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The new regulatory tools of the 2016 Health Law to fight drug shortages in France☆

François Bocquet[a,b,c,*], Albane Degrassat-Théas[a,b,c], Jérôme Peigné[a,b], Pascal Paubel[a,b,c]

[a] Law and Health Economics Department, Faculty of Pharmacy, Paris Descartes University, Sorbonne Paris Cité, 4 avenue de l'Observatoire, 75006 Paris, France'
[b] Health Law Institute (INSERM UMR S1145), Paris Descartes University, Sorbonne Paris Cité, 45 rue des Saints-Pères, 75006 Paris, France
[c] Pharmacy Department, General Agency of Equipments and Health Products (AGEPS), 7 rue du Fer à Moulin, 75005 Paris, France

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ABSTRACT

Drug shortages are becoming worrying for public health in the European Union. The French public authorities first took action against the causes of drug shortages in 2011 with a law, followed by a decree in 2012 to overcome the dysfunctions of the pharmaceutical distribution channel. These texts would establish emergency call centres implemented by pharmaceutical companies for pharmacists and for wholesalers to inform of shortages, and would oblige pharmaceutical companies to inform health authorities of any risk of potential shortage situation; they would also reinforce the declaration regime of the territory served by wholesalers. Through the Health Law of January 2016, France acquired new regulatory tools in order to fight against these shortages and wanted to target the drugs for which they are the most detrimental: the major therapeutic interest (MTI) drugs. Furthermore, this new text reinforces the legal obligations of pharmaceutical companies and of wholesalers for drug shortages and sets out the enforcement of sanctions in case of breach of these obligations. France's goal is ambitious: to implement coercive measures aiming at making the actors of the drug distribution channel aware of their responsibilities in order to take up the public health challenge triggered by drug shortages.

1. Policy background

The drug distribution channel has experienced an unprecedented number of shortages for several years. These shortages are a recurring problem for health systems worldwide [1–3]. The risk for public health is real as these shortages may have serious consequences for patients: interruption of treatments, medical procedure and drug treatment protocol delays, and higher rates of relapse among patients with cancer, HIV or other chronic diseases [4,5].

Any class of drugs may be disrupted by these shortages, which spare no therapeutic class (generic, biologic, orphan, paediatric, radiopharmaceuticals, etc.). Shortage instances are numerous: injectable antibiotics, injectable anti-cancer drugs, antidepressants, antipsychotics, tuberculosis, vaccines, HIV treatments and immunoglobins, are particularly in short supply [6–8].

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* Corresponding author at: Law and Health Economics Department, Faculty of Pharmacy, Paris Descartes University, Sorbonne Paris Cité, 4 avenue de l'Observatoire, 75006 Paris, France.
E-mail address: francois.bocquet@parisdescartes.fr (F. Bocquet).

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These shortages are linked to very heterogeneous factors [6]. The first type of causes relates to the products fabrication: manufacturing delay and quality issues. As almost 80% of the supply of pharmaceutical raw materials currently depends on Indian or Chinese suppliers, it creates serious supplying tensions especially when the required level from sanitary authorities regarding pharmaceutical quality is increasingly high. The worldwide shortage of propofol—common anaesthetic—depicts the manufacturing problems sometimes encountered by pharmaceutical suppliers [1]. In the same way, changes in procurement practices (registration with a stringent regulatory authority) can invalidate a previous supplier, as it recently happened with the antibiotic streptomycin [2]. The second type of causes is linked to economic or market-structure issues: company mergers, parallel exports/imports, distribution to countries with lower prices or with a high growth potential, marketing stoppages for commercial reasons, mass purchases from hospitals, unexpected increase of a drug use, resulting in a temporary shortage until the manufacturing capacity meets the demand (e.g. seasonal demands of flu vaccines). Besides, when manufacturing depends on a small number of facilities, shutdowns for various reasons may create problems, as it has frequently been the case with some radiopharmaceuticals or orphan drugs [3].

Pursuant to the 2001/83/EC EU Directive relating to medicinal products for human use [9], European national competent health authorities have to control the continuous supply of drugs; the pharmaceutical companies must warn them of any cessation of drugs, whether permanent or temporary. Furthermore, the pharmaceutical companies and wholesalers are responsible for an appropriate and continued supply to pharmacies. In practice, European national authorities are free to decide how to design their laws in order to comply with the goals of this directive [7].

As per 2012, France took legal steps to fight against these shortages with the Act # 2011–2012 of 29th December 2011 [10] and the decree # 2012-1096 of 28th September 2012 related to the supply of human drugs [11] (Fig. 1). In providing more constraining and coercive measures for the various actors of the distribution channel than in other countries, this decree aimed to structure the sanitary organisation to fight against these shortages and to strengthen the responsibilities of pharmaceutical companies commercialising drugs in France and wholesalers in this field. More than three years after the implementation of this decree, the French legislator has overcome an additional step in the fight against drug shortages with the enforcement of a new series of measures within the Health Law dated 26th January 2016 [12] (Fig. 2). In this paper, we provide an analysis of the recent legislative developments related to the battle against drug shortages in France.

2. Implementation and review three years after the 2012 decree enforcement

The decree of 28th September 2012 defines the shortage as the inability for a community or hospital pharmacy to deliver a drug to a patient within 72 h. According to the decree, this shortage situation for a drug without any available therapeutic alternative or which supply difficulties may lead to a risk of public health for patients thus creates an emergency procedure, where all the actors of the drug distribution channel shall join forces [11] (Fig. 1).

The text creates regulatory obligations for pharmaceutical companies commercialising drugs in France (i.e. pharmaceutical companies refer to the marketing authorisation holders and not to manufacturers) who must: ensure an appropriate and continuous supply of wholesalers for them to meet their public service obligations and the patients' needs. This decree also establishes permanent emergency call centres that shall be implemented by pharmaceutical companies and shall be accessible to community and hospital pharmacists as well as to wholesalers. These centres aim at taking care of drug shortages at any time and at allowing the effective distribution of the missing product. This action may take place in case of an effective shortage or on an anticipated basis, when the wholesaler or the reseller confirms the shortage. The 2012 decree provides for a quarterly report of these emergency supplies and declarations to be carried out by the pharmaceutical companies and sent to the French regional health authorities (*Agences régionales de santé*—ARS) specifying the provided quantities for each drug and their addresses. When a pharmaceutical company predicts a potential shortage situation or in case of an effective drug shortage, it informs the French National Agency of Medicine and Health Product Safety (*Agence Nationale de Sécurité du Médicament et des produits de santé*—ANSM) by consistently specifying the periods by which the shortages occurred, the available stocks, the conditions of availability and the estimated deadlines for availability, as well as the identification of the drugs that could be substituted to the ones missing. The ANSM must inform the health professionals of anticipated or effective shortages and must specify the potential recommendations to manage these shortages [11].

A key measure of the decree rests upon the reinforcement of the authorisation regime of the wholesalers' activity with the ANSM as it creates an authorisation obligation to change the distribution territory of the wholesaler subject to the ANSM. In addition to the public service obligations of the wholesaler [10], the latter must have—in view of an effective and sufficient distribution of drugs to meet the needs of the declared distribution territory—a selection of drugs including at least nine-tenths of the presentations of the drugs commercialised in France. The drugs bought by or left to the wholesaler are distributed to meet the needs of patients in France on a previously defined declared distribution territory [11].

The decree finally specifies that the wholesaler must not only have the drugs at the pharmacist's disposal, but also has to deliver them within a specific deadline following the request (8 h at the most whether in a drug shortage situation or not) (Fig. 1).

As a result of a fresh initiative from the French legislator, the various provisions included in the decree of 28th September 2012 [11] allowed to hold back the number of drug shortages in France but did not succeed in restraining them (50 in 2013, 150 in 2014 and 170 in 2015 to which the shortage risks and the other drugs under quota have to be added [13]). Pursuant to the decree enforce-

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