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Causes of drug shortages in the legal pharmaceutical framework

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ABSTRACT

Introduction: Different causes of drug shortages can be linked to the pharmaceutical legal framework, such as: parallel trade, quality requirements, economic decisions to suspend or cease production, etc. However until now no in-depth study of the different regulations affecting drug shortages is available. The aim of this paper is to provide an analysis of relevant legal and regulatory measures in the European pharmaceutical framework which influence drug shortages.
Methods: Different European and national legislations governing human medicinal products were analyzed (e.g. Directive 2001/83/EC and Directive 2011/62/EU), supplemented with literature studies.
Results: For patented drugs, external price referencing may encompass the largest impact on drug shortages. For generic medicines, internal or external reference pricing, tendering as well as price capping may affect drug shortages. Manufacturing/quality requirements also contribute to drug shortages, since non-compliance leads to recalls. The influence of parallel trade on drug shortages is still rather disputable.
Conclusion: Price and quality regulations are both important causes of drug shortages or drug unavailability. It can be concluded that there is room for improvement in the pharmaceutical legal framework within the lines drawn by the EU to mitigate drug shortages.

1. Introduction

Drug shortages affect various therapeutic drug classes all over the world (Balkhi et al., 2013; Gray and Manasse, 2012) and in some cases drug shortages can even jeopardize public health (Food and Drug Administration, 2011; Gogineni et al., 2013). Even though European markets are affected (Capstick et al., 2011; Giraldo et al., 2011; Tirelli et al., 2012), empirical studies unravelling the issue of drug shortages in Europe are scarce. Pauwels et al. highlighted that drug shortages, reported by the national health agencies of different European Member States, can be characterized as branded, oral drugs, affecting a variety of disease domains (Pauwels et al., 2014a). They also concluded that the origins of drug shortages are underreported by the reporting tools of national health authorities. Therefore it was put forward that a general reporting template could contribute to better insights in the causes of drug shortages in Europe and in fundamental solutions to mitigate those shortages (Pauwels et al., 2014a). Such general reporting template could be implemented in the centralized database, which is currently installed by the European Medicines Agency (EMA). However, only drugs which are in shortage at the same time in several European Member States are included in this database (European Medicines Agency, 2013).

Causes of drug shortages appear to be multi-factorial (Birgli®, 2013; Costelloe et al., 2014; Instituut voor Verantwoord Medicijngebruik, 2012; Pauwels et al., 2014a). An important cause of drug shortages seems to be shortcomings in the legal framework (Instituut voor Verantwoord Medicijngebruik, 2012). A recent study addressing European hospital pharmacies affirmed that regulatory rules have an influence on drug shortages (Pauwels et al., 2014b). Economic decisions (suspension or cessation of the product), inadequate policy measures (restricted drug production, allocation and quality requirements) and parallel trade are causes linked to the legal framework. However an in-depth understanding of how legislations, regulatory rules and lawsuits are related to drug shortages is

Abbreviations: US, United States of America; EMA, European Medicines Agency; GMP, good manufacturing practices; TFEU, Treaty on the Functioning of the European Union; EU, European Union; FAMHP, Federal Agency for Medicines and Health Products; MA, Market Authorization; MAH, market authorization holder; HTA, health technology assessments; UK, United Kingdom; EAEPC, European Association of Euro-Pharmaceutical Companies; FDA, Food and Drug Administration; FDASIA, Food and Drug Administration Safety and Innovation Act.

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lacking yet. The aim of this study is to provide an analysis of legal and regulatory measures in the EU relevant to drug shortages.

2. Methods

Different EU legislations considering drugs were studied, including the Directive 2001/83/EC relating to medicinal products for human use (The European Parliament and the Council of the European Union, 2011a), Directive 2011/62/EU on falsified medicines (The European Parliament and the Council of the European Union, 2011b), Directive 89/105/EEC also known as the Transparency Directive (The Council of the European Union, 1989) and Directive 2003/94/EC on good manufacturing practices (GMP) (The European Parliament and the Council of the European Union, 2003). The Treaty on the Functioning of the European Union (TFEU) (European Union, 2012) and other relevant (inter)national legislations were also investigated. Directives require Member States of the European Union (EU) to achieve a particular end result, for which appropriate rules should be designed in the national laws. Each Member State is free to decide how the implementation of these rules is executed (Application of EU law – European Commission [WWW Document], 2012). For that reason, the relevant Dutch, Belgian and UK laws were also investigated in order to allow comparison with the EU Directives. Differences which may be relevant to drug shortages were highlighted.

To identify rules for price and reimbursement procedures and parallel trade relevant in the context of drug shortages, explorative scientific literature reviews were performed searching MEDLINE, Embase and EconLit databases, using the following keywords: drug shortages, pricing, regulations and parallel trade. Gray literature was consulted as well, such as websites of the (inter)national regulatory bodies, (EMA, the Federal Agency for Medicines and Health Products (FAMHP) etc.) as well as documents of organizations concerning drug shortages and related causes.

3. Results

3.1. Definitions and concepts

A variety of definitions for 'drug shortages' are adopted by different organizations, for instance in the US, at least two different definitions are reported (Fox et al., 2014). In legal documents, the term 'unavailability' is mainly used (The European Parliament and the Council of the European Union, 2011a), with the meaning of 'not introducing new, innovative medicines on the market', while in other contexts (e.g. political documents), 'drug shortages' are rather defined as an 'interruption of the supply chain'. In this article, a distinction is made between the two concepts (unavailability of drugs and drug shortages), and both are investigated.

3.2. Obligations for manufacturers by the EU Dir 2001/83/EC

Following EU Dir 2001/83/EC, pharmaceutical manufacturers are subject to several obligations relevant before and after market entrance. Once market authorization (MA) has been obtained, the holder of a MA (MAH) has to inform the competent authority of the date of actual marketing (art 23a (The European Parliament and the Council of the European Union, 2011a)). Entering the market needs to occur within 3 years after obtaining the MA, otherwise the MA can be withdrawn (this is called the sunset clause: art 24 (The European Parliament and the Council of the European Union, 2011a)). The sunset clause aims to prevent that patients are deprived from access to new, innovative drugs that are developed and approved. Once the drug enters the market, the MAH and the distributors of that drug are responsible for an appropriate and continued supply to pharmacies as well as to the persons authorized to supply drugs to cover the needs of the patients (art 81 (The European Parliament and the Council of the European Union, 2011a)). As such, these rules tend to prevent drug shortages. Another obligation exists at the moment the drug eventually ceases being present on the market, either permanent or temporally. In that case, the manufacturer has to notify the competent authorities no less than 2 months before the cessation, unless exceptional circumstances apply (art 23a (The European Parliament and the Council of the European Union, 2011a)). This time limit should give authorities, pharmacists and prescribers of drugs, the time to look for alternative treatments.

National authorities are free to decide on how to adapt their laws in order to comply with the goals of this Directive. E.g. in France, manufacturers are obliged to notify competent authorities not only in case of actual shortages, but also for potential shortages. The time limit for manufacturers to notify the national authority is even one year before the definitive cessation. In addition, an approval of the French national authority is obligatory before the manufacturers can cease the production of drugs (Working Committee on Drug Shortages, 2012). Recently the Belgian law on human medicines adapted the time limit to report the permanent cessation of the supply of a reimbursable drug toward 6 months before the shortage period instead of the 2 months as described in Directive 2001/83/EC, valid from the 1st of January 2014 ("Wet houdende diverse bepalingen inzake gezondheid," 2014). This law also obliges MAH to report the cause and duration of the (temporally) cessation. The extension of the 2 months time period gives the health practitioners in Belgium and France the time to search for the best alternative treatment (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten, 2013; Working Committee on Drug Shortages, 2012).

3.3. Influence of pricing and reimbursement procedures on drug shortages

Pricing and reimbursement procedures allow national authorities to set or negotiate prices for pharmaceuticals. These prices are however influenced by many factors, such as the national gross domestic product (GDP) and willingness to pay, resulting in different prices between the Member States of the EU (Kanavos et al., 2011; Vogler et al., 2008). The differences in pricing procedures (see further) can lead to (high) price differences between Member States. These price gradients may result in practices of parallel trade, which can cause drug shortages (Bart, 2008; Forrester and Dawes, 2010) or the unavailability of drugs, since low price markets are avoided by manufacturers for market placement of new and innovative drugs for which high investments were made (Birgli®, 2013). The Greek market for instance reduced its pharmaceutical prices in an attempt to cut healthcare expenditures, resulting in a market with overall prices which are at least 20% lower compared to other countries in the EU. These measures resulted in a cessation of the supply of several pharmaceuticals by manufacturers in Greece ("'Medical stocks are down by 90 percent': Greece accuses pharma giants of slashing imports — RT News," 2013). In 2012, 203 drugs were withdrawn from the Greek market and for approximately one out of eight of these products, no generic alternative was available (yet) (Birgli®, 2013).

In most EU Member States, prices of reimbursable drugs or drugs on prescription are controlled (Vogler et al., 2008). The fact that prices for most pharmaceuticals are regulated on a national or regional level is remarkable in view of other tradable goods or services, where free markets determine the price of products (Killick, 2006). The principal aim of national authorities regulating prices of pharmaceutical products is to keep healthcare accessible for everyone. A disadvantage can be the creation of 'less attractive'