTENSIVES
C02A - ANTIADRENERGIC AGENTS, CENTRALLY ACTING
C02B - ANTIADRENERGIC AGENTS, GANGLION-BLOCKING
C02C - ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING
C02D - ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON
C02K - OTHER ANTIHYPERTENSIVES
C02L - ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION
C02N - COMBINATIONS OF ANTIHYPERTENSIVES IN ATC-GR. C02
C03 - DIURETICS
C03A - LOW-CEILING DIURETICS, THIAZIDES
C03B - LOW-CEILING DIURETICS, EXCL. THIAZIDES
C03C - HIGH-CEILING DIURETICS
C03D - POTASSIUM-SPARING AGENTS
C03E - DIURETICS AND POTASSIUM-SPARING AGENTS IN COMBINATION
C03X - OTHER DIURETICS
C07 - BETA BLOCKING AGENTS
C07A - BETA BLOCKING AGENTS
C07B - BETA BLOCKING AGENTS AND THIAZIDES
C07C - BETA BLOCKING AGENTS AND OTHER DIURETICS
C07D - BETA BLOCKING AGENTS, THIAZIDES AND OTHER DIURETICS
C07E - BETA BLOCKING AGENTS AND VASODILATORS
C07F - BETA BLOCKING AGENTS AND OTHER ANTIHYPERTENSIVES
C08 - CALCIUM CHANNEL BLOCKERS
C08C - SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS
C08D - SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS
C08E - NON-SELECTIVE CALCIUM CHANNEL BLOCKERS

C08G - CALCIUM CHANNEL BLOCKERS AND DIURETICS
C09 - AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
C09A - ACE INHIBITORS, PLAIN
C09B - ACE INHIBITORS, COMBINATIONS
C09C - ANGIOTENSIN II ANTAGONISTS, PLAIN

C09D - ANGIOTENSIN II ANTAGONISTS, COMBINATIONS
C09X - OTHER AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
C010 - LIPID MODIFYING AGENTS
C10A - LIPID MODIFYING AGENTS, PLAIN

D. – DERMATOLOGICALS

D01 - ANTIFUNGALS FOR DERMATOLOGICAL USE
D01A - ANTIFUNGALS FOR TOPICAL USE
D01B - ANTIFUNGALS FOR SYSTEMIC USE
D03 - PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS
D03B - ENZYMES
D05 - ANTIPSORIATICS
D05A - ANTIPSORIATICS FOR TOPICAL USE
D05B - ANTIPSORIATICS FOR SYSTEMIC USE
D06 - ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
D07 - CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS
D07A - CORTICOSTEROIDS, PLAIN
D08 - ANTISEPTICS AND DISINFECTANTS
D08A - ANTISEPTICS AND DISINFECTANTS
D11 - OTHER DERMATOLOGICAL PREPARATIONS
D11A - OTHER DERMATOLOGICAL PREPARATIONS

G. – GENITO URINARY SYSTEM AND SEX HORMONES

G01 - GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS
G02 - OTHER GYNECOLOGICALS
G02A - OXYTOCICS
G02B - CONTRACEPTIVES FOR TOPICAL USE
G02C - OTHER GYNECOLOGICALS
G03 - SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
G03A - HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE
G03B - ANDROGENS
G03C - ESTROGENS
G03D - PROGESTOGENS
G03G - GONADOTROPINS AND OTHER OVULATION STIMULANTS
G03H - ANTIANDROGENS
G03X - OTHER SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM

H. – SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS

H01 - PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES
H01A - ANTERIOR PITUITARY LOBE HORMONES AND ANALOGUES
H01B - POSTERIOR PITUITARY LOBE HORMONES
H01C - HYPOTHALAMIC HORMONES
H02 - CORTICOSTEROIDS FOR SYSTEMIC USE
H02A - CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
H02C - ANTIADRENAL PREPARATIONS

H03 - THYROID THERAPY
H03A - THYROID PREPARATIONS
H03B - ANTITHYROID PREPARATIONS
H03C - IODINE THERAPY
H04 - PANCREATIC HORMONES
H04A - GLYCOGENOLYTIC HORMONES
H05 - CALCIUM HOMEOSTASIS
H05A - PARATHYROID HORMONES AND ANALOGUES
H05B - ANTI-PARATHYROID AGENTS

J. – ANTIIFECTIVES FOR SYSTEMIC USE

J01 - ANTIBACTERIALS FOR SYSTEMIC USE
J01A - TETRACYCLINES
J01B - AMPHENICOLS
J01C - BETA-LACTAM ANTIBACTERIALS, PENICILLINS
J01D - OTHER BETA-LACTAM ANTIBACTERIALS
J01E - SULFONAMIDES AND TRIMETHOPRIM
J01F - MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
J01G - AMINOGLYCOSIDE ANTIBACTERIALS
J01M - QUINOLONE ANTIBACTERIALS
J01R - COMBINATIONS OF ANTIBACTERIALS
J01X - OTHER ANTIBACTERIALS
J02 - ANTIMYCOTICS FOR SYSTEMIC USE
J02A - ANTIMYCOTICS FOR SYSTEMIC USE
J04 - ANTIMYCOBACTERIALS
J04A - DRUGS FOR TREATMENT OF TUBERCULOSIS
J04B - DRUGS FOR TREATMENT OF LEPRA
J05 - ANTIVIRALS FOR SYSTEMIC USE
J05A - DIRECT ACTING ANTIVIRALS
J06 - IMMUNE SERA AND IMMUNOGLOBULINS
J06A - IMMUNE SERA
J06B - IMMUNOGLOBULINS
J07 - VACCINES
J07A - BACTERIAL VACCINES
J07B - VIRAL VACCINES
J07C - BACTERIAL AND VIRAL VACCINES, COMBINED

L. – ANTINEOPLASIC AND IMMUNOMODULATING AGENTS

L01 - ANTINEOPLASTIC AGENTS
L01A - ALKYLATING AGENTS
L01B - ANTIMETABOLITES
L01C - PLANT ALKALOIDS AND OTHER NATURAL PRODUCTS
L01D - CYTOTOXIC ANTIBIOTICS AND RELATED SUBSTANCES
L01X - OTHER ANTINEOPLASTIC AGENTS
L02 - ENDOCRINE THERAPY
L02A - HORMONES AND RELATED AGENTS

L02B - HORMONE ANTAGONISTS AND RELATED AGENTS
L03 - IMMUNOSTIMULANTS
L03A - IMMUNOSTIMULANTS
L04 - IMMUNOSUPPRESSANTS
L04A - IMMUNOSUPPRESSANTS

M. – MUSCULO-SKELETAL SYSTEM

M03 - MUSCLE RELAXANTS
M03A - MUSCLE RELAXANTS, PERIPHERALLY ACTING AGENTS
M03B - MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS
M03C - MUSCLE RELAXANTS, DIRECTLY ACTING AGENTS
M04 - ANTIGOUT PREPARATIONS
M04A - ANTIGOUT PREPARATIONS
M05 - DRUGS FOR TREATMENT OF BONE DISEASES
M05B - DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION

N. – NERVOUS SYSTEM

N01 - ANESTHETICS
N01A - ANESTHETICS, GENERAL
N01B - ANESTHETICS, LOCAL
N02 - ANALGESICS
N02A - OPIOIDS
N02B - OTHER ANALGESICS AND ANTIPYRETICS
N03 - ANTIEPILEPTICS
N03A - ANTIEPILEPTICS
N04 - ANTI-PARKINSON DRUGS
N04A - ANTICHOLINERGIC AGENTS
N04B - DOPAMINERGIC AGENTS
N05 - PSYCHOLEPTICS
N05A - ANTIPSYCHOTICS
N05B - ANXIOLYTICS
N06 - PSYCHOANALEPTICS
N06A - ANTIDEPRESSANTS
N06B - PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS
N06D - ANTI-DEMENTIA DRUGS
N07 - OTHER NERVOUS SYSTEM DRUGS
N07A - PARASYMPATHOMIMETICS
N07B - DRUGS USED IN ADDICTIVE DISORDERS
N07X - OTHER NERVOUS SYSTEM DRUGS

P. – ANTIPARASITIC PRODUCTS, INSECTICIDES, AND REPELLENTS

P01 - ANTIPROTOZOALS
P01A - AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISEASES

P01B - ANTIMALARIALS
P01C - AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS
P02 - ANTHELMINTICS
P02B - ANTITREMATODALS
P02C - ANTINEMATODAL AGENTS
P02D - ANTICESTODALS
P03 - ECTOPARASITICIDES, INCL. SCABICIDES, INSECTICIDES AND REPELLENTS
P03A - ECTOPARASITICIDES, INCL. SCABICIDES

R. – RESPIRATORY SYSTEM

R03 - DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
R03A - ADRENERGICS, INHALANTS
R03B - OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS
R03C - ADRENERGICS FOR SYSTEMIC USE
R03D - OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
R06 - ANTIHISTAMINES FOR SYSTEMIC USE
R06A - ANTIHISTAMINES FOR SYSTEMIC USE
R07 - OTHER RESPIRATORY SYSTEM PRODUCTS
R07A - OTHER RESPIRATORY SYSTEM PRODUCTS

S. – SENSORY ORGANS

S01 - OPHTHALMOLOGICALS
S01A - ANTIINFECTIVES
S01B - ANTIINFLAMMATORY AGENTS
S01E - ANTIGLAUCOMA PREPARATIONS AND MIOTICS
S01F - MYDRIATICS AND CYCLOPLEGICS
S01H - LOCAL ANESTHETICS
S01J - DIAGNOSTIC AGENTS
S01L - DRUGS AGAINST OCULO-VASCULAR DISORDERS
S01X - OTHER OPHTHALMOLOGICALS
S02 - OTOLOGICALS
S02A - ANTIINFECTIVES
S02B - CORTICOSTEROIDS

V. - VARIOUS

V01 - ALLERGENS
V01A - ALLERGENS
V03 - ALL OTHER THERAPEUTIC PRODUCTS
V03A - ALL OTHER THERAPEUTIC PRODUCTS
V04 - DIAGNOSTIC AGENTS
V04C - OTHER DIAGNOSTIC AGENTS
V08 - CONTRAST MEDIA
V08A - X-RAY CONTRAST MEDIA, IODINATED
V08B - X-RAY CONTRAST MEDIA, NON-IODINATED
V08C - MAGNETIC RESONANCE IMAGING CONTRAST MEDIA

V08D - ULTRASOUND CONTRAST MEDIA
V09 - DIAGNOSTIC RADIOPHARMACEUTICALS
V09A - CENTRAL NERVOUS SYSTEM
V09B - SKELETON
V09C - RENAL SYSTEM
V09D - HEPATIC AND RETICULO ENDOTHELIAL SYSTEM
V09E - RESPIRATORY SYSTEM
V09F - THYROID
V09G - CARDIOVASCULAR SYSTEM
V09H - INFLAMMATION AND INFECTION DETECTION
V09I - TUMOUR DETECTION
V09X - OTHER DIAGNOSTIC RADIOPHARMACEUTICALS
V10 - THERAPEUTIC RADIOPHARMACEUTICALS
V10A - ANTIINFLAMMATORY AGENTS
V10B - PAIN PALLIATION (BONE SEEKING AGENTS)
V10X - OTHER THERAPEUTIC RADIOPHARMACEUTICALS

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

The French reporting system for drug shortages: description and trends from 2012 to 2018. An observational retrospective study

	Item No	Recommendation		Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	OK	2 of 45
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	OK	2 of 45
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	OK	4 of 45
Objectives	3	State specific objectives, including any prespecified hypotheses	OK	4 & 5 of 45
Methods				
Study design	4	Present key elements of study design early in the paper	OK	5 of 45
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	OK	5 of 45
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection	OK	5&6 of 45
Variables	7	Clearly define all outcomes	OK	5&6 of 45
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement).	OK	5&6 of 45
Bias	9	Describe any efforts to address potential sources of bias	OK	6 of 45
Study size	10	Explain how the study size was arrived at	OK	5&6 of 45
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	OK	5&6 of 45
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	OK	5&6 of 45
		(*b*) Describe any methods used to examine subgroups and interactions	OK	5&6 of 45
		(*c*) Explain how missing data were addressed	OK	6 of 45
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA	NA
		(*e*) Describe any sensitivity analyses	NA	NA
Results				
Participants	13*	(a) Report numbers of products at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	OK	6,7 & 15 of 45
		(b) Give reasons for non-participation at each stage	NA	NA
		(c) Consider use of a flow diagram	NA	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic,	NA	NA

		clinical, social) and information on exposures and potential confounders		
		(b) Indicate number of products with missing data for each variable of interest	OK	15 of 45
Outcome data	15*	Report numbers of outcome events or summary measures	NA	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	OK	17 to 20 of 45
Discussion				
Key results	18	Summarise key results with reference to study objectives	OK	8 of 45
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	OK	10 of 45
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	OK	9&10 of 45
Generalisability	21	Discuss the generalisability (external validity) of the study results	OK	10 of 45
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	OK	12 of 45

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The French reporting system for drug shortages: description and trends from 2012 to 2018. An observational retrospective study

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The French reporting system for drug shortages: description and trends from 2012 to 2018. An observational retrospective study

Amine Benhabib,[1, 2] Said Ioughlissen, [1] Christelle Ratignier-Carbonneil, [1] Patrick Maison[1, 3]

[1] French National Agency for Medicines and Health Products Safety (ANSM), Saint-Denis, France

[2] Strasbourg Faculty of Pharmacy, Illkirch-Graffenstaden, France

[3] EA 7379, Paris Est Creteil University (UPEC) and CHIC Hospital, Créteil, France

Correspondance to: Patrick Maison, Agence Nationale de Sécurité des Médicaments et des Produits de Santé, 143-147 bd, Anatole France, F-93285 Saint-Denis Cedex ; Tel +331 55 87 35 23 ; Fax +331 55 87 35 23 ; Email : patrick.maison@ansm.sante.fr

Running head*:* The French reporting system for drug shortages

Keywords: Drug shortages, supply of medicines, short supply, major therapeutic interest, pharmacosurveillance, France, national reporting system

Word count: *(excluding the abstract, references, tables, boxes, or figures):* **3288**

Numbers of tables and figures: 5

ABSTRACT

Objectives

The aim was to provide figures for drug shortages in France and describe their characteristics, causes, and trends between 2012 and 2018.

Methods

Data from the national reporting system from the Agency of Medicine and Health Product Safety (ANSM) was analyzed. This database contains information regarding effective and predicted shortages of major therapeutic of interest (MTI) drugs (*i.e*. drugs whose shortage would be life-threatening or representing a loss of treatment opportunity for patients with a severe disease) which are mandatory reported by marketing authorization holders to the ANSM. Data are presented as numbers or percentages of pharmaceutical products (*i.e.* the product name and its formulation) reported on shortage between 2012 and 2018.

Results

There were 3530 pharmaceutical products reported on shortage during the period, including 1833 different active substances. Drugs on shortage were mostly old products (63.4%) with national marketing authorization procedures (62.8%), as well as injectable and oral forms (47.5% and 43.3%, respectively). Antiinfectives for systemic use ranked first (18%), followed by nervous and cardiovascular system drugs and by antineoplastic and immunomodulating agents (respectively 17.4%, 12.5% and 10.4%). The number of reported shortages presented a 4-fold increase between 2012 and 2018 and a sharp rise in 2017&2018, along with a rise in the number of active substances on shortage. The therapeutic classes concerned remained similar over time. Manufacturing and material supply issues were the main reported reasons for the shortage each year (30%) and there was an overall rise of pharmaceutical market reasons.

Conclusion

Drug shortages were increasingly reported in France. Preventive measures should specifically target the products the most on shortage, in particular old drugs, injectable, antiinfective, nervous system and cardiovascular system drugs as well as antineoplastic and immunomodulating agents.

Strengths and Limitations

- This is the first study to describe and analyse drug shortages in France using a national reporting system over a 7 years period, from 2012 to 2018.
- A drug shortage is according to pharmaceutical company's perspective and reflects the inability of a pharmaceutical company to produce a drug for national needs, whereas a short supply is according to patient's perspective and defines a the unavailability of a drug in a pharmacies.
- Trends of drug shortages were described according to both pharmaceutical products (defined as a combination of the active substance, the formulation and the packaging) and International Nonproprietary Name drugs, allowing a more detailed description and interpretation of drug shortages and their causes.
- Drug shortages were defined as both effective and predicted shortages of Major Therapeutic of Interest (MTI) drugs, which may not allow generalization to all drugs.
- Reporting predictive and effective shortages to ANSM will indeed be cases where the risk of shortage will not become a short supply, but these situations reflect a production problem and may lead to short supply.

INTRODUCTION

Drug shortages are a major public health threat worldwide occurring in all therapeutic classes.[1-7] According to the WHO, a drug shortage is defined as an insufficiency in the supply of medicines, health products and vaccines that are identified by the health system as essential to meet public health and patient need.[8] Drug shortages can have detrimental effects on patients care as they may result in delayed treatment or switches into alternative therapies, therefore leading to disease progression, increased risk of adverse effects or medication errors as well as rising healthcare costs.[9-11] Multiple reasons, such as manufacturing issues, regulatory issues or economic factors, in addition to increased global demand have been suggested to underlie drug shortages.[1, 3, 12, 13]

In France, the management of drug shortages and short supply was first regulated in 2012 with a decree dated September 28th, 2012 on the supply of human drugs.[14] This decree requires the pharmaceutical operators commercializing drugs in France to ensure an appropriate and continuous supply of wholesalers and hospitals within 72 hours. Marketing authorization holders were thus mandated to notify the French National Agency of Medicine and Health Product Safety (*Agence Nationale de Sécurité du Médicament et des produits de santé* – ANSM) of any effective or predicted drug shortages, specifying the available stocks, the estimated period of shortage, the deadline for the availability of the product, as well as the substitute drugs. In 2016, the French health law of January 26th and its decree of July 20th targeted the shortages of drugs of major therapeutic of interest (MTI) defined as drugs for which unavailability would be life-threatening or represent a loss of treatment opportunity.[15] The list of the therapeutic classes of MTI drugs was provided by the ministerial order of July 27th(Supplementary materials).[16] This definition relates to some ATC classes and thus comprises all drugs from the same therapeutic class, whether they are generics or brand names. The shortage of an MTI drug has to be reported by the marketing authorization holder (MAH) to the ANSM even when another competing equivalent MTI drug is available. MAH are not aware of the productions capacities of other MAHs and thus of the availability of equivalent MIT drugs at the time of the report. The impact of a shortage in terms of public health and production is then estimated by the ANSM. The decree of July 20th also warranted new regulatory tools in order to reinforce the legal obligations of pharmaceutical companies and wholesalers. Marketing authorization holders and operators were required to develop shortage management plans (*Plan de Gestion des Pénuries – PGP*), and wholesalers were not allowed to export MTI drugs that are on effective or predicted shortage. Responsibilities of pharmaceutical operators were also strengthened by the implementation of administrative or financial penalties in case of non-compliance.[15, 17]

According to a survey conducted in 2014, drug shortages were increasingly reported in Europe and occurred daily or weekly.[3] While the issue of drug shortages has been widely studied in the USA,[18-21] figures in Europe are scarce and national trends of drug shortages are not available.[22] The identification and surveillance of the most frequent drugs on shortage and the analysis of their causes may allow implementing targeted preventive measures in order to limit the negative impacts on patient care. The present study therefore aimed to describe the characteristics and trends of reported shortages of MTI drugs in France using the national reporting system from the Agency of Medicine and Health Product Safety (ANSM).

METHODS

This observational retrospective study analyzed the surveillance reporting system of drug shortages from the French National Agency of Medicine and Health Product Safety (ANSM) between 2012 and 2018. Since 2012, marketing authorization holders are indeed obliged to declare any effective or predicted shortage of MTI drugs to the ANSM. The reporting database contains the information reported by the marketing authorization holders via completed declaration forms. The following data were analyzed: (1) from declaration forms: dates or report, drugs names, active substances (International Nonproprietary Names (INN)), routes of administration, setting first impacted by the shortage (community pharmacy and/or hospital), reasons for the shortages (available since 2015); (2) from the marketing authorization dossier and the summary of the product characteristics: dates and procedures of marketing authorization grants, storage conditions; and (3) ATC codes according to the WHO Collaborating Centre for Drug Statistics Methodology.[23]

Marketing authorization holders (MAH) shall follow the manufacturing circuit of its drugs, and reporting to the ANSM is required for each dysfunction that may result in effective or predictive shortages. A drug shortage reflects the inability of a pharmaceutical company to produce a drug and maintain its marketing at a national level, whereas the short supply defines the unavailability of a drug in pharmacies. In addition, a short supply assesses the sanitary risk in the scope of the pharmacy practice whereas drug shortages highlight issues in pharmaceutical production. According to these definitions of drug shortages, short supply was not considered in present study.

Reports of drug shortage were therefore defined as both effective and predicted shortages of MTI drugs recorded by the ANSM each year.

Duration of the marketing authorization grant was defined as the difference between the years of the shortage reports and the year when the marketing authorization was granted.

Causes of shortages were categorized into: (1) manufacturing issues, including the stage of manufacturing or packaging of the final product ; (2) material issues, *i.e.,* defect in raw materials, excipients, packaging and semi-finished or bulk pharmaceuticals ; (3) pharmaceutical market, *i.e.,* related to the difficulty of the operator to purchase products, including insufficient production capacity ; (4) regulatory issues, *i.e.*, new regulation directly related to the delayed marketing ; and (5) inventory and storage practices, *i.e.,* stock errors or inappropriate management of expiry date.

Data were presented in numbers or in percentages of pharmaceutical products reported on shortage. Pharmaceutical products were defined as a combination of the International Nonproprietary Name (INN), the formulation and the packaging and are identified by the *code identifiant de spécialité* (CIS). Therefore, a shortage of a pharmaceutical product does not necessarily imply the shortages of all drugs with the same INN.

There were no missing data except for marketing authorization procedures and duration of marketing authorization grants.

Patient and public involvement

Patients were not directly involved in the design, planning and conception of this study.

RESULTS

Between the years 2012 and 2018, 3530 pharmaceutical products were reported of on shortage, including 1833 different International Nonproprietary Name (INN) drugs. The overall characteristics of the pharmaceutical products reported on shortage from 2012 to 2018 are presented in **table 1**. Drugs with a marketing authorization granted more than 10 years ago (63.4%) and according to a national procedure (62.8%) were the most concerned. Generics drugs accounted for 34% of shortages overall and for 17% of old drugs (marketing authorization grant > 10 years). Community pharmacies and hospitals were similarly first impacted by shortages. Injectable and oral were the most commonly affected forms (with respectively 47.5% and 43.3%). With regards to ATC classes, antiinfectives for systemic use ranked first with 18% of total shortage reports, followed by nervous and cardiovascular system drugs as well as by antineoplastic and immunomodulating agents (with

respectively 17.4%, 12.5% and 10.4) (**table 1**). Antibacterial for systemic use and vaccines accounted for 53% and 19% of antiinfectives shortages, respectively. Antiepileptic, anesthesic and analgesic products were among the most common nervous system drugs on shortage (22%, 18% and 16%, respectively). Cephalosporins were the most common antibacterial drug class reported on shortage.

Trends in the number of pharmaceutical products and INN drugs reported on shortage were shown in **figure 1**. There was a 4-fold increase in the total products on shortage between 2012 and 2018, to reach 917 shortages in 2018. The numbers of INN on shortage were similar in 2013 and 2017 but presented a 2-fold increase between the years 2012 and 2018, to reach a peak in 2018 (n=399) (**figure 1**).

Injectable and oral forms remained the two main pharmaceutical forms on shortage each year (from 51% to 37% and 40% to 56% between 2012 and 2018 for injectable and oral forms, respectively).

All therapeutic classes were reported on shortage each year. **Figure 2** presents the trends in proportions of shortage of pharmaceutical products by ATC classes from 2012 to 2018. The distribution of ATC classes reported on shortage was similar over time. Antiinfectives for systemic use, nervous system drugs as well as antineoplastic and immunomodulating agents ranked among the first classes on shortage until 2017. Shortages of cardiovascular system drugs were increasingly reported since 2012 and a sharp rise occurred in 2018 (n=216 reports). Cardiovascular drugs ranked first in 2018 (24%), explained by products of valsartan accounting for half of shortages. The proportion of nervous system drugs, antiinfectives and antineoplastic and immunomodulating agents on shortage was relatively stable over the years (**figure 2**). Yet, a continuous increase of shortages was observed for nervous system drugs that ranked second in 2018 (n=181 reports) (**figure 2**). In 2018, antiepileptics accounted for the most reported class of nervous system drugs on shortage (34%), of which 13 were topiramate-based products. There was also a rise in shortages of antiinfective products in 2017 (n=122), driven in half by antibacterial drugs, in particular cephalosporins (n=23). Among antiinfectives, antibacterial drugs were the first class reported on shortage each year between 2012 and 2018, followed by vaccines (data not shown).

Figure 3 presents the trends in the proportion of shortage of pharmaceutical products by duration of marketing authorization grant from 2012 to 2018. During that period, drugs with an old marketing authorization grant (of more than 10 years) were the most reported on shortage.

Drug shortages first impacting hospital settings accounted for half of the shortages in 2017 and for a third in other years. Similar trends in the proportion of shortage were observed for settings first impacted (data not shown).

Trends in the reported causes of shortages between 2015 and 2018 are shown in **figure 4**. Manufacturing and material supply issues were the main reasons each year with approximately 30% of the shortage share. There was an overall rise of pharmaceutical market reasons.

DISCUSSION

Based on the French national reporting system, the present study described the characteristics of MTI drugs reported on shortage in France between 2012 and 2018 as mostly: old drugs, drugs with national marketing authorization procedures and injectables. Both hospital and community pharmacies were similarly affected by shortages and one third of them first occurred in hospital settings. Four therapeutic classes (antiinfectives, nervous system, cardiovascular system drugs, antineoplastics and immunomodulating agents) remained the most on shortage with the same distribution over the years. The number of pharmaceutical products reported on shortage increased by 4-fold between 2012 and 2018, along with a rise in the number of INN drugs. In 2018, the number of pharmaceutical products on shortage reached a peak, with 399 different active substances from all therapeutic classes affected by shortage. Compared with the number (n=2 800) of approved and marketed INN drugs in France in 2016,[24] there were approximately 13% of INN drugs on shortage in 2018 and 60% during the 2012-2018 period.

The present rise in drug shortages in France is concomitant with the observed trends in the USA, reflecting the international public health challenge of drug shortages. According to the University of Utah Drug Information Service (UUDIS), new drugs on shortage in the USA were found to triple between 2004 and 2018, although a decrease occurred since 2012.[25] Comparisons of figures between the two countries are yet limited by differences in definitions of drug shortage [2] as well as differences in pharmaceutical products, blister packaging being less used in the USA.

The four therapeutic classes most impacted by shortages in the present study were antiinfectives for systemic use, nervous system drugs, cardiovascular drugs and antineoplastic and immunomodulating agents, in accordance with previous results from a European review finding that these same four classes represented over 50% of reported shortage.[4] We found that antiinfectives for systemic use represented the first therapeutic class reported on shortage until 2018 (18%) among which antibacterial drugs ranked first each year. This trend is well documented across the United States. Antimicrobials were the most common drug class on shortage in critical care (2001-2016) and emergency medicine practice (2001-2014), representing respectively 20% and 24% of US shortages.[19,

[20] Cephalosporins were the most common antibacterial drug class, in accordance with findings from a US study using the UUDIS database from 2001 to 2013.[26] Shortages of antimicrobials may not have alternative production sources and may thus require the use of less effective or more toxic alternatives,[20, 26] leading to worse patient outcomes.[18] In a European survey, antiinfectives were also found to be the most common drugs on shortage in hospital pharmacies in 2013, along with cancer drugs.[22] The burden of cancer drug shortages was previously highlighted in the United States[27, 28] and more recently in a hospital paediatric hemato-oncology unit in Belgium.[7] A lack of market attractiveness and low profitability has been suggested as a cause of shortages, due to prompting the discontinuation of some long-standing or lower-priced products such as antibiotics and oncologic medicines.[1]

In the present study, cardiovascular drugs were one of the first therapeutic classes on shortage and the first in 2018 (28%). This was driven by shortages of valsartan products resulting from the detection in 2018 of impurities in the active substance of valsartan-based medicines. As a precaution, all potentially impacted batches of valsartan containing drugs were recalled in France since July 2018.[29] Shortage of cardiovascular drugs was also common in the USA.[20, 30]

In this study, shortages mostly involved injectable products each year. This finding is consistent with previous surveys in Europe and USA.[4, 20] Injectable products are at increased risk of shortage related to quality control concerns because of the complexities associated with manufacturing a sterile product.[2] Oral drugs also accounted for a large share of shortages in our study, reflecting that causes of drug shortages goes beyond pure manufacturing problems related to technical issues or quality problems.

According to our results, old drugs were the most reported on shortage during the period from year 2012 to year 2018, with 63.4% of drug shortages while there were 45% of old products on the market in 2018 in France. Age of the marketing authorization is thus likely to be a major determinant of drug shortage, in accordance with a US study finding that the age of drug was a strong risk factor for shortage in oncology.[27] According to the authors, this result suggested that policies focused predominately on promoting increases in distinct suppliers and that competition may not alleviate drug shortages.

The reasons behind drug shortages are complex and many factors may contribute simultaneously. In France, the increase in drug shortage reports may in part be related to changes in the regulations. Since 2012, marketing authorization holders are required to report shortages and otherwise subjected to financial sanctions since 2016. Regulatory changes may impact the reporting of drug shortage. Yet, not all drugs were affected by shortage in our study, which goes beyond regulatory

changes and is more concordant with increased needs along with inadequate production and supply issues. Raw material shortages and production issues have been considered global and as having similar impacts in European countries.[3, 4, 12] Manufacturing problems stem from concentration and rationalization of pharmaceutical manufacturing, as well as globalization.[3] In our study, material and manufacturing issues were the main causes of shortages each year and a rise in shortages related to pharmaceutical market was observed over the years. One explanation may be a rise in the global use of pharmaceutical products worldwide. The structure of the pharmaceutical market was previously found to be a key determinant of drug shortages in Finland.[12] In our study, pharmaceutical market issues included hospital trade and competitive bidding tenders that may contribute to compromise the supply of MTI drugs at hospital.

Some limitations to the present study should be noted. First, the results were relating to shortage of MTI drugs from national stocks supplies, which may not allow generalization to all drugs, although MTI drugs include all therapeutic classes. Second, the data were sourced from statement reports of marketing authorization holders and missing data cannot be ruled out. According to the definition of drug shortages in France, short supply was not considered in the present study. The combination of data from both authorities and pharmacy practice has been suggested to improve the surveillance.[31] This requires a standardization of definition of drug shortages between European members. Yet, the financial penalty for non-compliance with mandatory declaration of marketing authorization holders limits the cases of under-reporting and shortages of MTI drugs would obviously be reported to the ANSM by health professionals or patients otherwise. Third, the data relating to effective and predicted drug shortages may not reflect the effective short supplies, thus limiting the clinical interpretations of the present results. Fourth, reporting effective or predictive shortages to ANSM is required. There will indeed be cases where the risk of shortage will not become a short supply, but these two situations both reflect a production problem and may lead to short supply.

Strengths of the present study include the analysis of a national reporting system over a 7 years period. This is the first study to analyze the issue of drug shortages in France. Trends of drug shortages were described according to pharmaceutical products and INN drugs, allowing a more detailed description and interpretation of drug shortages and their causes.

Reporting of drug shortages has been required to be standardized between all European member States as well as coordination of legal and organizational strategies.[3, 4] A European collaboration (Task Force) set up by the European Medicine Agency is ongoing since 2016, to provide support and advice to tackle disruptions in supply of medicines and ensure their continued availability.[32] According to Woodcock &al,[33] it would be useful to stimulate investments to increase industrial

production capacities, in particular for injectable drugs. Moreover, data of the financial impact of drug shortages are lacking. A calculation of the opportunity cost would be an argument to stimulate these investments.

CONCLUSION

Shortage reports of major therapeutic of interest drugs were frequent and increasing over the 2012 to 2018 period in France. Preventive measures, including contingency plans, should particularly target old drugs, injectables, antiinfectives, nervous system, cardiovascular system drugs as well as antineoplastic and immunomodulating agents. The issue of drug shortages goes beyond national concerns. Many drugs reported on shortages being granted by a European marketing authorization. Even if the characteristics of drugs and reasons of shortages found in the present study are likely to be generalized to Europe, further studies are needed to address drug shortages at the European level.

Contributors

AB contributed to data collection and data analysis. PM designed the project. SI, CRC and PM contributed to methods of the study. All authors contributed to the interpretation of data and to the writing of the manuscript.

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Data sharing

Data were reported from the pharmaceutical companies and confidential

Competing interests :

None

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Table 1 Characteristics of pharmaceutical products reported on shortage in 2012-2018

	2012-2018 n (%)
Total	**3530 (100)**
Marketing authorization procedures	
National	2217 (62.8)
European	1249 (35.4)
Unavailable data	64 (1.81)
Duration of marketing authorization grants	
> 10 years	2237 (63.4)
≤ 10 years	1212 (34.3)
Unavailable data	81 (2.30)
Pharmaceutical forms	
Oral	1529 (43.3)
Injectable	1675 (47.5)
Others	326 (9.24)
Storage conditions	
Ambient temperature	2995 (84.8)
+2°C < Temperature < +8°C	533 (16.0)
- 18°C < Temperature	2 (0.00)
ATC Classes	
Alimentary tract and metabolism	217 (6.15)
Antiinfectives for systemic use	634 (18.0)
Antineoplastic and immunomodulating agents	367 (10.4)
Antiparasitic products, insecticides and repellents	39 (1.10)
Blood and blood forming organs	312 (8.84)
Cardiovascular system	442 (12.5)
Dermatologicals	59 (1.67)
Genitourinary system and reproductive hormones	151 (4.30)
Musculoskeletal system	155 (4.40)
Nervous system	613 (17.4)
Respiratory system	119 (3.40)
Sensory organs	97 (2.80)
Systemic hormonal preparations	160 (4.53)
Various/others	165 (4.70)

Figures legends

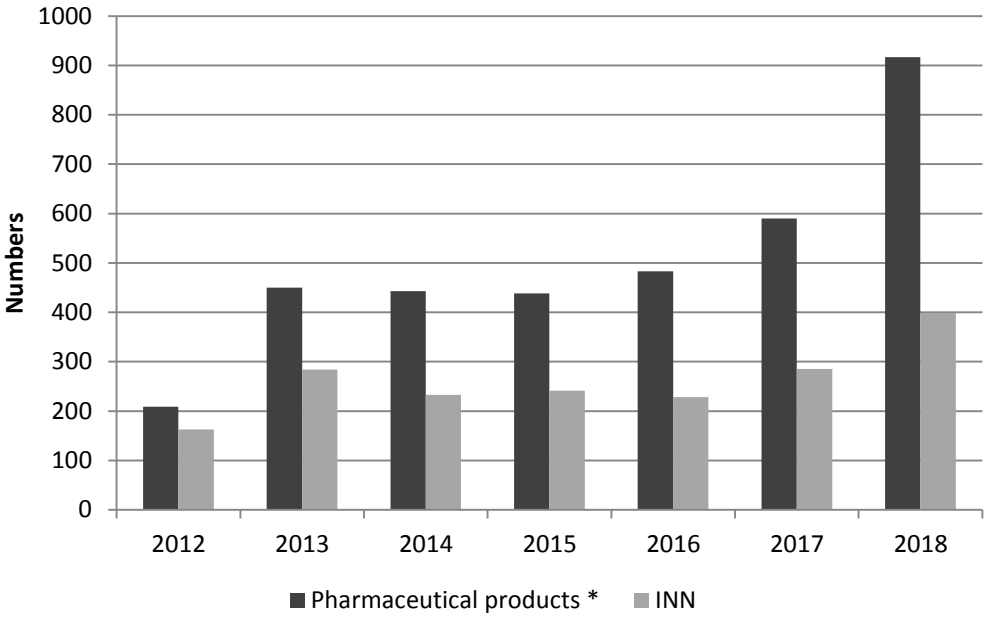
Figure 1 Trends in shortages by numbers of pharmaceutical products and International Nonproprietary Name drugs (INN) (2012-2018) in France.

Figure 2 Trends in the proportion of pharmaceutical products on shortage by ATC classes (2012-2018)

Figure 3 Trends in the proportion of pharmaceutical products on shortage by duration of marketing authorization grants

Figure 4 Trends in the causes of shortages of pharmaceutical products in 2015-2018

Figure 1 Trends in shortages by numbers of pharmaceutical products and International Nonproprietary Name drugs (INN) (2012-2018) in France.



*** Pharmaceutical products:** defined by a combination of the International Nonproprietary Name (INN), the formulation and the packaging

Figure 2 Trends in the proportion of pharmaceutical products on shortage by ATC classes (2012-2018)

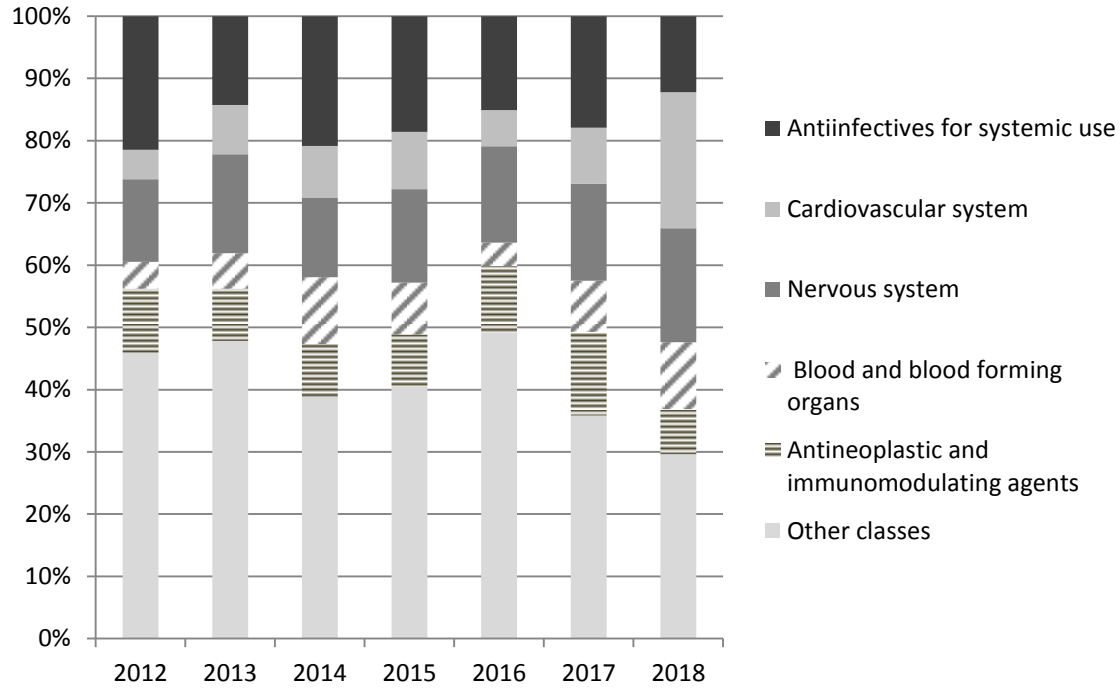


Figure 3 Trends in the proportion of pharmaceutical products on shortage by duration of marketing authorization grants (2012-2018)

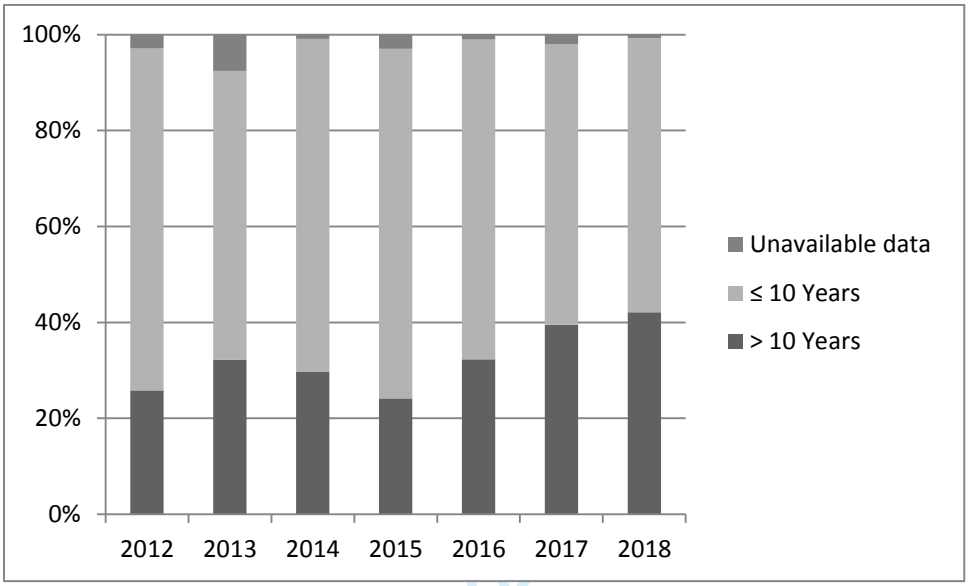
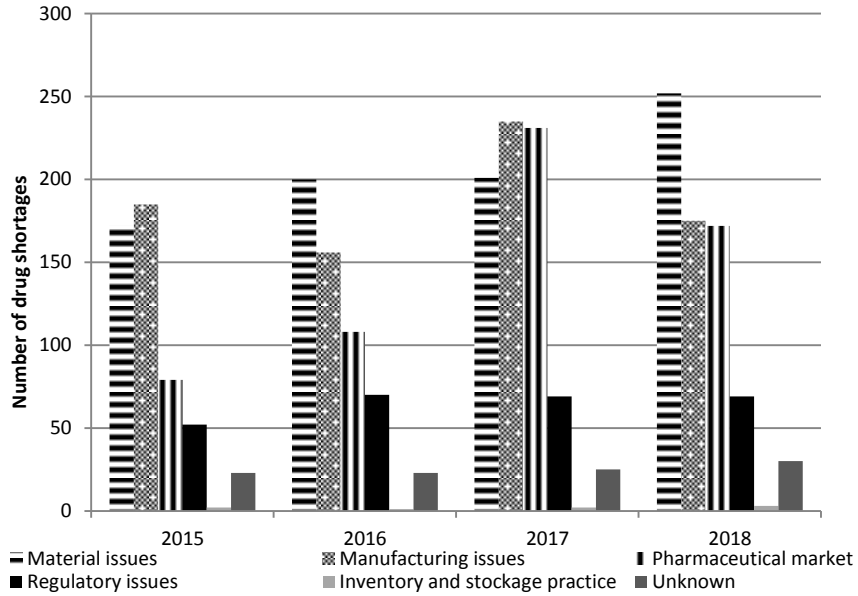


Figure 4 Trends in the causes of shortages of pharmaceutical products in 2015-2018



Order of 27 July 2016 fixing the list of therapeutic classes containing major therapeutic of interest drug mentioned in Article L. 5121-31 of the Public Health Code

A. – ALIMENTARY TRACT AND METABOLISM

A02 - DRUGS FOR ACID RELATED DISORDERS
A02B - DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)
A03 - DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS
A03B - BELLADONNA AND DERIVATIVES, PLAIN
A04 - ANTIEMETICS AND ANTINAUSEANTS
A04A - ANTIEMETICS AND ANTINAUSEANTS
A05 - BILE AND LIVER THERAPY
A05A - BILE THERAPY
A05B - LIVER THERAPY, LIPOTROPICS
A06 - DRUGS FOR CONSTIPATION
A06A - DRUGS FOR CONSTIPATION
A07 - ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ ANTIINFECTIVE AGENTS
A07A - INTESTINAL ANTIINFECTIVES
A07E - INTESTINAL ANTIINFLAMMATORY AGENTS
A10 - DRUGS USED IN DIABETES
A10A - INSULINS AND ANALOGUES
A10B - BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS
A11 - VITAMINS
A11C - VITAMIN A AND D, INCL. COMBINATIONS OF THE TWO
A11D - VITAMIN B1, PLAIN AND IN COMBINATION WITH VITAMIN B6 AND B12
A11H - OTHER PLAIN VITAMIN PREPARATIONS
A11J - OTHER VITAMIN PRODUCTS, COMBINATIONS
A12 - MINERAL SUPPLEMENTS
A12A - CALCIUM
A12B - POTASSIUM
A12C - OTHER MINERAL SUPPLEMENTS
A16 - OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS
A16A - OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS

B. – BLOOD AND BLOOD FORMING ORGANS

B01 - ANTITHROMBOTIC AGENTS
B01A - ANTITHROMBOTIC AGENTS
B02 - ANTIHEMORRHAGICS
B02A - ANTIFIBRINOLYTICS
B02B - VITAMIN K AND OTHER HEMOSTATICS
B03 - ANTIANEMIC PREPARATIONS
B03A - IRON PREPARATIONS
B03B - VITAMIN B12 AND FOLIC ACID
B03X - OTHER ANTIANEMIC PREPARATIONS
B05 - BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS
B05A - BLOOD AND RELATED PRODUCTS

B05B - I.V. SOLUTIONS
B05D - PERITONEAL DIALYTICS
B05X - I.V. SOLUTION ADDITIVES
B05Z - HEMODIALYTICS AND HEMOFILTRATES
B06 - OTHER HEMATOLOGICAL AGENTS
B06A - OTHER HEMATOLOGICAL AGENTS

C. – CARDIOVASCULAR SYSTEM

C01 - CARDIAC THERAPY
C01A - CARDIAC GLYCOSIDES
C01B - ANTIARRHYTHMICS, CLASS I AND III
C01C - CARDIAC STIMULANTS EXCL. CARDIAC GLYCOSIDES
C01D - VASODILATORS USED IN CARDIAC DISEASES
C01E - OTHER CARDIAC PREPARATIONS
C02 - ANTIHYPERTENSIVES
C02A - ANTIADRENERGIC AGENTS, CENTRALLY ACTING
C02B - ANTIADRENERGIC AGENTS, GANGLION-BLOCKING
C02C - ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING
C02D - ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON
C02K - OTHER ANTIHYPERTENSIVES
C02L - ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION
C02N - COMBINATIONS OF ANTIHYPERTENSIVES IN ATC-GR. C02
C03 - DIURETICS
C03A - LOW-CEILING DIURETICS, THIAZIDES
C03B - LOW-CEILING DIURETICS, EXCL. THIAZIDES
C03C - HIGH-CEILING DIURETICS
C03D - POTASSIUM-SPARING AGENTS
C03E - DIURETICS AND POTASSIUM-SPARING AGENTS IN COMBINATION
C03X - OTHER DIURETICS
C07 - BETA BLOCKING AGENTS
C07A - BETA BLOCKING AGENTS
C07B - BETA BLOCKING AGENTS AND THIAZIDES
C07C - BETA BLOCKING AGENTS AND OTHER DIURETICS
C07D - BETA BLOCKING AGENTS, THIAZIDES AND OTHER DIURETICS
C07E - BETA BLOCKING AGENTS AND VASODILATORS
C07F - BETA BLOCKING AGENTS AND OTHER ANTIHYPERTENSIVES
C08 - CALCIUM CHANNEL BLOCKERS
C08C - SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS
C08D - SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS
C08E - NON-SELECTIVE CALCIUM CHANNEL BLOCKERS

C08G - CALCIUM CHANNEL BLOCKERS AND DIURETICS
C09 - AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
C09A - ACE INHIBITORS, PLAIN
C09B - ACE INHIBITORS, COMBINATIONS
C09C - ANGIOTENSIN II ANTAGONISTS, PLAIN

C09D - ANGIOTENSIN II ANTAGONISTS, COMBINATIONS
C09X - OTHER AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM
C010 - LIPID MODIFYING AGENTS
C10A - LIPID MODIFYING AGENTS, PLAIN

D. – DERMATOLOGICALS

D01 - ANTIFUNGALS FOR DERMATOLOGICAL USE
D01A - ANTIFUNGALS FOR TOPICAL USE
D01B - ANTIFUNGALS FOR SYSTEMIC USE
D03 - PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS
D03B - ENZYMES
D05 - ANTIPSORIATICS
D05A - ANTIPSORIATICS FOR TOPICAL USE
D05B - ANTIPSORIATICS FOR SYSTEMIC USE
D06 - ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE
D07 - CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS
D07A - CORTICOSTEROIDS, PLAIN
D08 - ANTISEPTICS AND DISINFECTANTS
D08A - ANTISEPTICS AND DISINFECTANTS
D11 - OTHER DERMATOLOGICAL PREPARATIONS
D11A - OTHER DERMATOLOGICAL PREPARATIONS

G. – GENITO URINARY SYSTEM AND SEX HORMONES

G01 - GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS
G02 - OTHER GYNECOLOGICALS
G02A - OXYTOCICS
G02B - CONTRACEPTIVES FOR TOPICAL USE
G02C - OTHER GYNECOLOGICALS
G03 - SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
G03A - HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE
G03B - ANDROGENS
G03C - ESTROGENS
G03D - PROGESTOGENS
G03G - GONADOTROPINS AND OTHER OVULATION STIMULANTS
G03H - ANTIANDROGENS
G03X - OTHER SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM

H. – SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS

H01 - PITUITARY AND HYPOTHALAMIC HORMONES AND ANALOGUES
H01A - ANTERIOR PITUITARY LOBE HORMONES AND ANALOGUES
H01B - POSTERIOR PITUITARY LOBE HORMONES
H01C - HYPOTHALAMIC HORMONES
H02 - CORTICOSTEROIDS FOR SYSTEMIC USE
H02A - CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN
H02C - ANTIADRENAL PREPARATIONS

H03 - THYROID THERAPY
H03A - THYROID PREPARATIONS
H03B - ANTITHYROID PREPARATIONS
H03C - IODINE THERAPY
H04 - PANCREATIC HORMONES
H04A - GLYCOGENOLYTIC HORMONES
H05 - CALCIUM HOMEOSTASIS
H05A - PARATHYROID HORMONES AND ANALOGUES
H05B - ANTI-PARATHYROID AGENTS

J. – ANTIIFECTIVES FOR SYSTEMIC USE

J01 - ANTIBACTERIALS FOR SYSTEMIC USE
J01A - TETRACYCLINES
J01B - AMPHENICOLS
J01C - BETA-LACTAM ANTIBACTERIALS, PENICILLINS
J01D - OTHER BETA-LACTAM ANTIBACTERIALS
J01E - SULFONAMIDES AND TRIMETHOPRIM
J01F - MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
J01G - AMINOGLYCOSIDE ANTIBACTERIALS
J01M - QUINOLONE ANTIBACTERIALS
J01R - COMBINATIONS OF ANTIBACTERIALS
J01X - OTHER ANTIBACTERIALS
J02 - ANTIMYCOTICS FOR SYSTEMIC USE
J02A - ANTIMYCOTICS FOR SYSTEMIC USE
J04 - ANTIMYCOBACTERIALS
J04A - DRUGS FOR TREATMENT OF TUBERCULOSIS
J04B - DRUGS FOR TREATMENT OF LEPRA
J05 - ANTIVIRALS FOR SYSTEMIC USE
J05A - DIRECT ACTING ANTIVIRALS
J06 - IMMUNE SERA AND IMMUNOGLOBULINS
J06A - IMMUNE SERA
J06B - IMMUNOGLOBULINS
J07 - VACCINES
J07A - BACTERIAL VACCINES
J07B - VIRAL VACCINES
J07C - BACTERIAL AND VIRAL VACCINES, COMBINED

L. – ANTINEOPLASIC AND IMMUNOMODULATING AGENTS

L01 - ANTINEOPLASTIC AGENTS
L01A - ALKYLATING AGENTS
L01B - ANTIMETABOLITES
L01C - PLANT ALKALOIDS AND OTHER NATURAL PRODUCTS
L01D - CYTOTOXIC ANTIBIOTICS AND RELATED SUBSTANCES
L01X - OTHER ANTINEOPLASTIC AGENTS
L02 - ENDOCRINE THERAPY
L02A - HORMONES AND RELATED AGENTS

L02B - HORMONE ANTAGONISTS AND RELATED AGENTS
L03 - IMMUNOSTIMULANTS
L03A - IMMUNOSTIMULANTS
L04 - IMMUNOSUPPRESSANTS
L04A - IMMUNOSUPPRESSANTS

M. – MUSCULO-SKELETAL SYSTEM

M03 - MUSCLE RELAXANTS
M03A - MUSCLE RELAXANTS, PERIPHERALLY ACTING AGENTS
M03B - MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS
M03C - MUSCLE RELAXANTS, DIRECTLY ACTING AGENTS
M04 - ANTIGOUT PREPARATIONS
M04A - ANTIGOUT PREPARATIONS
M05 - DRUGS FOR TREATMENT OF BONE DISEASES
M05B - DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION

N. – NERVOUS SYSTEM

N01 - ANESTHETICS
N01A - ANESTHETICS, GENERAL
N01B - ANESTHETICS, LOCAL
N02 - ANALGESICS
N02A - OPIOIDS
N02B - OTHER ANALGESICS AND ANTIPYRETICS
N03 - ANTIEPILEPTICS
N03A - ANTIEPILEPTICS
N04 - ANTI-PARKINSON DRUGS
N04A - ANTICHOLINERGIC AGENTS
N04B - DOPAMINERGIC AGENTS
N05 - PSYCHOLEPTICS
N05A - ANTIPSYCHOTICS
N05B - ANXIOLYTICS
N06 - PSYCHOANALEPTICS
N06A - ANTIDEPRESSANTS
N06B - PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS
N06D - ANTI-DEMENTIA DRUGS
N07 - OTHER NERVOUS SYSTEM DRUGS
N07A - PARASYMPATHOMIMETICS
N07B - DRUGS USED IN ADDICTIVE DISORDERS
N07X - OTHER NERVOUS SYSTEM DRUGS

P. – ANTIPARASITIC PRODUCTS, INSECTICIDES, AND REPELLENTS

P01 - ANTIPROTOZOALS
P01A - AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISEASES

P01B - ANTIMALARIALS
P01C - AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS
P02 - ANTHELMINTICS
P02B - ANTITREMATODALS
P02C - ANTINEMATODAL AGENTS
P02D - ANTICESTODALS
P03 - ECTOPARASITICIDES, INCL. SCABICIDES, INSECTICIDES AND REPELLENTS
P03A - ECTOPARASITICIDES, INCL. SCABICIDES

R. – RESPIRATORY SYSTEM

R03 - DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
R03A - ADRENERGICS, INHALANTS
R03B - OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS
R03C - ADRENERGICS FOR SYSTEMIC USE
R03D - OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
R06 - ANTIHISTAMINES FOR SYSTEMIC USE
R06A - ANTIHISTAMINES FOR SYSTEMIC USE
R07 - OTHER RESPIRATORY SYSTEM PRODUCTS
R07A - OTHER RESPIRATORY SYSTEM PRODUCTS

S. – SENSORY ORGANS

S01 - OPHTHALMOLOGICALS
S01A - ANTIINFECTIVES
S01B - ANTIINFLAMMATORY AGENTS
S01E - ANTIGLAUCOMA PREPARATIONS AND MIOTICS
S01F - MYDRIATICS AND CYCLOPLEGICS
S01H - LOCAL ANESTHETICS
S01J - DIAGNOSTIC AGENTS
S01L - DRUGS AGAINST OCULO-VASCULAR DISORDERS
S01X - OTHER OPHTHALMOLOGICALS
S02 - OTOLOGICALS
S02A - ANTIINFECTIVES
S02B - CORTICOSTEROIDS

V. - VARIOUS

V01 - ALLERGENS
V01A - ALLERGENS
V03 - ALL OTHER THERAPEUTIC PRODUCTS
V03A - ALL OTHER THERAPEUTIC PRODUCTS
V04 - DIAGNOSTIC AGENTS
V04C - OTHER DIAGNOSTIC AGENTS
V08 - CONTRAST MEDIA
V08A - X-RAY CONTRAST MEDIA, IODINATED
V08B - X-RAY CONTRAST MEDIA, NON-IODINATED
V08C - MAGNETIC RESONANCE IMAGING CONTRAST MEDIA

V08D - ULTRASOUND CONTRAST MEDIA
V09 - DIAGNOSTIC RADIOPHARMACEUTICALS
V09A - CENTRAL NERVOUS SYSTEM
V09B - SKELETON
V09C - RENAL SYSTEM
V09D - HEPATIC AND RETICULO ENDOTHELIAL SYSTEM
V09E - RESPIRATORY SYSTEM
V09F - THYROID
V09G - CARDIOVASCULAR SYSTEM
V09H - INFLAMMATION AND INFECTION DETECTION
V09I - TUMOUR DETECTION
V09X - OTHER DIAGNOSTIC RADIOPHARMACEUTICALS
V10 - THERAPEUTIC RADIOPHARMACEUTICALS
V10A - ANTIINFLAMMATORY AGENTS
V10B - PAIN PALLIATION (BONE SEEKING AGENTS)
V10X - OTHER THERAPEUTIC RADIOPHARMACEUTICALS

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

The French reporting system for drug shortages: description and trends from 2012 to 2018. An observational retrospective study

	Item No	Recommendation		Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	OK	2 of 45
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	OK	2 of 45
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	OK	4 of 45
Objectives	3	State specific objectives, including any prespecified hypotheses	OK	4 & 5 of 45
Methods				
Study design	4	Present key elements of study design early in the paper	OK	5 of 45
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	OK	5 of 45
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection	OK	5&6 of 45
Variables	7	Clearly define all outcomes	OK	5&6 of 45
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement).	OK	5&6 of 45
Bias	9	Describe any efforts to address potential sources of bias	OK	6 of 45
Study size	10	Explain how the study size was arrived at	OK	5&6 of 45
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	OK	5&6 of 45
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	OK	5&6 of 45
		(*b*) Describe any methods used to examine subgroups and interactions	OK	5&6 of 45
		(*c*) Explain how missing data were addressed	OK	6 of 45
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA	NA
		(*e*) Describe any sensitivity analyses	NA	NA
Results				
Participants	13*	(a) Report numbers of products at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	OK	6,7 & 15 of 45
		(b) Give reasons for non-participation at each stage	NA	NA
		(c) Consider use of a flow diagram	NA	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic,	NA	NA

		clinical, social) and information on exposures and potential confounders		
		(b) Indicate number of products with missing data for each variable of interest	OK	15 of 45
Outcome data	15*	Report numbers of outcome events or summary measures	NA	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	OK	17 to 20 of 45
Discussion				
Key results	18	Summarise key results with reference to study objectives	OK	8 of 45
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	OK	10 of 45
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	OK	9&10 of 45
Generalisability	21	Discuss the generalisability (external validity) of the study results	OK	10 of 45
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	OK	12 of 45

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.