

TITLE: Causes of drug shortages in the legal pharmaceutical framework

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1 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 analysed (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.

2 HIGHLIGHTS

- Analysis of the European legal pharmaceutical framework which may influence shortages
- Pricing procedures may influence drug shortages as well as drug unavailability
- Market withdrawals can be caused by manufacturing/quality requirements
- The legal framework leaves room for improvement to mitigate drug shortages

3 KEYWORDS

- Drug shortages
- Legal framework

- Pricing
- Quality requirements
- Parallel trade
- Quota
- Market authorization

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5 INTRODUCTION¹

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 (Kim Pauwels et al., 2014). 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 (Kim Pauwels et al., 2014). 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; Kim Pauwels et al., 2014). An important cause of drug shortages seems to be shortcomings in the legal framework (Instituut voor Verantwoord

¹ ABBREVIATIONS

United States of America (US)
European Medicines Agency (EMA)
Good Manufacturing Practices (GMP)
Treaty on the Functioning of the European Union (TFEU)
European Union (EU)
Federal Agency for Medicines and Health Products (FAMHP)
Market Authorization (MA)
Market Authorization Holder (MAH)
Health Technology Assessments (HTA)
United Kingdom (UK)
European Association of Euro-Pharmaceutical Companies (EAEPC)
Food and Drug Administration (FDA)
Food and Drug Administration Safety and Innovation Act (FDASIA)

Medicijngebruik, 2012). A recent study addressing European hospital pharmacies affirmed that regulatory rules have an influence on drug shortages (K. Pauwels et al., 2014). 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 lacking yet. The aim of this study is to provide an analysis of legal and regulatory measures in the EU relevant to drug shortages.

6 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," 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. Grey 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 organisations concerning drug shortages and related causes.

7 RESULTS

7.1 DEFINITIONS AND CONCEPTS

A variety of definitions for ‘drug shortages’ are adopted by different organisations, 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.

7.2 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 authorisation (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 three 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 two 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 towards six months before the shortage period instead of the two 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 (temporarily) cessation. The extension of the two month 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).

7.3 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’ markets, leading to retraction of manufacturers and thus the removal of new, innovative drugs from the market due to low price markets.

In the next paragraphs, a distinction is made between pricing procedures for patented drugs, generic medicines and off-patent pharmaceuticals. Because Denmark and Germany use a free price setting mechanism, both countries indirectly control the prices of reimbursable pharmaceuticals by their reimbursement system. Therefore, reimbursement procedures are investigated as well (Vogler et al., 2008).

7.3.1 PRICING PROCEDURES FOR PATENTED DRUGS

Different pricing procedures for patented drugs were studied, such as cost-plus pricing, Pharmaceutical Price Regulation Scheme, price negotiations, pharmaco-economic evaluations,

external price referencing and free pricing (Kanavos et al., 2011; Rietveld and Haaijer-ruskamp, 2002; Vogler et al., 2008). However, only external price referencing seems to have an influence on drug shortages.

External price referencing uses the average or the lowest price of different reference countries for the price-setting of pharmaceuticals. This pricing procedure may influence drug shortages, since it results in a general price decrease when one country reduces its price. This pricing mechanism is the tool which has been most widely used by the EU Member States to set prices for new pharmaceuticals (Kanavos et al., 2011). If the price of a certain pharmaceutical product is too low, manufacturers can decide to withdraw their product from the market, which may result in the unavailability of that drug (Birgli®, 2013; Kanavos et al., 2011). Low price markets also incite to parallel export, which can result in drug shortages (Kanavos et al., 2011). Not all countries will consider production costs in price setting, which is another disadvantage of external price referencing (Vogler et al., 2008), refraining manufacturers to improve the production process or to invest in quality.

7.3.2 PRICING PROCEDURES FOR GENERIC MEDICINES AND PHARMACEUTICALS OFF PATENT

Pricing mechanisms, such as tendering, price capping, internal or external price referencing were investigated for generic medicines (Kanavos et al., 2011; Rietveld and Haaijer-ruskamp, 2002; Vogler et al., 2008).

Tendering is a competitive bidding process to set the price for a pharmaceutical. The best bidder, according to strict, predefined criteria, has the right to supply the whole market with that pharmaceutical (Douven and Meijer, 2008; Dylst et al., 2011; Kanavos et al., 2011). Tendering is an effective way in reducing prices of a selected (group of) pharmaceuticals but may result in fewer manufacturers of those pharmaceuticals on the market (Kanavos et al., 2011, 2009), leading to a market which is more vulnerable for drug shortages. For instance, drug shortages arising from production problems by the winner of the tender are difficult or impossible to mitigate by other

manufacturers originally not selected for the tender (Kanavos et al., 2011). In view of the fact that it will take between four and six months to plan the production of that drug.

Price capping sets price ceilings on generic and originator products after the expiration of the originator's patent. They are often set according to the price of the patented drug (Kanavos et al., 2011). This procedure may increase the vulnerability of the pharmaceutical market to drug shortages. In some countries the price of generic medicines is set at a certain percentage below the price of the originator. In this way the manufacturer of the original drug can decrease its price to a point where it is no longer financially sustainable to produce generic medicines, causing those to disappear from the market (Bongers and Carradinha, 2009). This will lead to a reduced number of manufacturers and eventually drug shortages, especially in case of capacity issues. Another consequence of price capping appears to be its influence on the availability of generic drugs: a European study indicated that price capping delays the uptake of generic medicines compared to other price procedures (Kanavos et al., 2011).

Internal price referencing bases its price on identical or equivalent medicines of the generic within the same country (Vogler et al., 2008) and may lead to drug shortages in a similar way as external price referencing. If one product lowers in price, the price of identical or equivalent drugs will also decrease. However, this procedure is more used for reimbursement procedures than actually price setting (Vogler et al., 2008). Gradually more countries use external price referencing for generic medicines as well to decrease health care expenditures.

7.3.3 REIMBURSEMENT PROCEDURES

While costs of new health care technologies are rising, the health care budgets are subject to constraint. Therefore Member States concluded that not all new pharmaceuticals can be reimbursed (Kanavos et al., 2011). Different reimbursement procedures, used by the EU Member States, were investigated such as: positive and negative formularies, reference price system, health technology assessments (HTA), pharmaco-economic evaluations and contracts.

Health technology assessments (HTA) and pharmaco-economic evaluations are increasingly adopted in reimbursement decisions. In Denmark, HTA outcomes are even used indirectly to set prices. If the manufacturer wants to get its pharmaceutical reimbursed and it turns out cost-ineffective, the original price was most probably set too high by the manufacturer (Kanavos et al., 2011). In that case, the manufacturer is not allowed to enter the market, resulting in the unavailability of a drug for which alternative treatments with better cost-benefit ratio are available.

Reimbursement procedures can have an impact on the availability of reimbursed drugs due to Directive 2011/24/EU. This Directive defines rules for the application of patients' rights in cross border healthcare (The European Parliament and the Council of the European Union, 2011c) and is a consequence of the lawsuits of Decker and Kohl (respectively C-120/95 and C 158/96). These case laws rule on the rights of EU Member States patients to receive healthcare in other EU Member States, reimbursed by the Member State of affiliation (Aagaard and Kristensen, 2014). Patients might get their treatment in the Member State with the lowest price and will be reimbursed by the Member State of affiliation. This can result in the withdrawal of the MA by manufacturers in the low priced countries. Finally, patients in Member States with lower prices can still get their treatment in other EU Member States, though it will not be reimbursed anymore (Aagaard and Kristensen, 2014).

7.4 INFLUENCE OF PARALLEL TRADE ON DRUG SHORTAGES

The installation of the idea of a common internal EU market without restrictive national borders is proclaimed in the Treaty on the Functioning of the EU (TFEU). The key concept of free movement of goods across European countries is embedded in articles 34-36 of the TFEU (European Union, 2012). All kinds of goods moving around in different European markets are envisioned; however the pharmaceutical market is somehow special. Most markets are price setters, meaning the manufacturer decides the price as a function of the demand, leading to small fluctuations between countries. The price setting of goods in the pharmaceutical market is regulated by the national authorities and therefore, especially in case of reimbursable drugs, such markets are price takers

rather than price setters. This can lead to major differences in prices for pharmaceuticals between countries. This important difference compared to price setter markets means that opening the borders may lead to high profits for parallel traders and drug shortages in low-priced countries due to parallel export (Killick, 2006). These shortages can jeopardize public health.

Parallel import occurs when the price for a drug is lower in the country of export and parallel export occurs when the price is higher in the country of destination compared to the country of export. As long as parallel export does not affect the stocks of the drug in the country of supply in order to comply with national demands, parallel trade can be a solution for drug shortages in receiving countries, since unavailable drugs in that particular country may be imported without major legal constraints. However, if the exporting country exceeds the national demand for a particular drug, which is often the case, parallel export results in drug shortages.

Some low price Member States are very susceptible to parallel exports, e.g. Greece, Poland, United Kingdom (UK), Slovakia etc. (Killick, 2006; Melck, 2012). As a reaction to drug shortages caused by parallel exports, some EU Member States tried to change their legal framework to complicate the export of drugs (European Association of Euro-Pharmaceutical Companies (EAEPC), 2013). The restriction on imports or exports of goods in the EU is prohibited unless these are justified on grounds of public morality, public policy or public security (art 36 TFEU (European Union, 2012)). In Spain, GSK tried to implement a dual pricing system, allowing the sale of a certain drug at one price in one country and applying a different price for exporting the same drug (European Association of Euro-Pharmaceutical Companies (EAEPC), 2014a). This was considered to be illegal in 2001 by the European Commission (GlaxoSmithKline Services and Others v Commission and Others, 2009). Slovakia attempted to restrict export of prescription medicines, which seems contrary to EU rules (European Association of Euro-Pharmaceutical Companies (EAEPC), 2014b). However, the European commission has not made the actual decision on this matter. In March 2013, also the Estonian Parliament tried to change its legislation by only allowing export if the wholesalers have the consent

of the manufacturer and of the national drug agency. However, the EAEPC argued that this would be contrary to article 35 of the TFEU and therefore submitted a complaint to the European Commission (European Association of Euro-Pharmaceutical Companies (EAEPC), 2013; European Union, 2012). Until now, no decision has been made by the European Commission.

7.4.1 MEASUREMENTS COMPLICATING PARALLEL TRADE

It was the pharmaceutical manufacturer Bayer who discovered that the UK sales of a particular drug dramatically decreased over several years. Parallel import from France and Spain covered the rest of the UK needs and therefore the company decided to introduce quota in these countries. Quota are precisely calculated amounts according to the needs of a particular population, including a margin and avoiding surpluses (Sapentis, 2013).

The primary aim of quota is to reduce parallel trade of pharmaceuticals. According to the European Court of Justice, manufacturers using quota comply with their obligation to guarantee an appropriate and continued supply (Bayer AG vs Commission of the European Communities, 2000). In another important case, the pharmaceutical manufacturer was accused of abusing its dominant market position after refusing an excessive order for a certain product. The manufacturer defended the refusal by indicating that the requested order, which satisfied the continued and appropriate supply, was already fulfilled. The European Court of Justice again decided in favour of the manufacturer (Syfait vs GlaxoSmithKline, 2005). These judgements can be interpreted indirectly as rulings complicating parallel trade, since quota decrease incentives for parallel exports.

To avoid drug shortages induced by quota and to ensure the continued supply of drugs by manufacturer, as stated in Directive 2001/83/EC (The European Parliament and the Council of the European Union, 2011a), the latter set up a fall-back system, e.g. contingency mechanisms (All-Party Pharmacy Group, 2012). When wholesalers determine inadequate supply stock due to quota, pharmacists can order drugs directly at the manufacturer and the manufacturer needs to deliver the product within 24 hours (All-Party Pharmacy Group, 2012; Koninklijke Apothekersvereniging van

Antwerpen (KAVA), 2009). This back-up system implies that manufacturers still have a stock of pharmaceutical products (Birgli®, 2013). Despite the existence of such back-up systems, complaints against them have recently been raised in different Member States, since in reality the order was not delivered in time by the manufacturer, hereby breaking the law, though no sanctions were imposed (Collins, 2013; Cuyckens, 2014).

Another approach of manufacturers to avoid drug shortages caused by parallel export is to change the distribution supply chain of pharmaceuticals (All-Party Pharmacy Group, 2012). In most EU Member States, the manufacturer supplies the wholesaler, who distributes the drugs to smaller wholesalers or directly to community pharmacists (Mayer, 2012). Contrary, hospital pharmacies are able to directly order their drugs by manufacturers. In the UK some manufacturers adopt a direct to pharmacists' distribution system (All-Party Pharmacy Group, 2012). This system allows manufacturers to work with one exclusive wholesaler, who delivers the drugs directly to the pharmacists (Kanavos et al., 2011).

7.5 INFLUENCE OF MANUFACTURING/QUALITY REQUIREMENTS ON DRUG SHORTAGES

Pharmaceuticals distributed for human use in the EU need to be safe, effective and of sufficient quality. The production is carefully regulated by rules on good manufacturer practices (GMP) and several other strict requirements to assure high quality drugs (The European Parliament and the Council of the European Union, 2003). Over the past years, drug shortages caused by manufacturing/GMP compliance problems were responsible for several public health crises (European Medicines Agency, 2012). When audits reveal violations on GMP, the production process might be ceased until the problems are solved, depending on the kind of the violation (Instituut voor Verantwoord Medicijngebruik, 2012). Drug shortages can easily occur in case of an interruption of the production processes (by the manufacturer itself or by national authorities) (Instituut voor Verantwoord Medicijngebruik, 2012; ISPE, 2013), unless there are sufficient manufacturers of the same drug to cover the demands and needs (Birgli®, 2013).

255 Another upcoming quality related problem might find its basis in the Falsified Medicines Directive
256 (The European Parliament and the Council of the European Union, 2011b), which covers new rules on
257 the import of active substances. This Directive is the consequence of past experiences with poor
258 quality of active substances coming from China, such as heparin (Center for Drug Evaluation and
259 Research, 2012). According to this Directive, non-European manufacturing facilities for active
260 substances have to comply with the European GMP rules to allow those drugs to be imported in the
261 EU. China and India (lacking GMP requirements) provide 80% of the active substances for the
262 production of drugs sold on European and US markets. Therefore the Falsified Medicine Directive can
263 (unintentionally) trigger more drug shortages in European countries (Birgli®, 2013; Instituut voor
264 Verantwoord Medicijngebruik, 2012).

265 However, quality related drug shortages do not only cover problems with the quality of the drug, it
266 can also be induced by the strict regulations for the product information which should be reported
267 on the leaflet or on the package (European Medicines Agency, 2014). Errors on the leaflet or on the
268 package can cause the recall of different batches.

269 Recently, EU labelling obliges the MAH to indicate on the leaflet the name of the manufacturer of the
270 active pharmaceutical ingredient as well as the name of the manufacturer who is responsible for the
271 batch release (i.e. the actual manufacturer of the drug) (European Medicines Agency, 2014).
272 Therefore purchasers of drugs can base their decision on quality, as the actual source of production
273 (i.e. manufacturer who is responsible for the batch release) is reported. For instance, if the
274 manufacturer who is responsible for the batch release already experienced different quality issues,
275 purchasers take this in consideration for the purchase of that product. In this way, manufacturers
276 and MAH are forced to invest in the quality of the products.

277 To comply with manufacturing and quality requirements manufacturers have to invest and in the
278 maintenance of their production sites. However, due to the fixed prices of drugs set by the national

authorities, manufacturers are sometimes compelled to stop the production because the quality of the drug can no longer be guaranteed (Instituut voor Verantwoord Medicijngebruik, 2012).

7.6 WITHDRAWAL OF THE MARKET AUTHORISATION RESULTING IN DRUG UNAVAILABILITY

The withdrawal of the MA can occur either by the national authorities or by the manufacturer itself. When the drug is harmful for humans, lacks therapeutic efficacy, has an unfavourable risk-benefit balance or has a qualitative and/or quantitative composition not as declared, the national authorities have the right to withdraw the MA (art 116 of Directive 2001/83/EC) (The European Parliament and the Council of the European Union, 2011a). The permanent withdrawal of the MA is an ultimate measure and will only be considered if other measures appear insufficient. First a warning is given to the manufacturers to improve the quality, safety and/or efficacy of the drug. If no improvement can be obtained, other measurements will be taken such as changes in the package leaflet or a change in the status of an OTC drug towards a drug on prescription, e.g. domperidone. To prevent hasty decisions, the withdrawal will only be executed after a hearing of the pharmaceutical company to defend its position (The European Parliament and the Council of the European Union, 2011a). These withdrawal decisions will lead to the unavailability of drugs, though national authorities carefully consider risks for public health.

The pharmaceutical company has also the right to retreat the drug from the market at any time, leading to drug shortages or the unavailability of drugs. The number of revocations of licenses by manufacturers in the Netherlands is more than tenfold compared with the withdrawals ordered by the national authority (Instituut voor Verantwoord Medicijngebruik, 2012). The reason for these revocations is often economically driven; e.g. the product did not have the expected margin of profit (Instituut voor Verantwoord Medicijngebruik, 2012) or there is lack of money to invest in the production process to fulfil to the different quality demands. However, moral opinions or a change of drug status from OTC to prescription may also influence a particular decision. At the EU as well as at

national level, discussions to prevent or to regulate the withdrawals by the manufacturers are ongoing, for situations where the quality, safety and efficacy of the drug are sufficient (Instituut voor Verantwoord Medicijngebruik, 2012). However, the outcome of such discussions is not binding and the pharmaceutical producer remains master of its product.

8 DISCUSSION

This study provides an overview of the legal framework influencing drug shortages. It appears that price and quality requirements seem to strengthen each other as causes for drug shortages (Instituut voor Verantwoord Medicijngebruik, 2012). If the price is set low, the margin of profit will also be low, resulting in no margins to measure up with the multiplicity of quality demands or to invest in production processes (Instituut voor Verantwoord Medicijngebruik, 2012). Worst case scenarios start when manufacturers withdraw their product from the market, leading to a more vulnerable market for drug shortages due to a decreased number of manufacturers.

8.1 COMPARISON OF THE LEGISLATIVE FRAMEWORK OF THE EU WITH THE US

In the US, the Food and Drug Administration (FDA) is the department responsible for mitigating or preventing US-based drug shortages. Comparing the regulatory frameworks of the US and EU, some remarkable differences are noticed, summarized in Table 1.

TABLE 1: KEY DIFFERENCES BETWEEN EU DIRECTIVE 2001/83/EC AND THE US LEGISLATION (THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION, 2011A; FOOD AND DRUG ADMINISTRATION SAFETY AND INNOVATION ACT, 2012)

	EU Directive 2001/83/EC	US legislation
Type of reported drug shortages	Every cessation (temporarily or permanent) of a pharmaceutical product	Life-supporting, life-sustaining or intended for use in the prevention or treatment of a debilitating disease or

		condition, including any such drug used in emergency medical care or during surgery
Time of reporting	2 months before shortages drug shortages	6 months before shortages
	When a drug shortage occurs	When a drug shortage is likely to occur

318 In the EU, every cessation of the supply of a drug (temporally or permanent) has to be reported to
319 the competent authorities, though it is up to the Member States to take action following this
320 information. US manufacturers only have to report shortages when it concerns a drug which is “life-
321 supporting, life-sustaining or intended for use in the prevention or treatment of a debilitating disease
322 or condition, including any such drug used in emergency medical care or during surgery” (sec 1001 of
323 FDA Safety and Innovation Act (FDASIA)) (Food and Drug Administration Safety and Innovation Act,
324 2012). However, reporting is obliged when drug shortages are likely to disrupt the supply chain (Food
325 and Drug Administration Safety and Innovation Act, 2012). The six months time limit in the US to
326 report a drug shortage to the FDA is seen as necessary to prevent potential drug shortages (Food and
327 Drug Administration, 2013a). Considering the newly reported drug shortages in the US, this approach
328 seems to pay off (Food and Drug Administration, 2013a).

329 In the US, the FDA will investigate the impact of a possible drug shortage and will, together with the
330 manufacturer, search for solutions (Food and Drug Administration, 2013b). In this way, the US is
331 more efficient compared to Europe and most Member States. The EMA database will only report
332 those shortages which occur in several Member States at the same time and in Belgium, the FAMPH
333 posts every day a list of drug shortages in Belgium on their website (Federaal Agentschap voor
334 Geneesmiddelen en Gezondheidsproducten, 2014). However, in both cases it is up to the
335 pharmacists or other health care practitioners to look for alternatives, which is in detriment for the
336 patient, since alternative drugs can be less effective than the original one, can be more costly to the

patient and can sometimes pose a greater risk for interactions with other drugs (Food and Drug Administration, 2013b).

When a potential shortage is reported to the FDA, it is mandatory in the US to disclose the reason for the disruption of supply (sec 1001 of the FDASIA) (Food and Drug Administration Safety and Innovation Act, 2012). Reporting the reasons for discontinuance of supply is not mentioned as a requirement in the EU directive, although this might give some interesting insights in the causes of European drug shortages. In the Netherlands, the database Farmanco of the Royal Dutch Association for the Advancement of Pharmacy asks to list the reason for reported drug shortages (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, 2014), as well as the Italian Medicines Agency (The Italian Medicines Agency, 2014) and the Belgian FAMPH, but still these declarations are rather vague (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten, 2014).

8.2 CONSEQUENCES OF PRICE AND REIMBURSEMENT PROCEDURES ON DRUG SHORTAGES

The price of a medical product is not only defined by the pricing procedures itself, several other factors are also relevant, such as: the national gross domestic product. In countries with a lower income per capita, prices of pharmaceuticals seem to be lower (Kanavos et al., 2011). Pricing and reimbursement procedures may have an impact on drug shortages and especially on the availability of drugs for the reason that manufacturers carefully consider whether or not placing a new product on a “low-price” market (Birgli®, 2013). For example in the low-price market of Poland, the removal of drugs from the market is observed. Moreover, the introduction of new and innovative products on the Polish market is delayed, due to the very low prices for drugs and the new reimbursement act based on internal reference pricing combined with limited prices. In addition, differences in the velocity of price and reimbursement procedures may negatively influence the availability of drugs (Birgli®, 2013), despite the timeframe set by the Transparency Directive (The Council of the European Union, 1989).

Differences in pricing and reimbursement procedures across countries may be the foundation for parallel trade, however the influence of parallel trade on drug shortages is disputable (Birgli®, 2013; Kanavos et al., 2011; Killick, 2006; Melck, 2012). To reduce parallel export, quotas were introduced. However, quota cannot be seen as a solution for drug shortages induced by parallel trade (export), since the market share of parallel trade did not change after the introduction of quota (Pharmafile, 2009). For example the parallel trade market of the UK used to be the largest in Europe; however Germany overtook that position due to the decrease of the exchange rate GBP/EUR (Pharmafile, 2009). Whitehead defined quota as “a sticking plaster not a cure” (ABPI, 2012) and they are thus not a long term solution for drug shortages.

8.3 CONSEQUENCES OF MANUFACTURING AND QUALITY REQUIREMENTS

Quality related problems cover a broad range of causes for drug shortages, among them: problems with quality of the active pharmaceutical ingredient, quality related problems with production process, problems with quality of the drug in the final pharmaceutical form, problems with the quality of the leaflet or packaging, etc. In Europe, non compliance with quality regulations is a main cause of drug shortages (European Medicines Agency, 2012), and the costs to comply with the quality requirements in the regulatory framework are high and should, in the end, be recovered (e.g. compliance with quality requirements) (Instituut voor Verantwoord Medicijngebruik, 2012). However due to repetitive price drops, *inter alia* due to the economic and financial hardship, there is no margin left for quality improvements. This can result in market withdrawals and thus unavailability of drugs. A possible solution for this problem might be to set minimum prices for drugs, to allow manufacturers to increase prices when investing in quality of drugs.

In the US, more than half of the drug shortages reported in 2012 were caused by quality problems, due to a strict policy on quality regulations for pharmaceuticals (Food and Drug Administration, 2013a). The FDA assesses whether a facility fulfils the high quality demands through inspections. Each two years, nearly every major sterile injectable manufacturer, based domestically and

producing for the US market, is inspected by the FDA. In case of serious quality problems, the FDA has the authority to close the manufacturing facility, resulting in temporary drug shortages (Woodcock and Wosinska, 2013). In Europe, a particular plant (Ebewe Pharma) in Austria also received a warning from the FDA, advising Sandoz to meet up with the quality requirements (“FDA Issues Warning Letter to Novartis’s Austrian Plant,” 2013).

When life-savings drugs are declined from entering the market due to manufacturing/quality requirement problems (e.g. typing error on the package or leaflet, other dosage for which license was granted, etc.) and therefore the problem has no influence on the efficacy, quality or safety of the pharmaceutical product itself, the national authority might bend the rules by allowing the use of the product anyway. This is only a temporary solution and will not help in order to prevent shortages.

8.4 POSSIBLE SOLUTIONS FOR DRUG SHORTAGES

Pricing procedures can be considered as a major base of legal causes of drug shortages. A revision of existing pricing procedures may help reducing drug shortages. For example one general pricing procedure for either patented, off patent or generic medicines could set similar prices for those particular pharmaceutical product categories, resulting most probably in smaller price differences across Member States. However, as mentioned above, price setting of pharmaceuticals depends on different parameters, among them GDP and willingness to pay (Kanavos et al., 2011; Vogler et al., 2008). Therefore the price of a pharmaceutical drug should be balanced between pharmaceutical profitability and consumer access to drugs (= affordability).

A more feasible solution to avoid temporary drug shortages is to oblige manufacturers, e.g. by legislations, to build stock for a certain period (Instituut voor Verantwoord Medicijngebruik, 2012). Thereby in case of production problems, health practitioners have a timeframe to seek for alternatives, if necessary. However, costs come along with the space necessary for building stocks and the loss of expired products.

407 When the MAH is not able to produce a new and innovative drug due to technical complications,
408 transferring the MA and/or other intellectual property rights to willing producers should be
409 considered as a way to avoid drugs unavailability. However, the transfer of the MA is not often used
410 as a solution (Instituut voor Verantwoord Medicijngebruik, 2012).

411 A (inter)national agency responsible for the availability of pharmaceuticals on the EU market can
412 actively look for solutions for drug shortages (Instituut voor Verantwoord Medicijngebruik, 2012),
413 such as contacting manufacturers of equivalent products, searching for possible import options, etc.
414 similar to the activities performed by the FDA in the US. This can take the form of a new department
415 at an (inter)national agency that publishes information on a website, avoiding duplication by
416 pharmacists searching for solutions on their own. One hurdle for this possible solution is the costs
417 coming along with the new department, especially in the current era of economic downturn. Another
418 problem might be the overload of work if such agency has to investigate the severity for each
419 shortage, considering the large amount of pharmaceuticals in shortage. Therefore the focus for such
420 agency could be considered to limit the scope to life-saving drugs, as in the US. Prioritising drug
421 shortages is another way to avoid the overload of work, for instance those drugs without a generic or
422 other alternative treatment have the highest priority.

423 Further harmonization of the regulatory frameworks for drug approvability, manufacturing and
424 quality standards between the US and Europe, will contribute to a better cooperation between US
425 and EU. This might mitigate the problem of drug shortages for both as it will ease the barriers to
426 trade drugs. In the US, the requirements to import drugs are recently loosened, still there is room for
427 improvement (Food and Drug Administration Safety and Innovation Act, 2012). An example of
428 different regulations on quality requirements: in Europe, manufacturers are obliged to indicate the
429 manufacturer of the API as well as the manufacturer who is responsible for the batch release (=
430 actual manufacturer, is not always the same as the MAH). In the US only the MAH is documented.

431 This study on the causes of drug shortages in the legal pharmaceutical framework identified different
432 reasons for drug shortages. However until now, it remains unclear how many drug shortages are
433 provoked by the legal framework, therefore further research on the share of the legal framework
434 causing drug shortages is necessary. Along with these research results, all stakeholders (EU, national
435 agencies, pharmaceutical manufacturers, prescribers, patients, pharmacists, etc.) should discuss
436 which measurements can be taken to prevent drug shortages induced by the legal framework.

437

438 **9 TABLES WITH CAPTIONS**

439	Table 1: Key differences between EU Directive 2001/83/EC and the US legislation (The European	
440	Parliament and the Council of the European Union, 2011a; Food and Drug Administration Safety and	
441	Innovation Act, 2012)	17
442		

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