

Universidade de Lisboa

Faculdade de Farmácia



Medicines Shortages and Parallel Trade
Public Policy and Regulation cross-country analysis
between Portugal and the Netherlands

João Miguel Ramos Diogo

Mestrado Integrado em Ciências Farmacêuticas

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Trabalho de Campo de Mestrado Integrado em Ciências Farmacêuticas
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At the Faculty of Pharmacy of the University of Lisbon, this work has been under orientation and supervision of Prof. Dr. Ana Paula Martins.

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I. Abstract

Medicine shortages have consistently been causing considerable and worrying impact among health systems and hence patients in European Union (EU) and all across the world. Simultaneously, Pharmaceutical Parallel Trade (PPT) has also been recently subject of huge attention and controversy within the broader plan of the discussion regarding the envisioned single european market of medicines.

A holistic analysis of the current regulatory and economic frameworks closely related to these two concepts has brought up the intention of performing an insightful evaluation on the dynamic correlation between them; on how one might play a role either as a cause or a consequence of the other, how they affect the performance of healthcare services and then holistically looking at how National Competent Authorities (NCA) manage their efforts and mechanisms to provide effective answers, avoiding further negative impact. Access to quatitative evidence of the due clinical and economic impact remains a national and international challenge. Nevertheless, this investigation points to the strengthening of the logical assumption that parallel trade has a higher potential of impacting the national supply chain of countries with lower prices on medicines, as is the case of Portugal. In The Netherlands, despite evidenced efforts, regulatory focus and measures towards this practice to prevent shortages seem less robust than is the case with Portugal.

Key concepts: medicines, medicine shortages, parallel trade, pharmaceutical public policy.

II. Resumo

As falhas de abastecimento de medicamentos têm causado considerável e preocupante impacto ao nível dos sistemas de saúde - e, portanto, aos doentes – da União Europeia e do Mundo. Simultaneamente, e em particular no contexto europeu, o comércio paralelo de medicamentos tem sido alvo de aumentada ênfase e controvérsia no seio do plano alargado de discussão a respeito do mercado único de produtos farmacêuticos. O presente trabalho propõe uma análise holística da conjuntura regulamentar e económica que está adjacente aos efeitos reais destes dois fenómenos ao nível de dois contextos nacionais concretos, com a intenção de proceder a uma avaliação comparativa e reflexiva da correlação causal que alegadamente de um em relação ao outro. Para o efeito, optou-se por um enfoque no impacto que concerne a prática de farmácia comunitária. Pretende-se recorrer a esta investigação em contexto específico com a intenção de, por um lado, complementar a literatura existente quanto ao seu impacto ao nível do desempenho dos serviços de prestação de cuidados farmacêuticos e, por outro, perceber o panorama de ação legal e regulamentar em resposta ao impacto das falhas de abastecimento potencialmente derivadas de comércio paralelo nas duas realidades abordadas.

O exercício analítico desenvolvido para o efeito leva à conclusão de que se revela ainda desafiante comprovar quantitativamente a dita relação causal, embora o mercado de abastecimento denuncie ineficiências que para ela apontem. Embora o presente trabalho não tenha permitido, por isso mesmo, concretizar a intenção inicial de prestar um contributo nesse sentido, reforça ainda assim a premissa difundida de que o comércio paralelo de medicamentos congrega um potencial mais elevado de causar impacto nos circuitos nacionais de abastecimento de Estados Membros com um nível de preços de medicamentos mais baixo, como é o caso de Portugal. Na Holanda, pese embora haja evidência de esforços desencadeados no sentido de prevenir a influência negativa de exportação paralela de medicamentos no circuito de abastecimento, o foco e as medidas adotadas nesse sentido demonstram-se menos robustas do que em Portugal. O paradigma atual, corroborado pelo presente documento, denota um desfasamento entre o conjunto de benefícios e riscos aplicáveis a cada Estado Membro da União Europeia, estando os países com preços mais elevados em melhor posição de absorver os eventuais benefícios e os países com preços mais reduzidos de medicamentos não só em maior dificuldade de alcançar os elencados benefícios, como cumulativamente mais vulneráveis aos riscos inerentes a esta prática.

III. Acknowledgments

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IV. Methods

This research project mostly intended to access and process information of two basic natures: statistical data that could illustrate the causal link between parallel traded products and actual shortages, filling the gap that is mainly highlighted throughout the existing literature concerning this issue, and regulatory and legislative documentation that reflect the two national approaches over time. Where statistics are concerned, data for shortage notifications in Portugal was requested to INFARMED. It was possible to access a list of shortage notifications submitted by MAH comprised within the period of January 2013 until may 2017. For each notification, the field “motive of shortage” was missing, as well as ATC classification. The list was further processed so that ATC code for each shortage was accessible. Remaining quantitative elements were available for public consultation. As for the remaining content concerning both national policy-making approaches, an exhaustive search from a wide array of sources was performed, relying mostly on official sources namely INFARMED’s archive and Diário da República (Official Diary of the Republic) for the case of Portugal and CBG/MEB’s archive and Rijksoverheid’s (Government of The Netherlands) official archive for the case of The Netherlands. In complementarity, the curricular internship in community pharmacy that occurred in parallel to the research itself was also a good source of evidence that helped in better understanding these issues when applied to the daily practice of pharmacists.

V. List of abbreviations

- API** – Active Pharmaceutical Ingredient
- APIFARMA** – Associação Portuguesa de Indústria Farmacêutica
- CBG/MEB** – College ter beoordeling van Geneesmiddelen/Medicines Evaluation Board
- CEFAR** - Centre for Health Studies and Evaluation
- CIMI** – Centro de Informação do Medicamento
- EAHP** – European Association of Hospital Pharmacists
- EC** – European Commission
- ECJ** – European Court of Justice
- EFPIA** – European Federation of Pharmaceutical Industries and Associations
- EMA** – European Medicines Agency
- EU** – European Union
- EEA** – European Economic Area
- FDA** – Food and Drug Agency
- IGZ** – Inspectorate of Health
- INFARMED** – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P
- IP** – Intellectual Property
- IVM** – Institute for the Responsible Use of Medicines
- KNMP** - Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie / Royal Dutch Pharmacists Association
- MAH** – Market Authorisation Holder
- MS** – Member State
- NCA** – National Competent Authority
- PGEU** – Pharmaceutical Group of the European Union
- PPT** – (Pharmaceutical) Parallel Trade
- RIVM** – National Institute for Public Health and Environment
- TFEU** – Treaty of Functioning of the European Union
- TRIPS** - Trade-Related Aspects of Intellectual Property Rights
- VWS** – Ministry of Health, Welfare and Sports

VI. List of Figures

Figure 1 - Possible factors contributing to medicine shortages along the supply chain of pharmaceutical products. Source: own authorship.	19
Figure 2 - General scheme of the commercial supply chain of medicines, composed by both the regular pathway and the parallel pathway. For illustrative purposes only, as of course other relevant details are missing. Source: own authorship.....	24
Figure 3 - Shortages by API. ATC Code Classification (2013-may 2017) Source: INFARMED, CIMI.....	30
Figure 4 - Shortages by Notification. ATC Code Classification (2013-may 2017) Source: INFARMED, CIMI.....	31
Figure 5 - Perception of shortages in pharmacies, according to ATC code criteria (2012-2016). Source: Deloitte	31
Figure 6 - Timeline of policies to address shortages and parallel trade of medicines in Portugal. Source: own authorship	34
Figure 7 - Number of shortages notified to Farmanco, by type. (2004-2015). Source: Farmanco KNMP	36
Figure 8 - Timeline of policies to address causes of medicines shortages in the Netherlands. Source: own authorship.....	39
Figure 9 - Evolution over time of national market shares, in percentage (%), of parallel imported products among top importer countries. Source: EFPIA "The Pharmaceutical Industry in Figures" (1997-2015).....	40
Figure 10 - Evolution of the number of Parallel Import Authorisations requested vs conceded by the Medicines Evaluation Board. Source: MEB Reports (2006-2015).....	41

VII. List of Tables

Table 1 - Criteria to define a medicine shortage, as implemented by INFARMED by the Deliberation nº 050/CD/2012	27
Table 2 - Top 20 products in shortage (Aug 2013- Jul 2014) registered in portuguese community pharmacies. Source: CEFAR; own adaptation.	32
Table 3 - Top 10 shortages (Dec 2015) out of total shortages registered in community pharmacies, and top 10 shortages comprising products requiring export notification to INFARMED. Source: CEFAR; own adaptation.....	33
Table 4 - Medicines with Authorisation for Parallel Import, in Portugal (as accessed in November 4th, 2017). Source: Infomed.	35

VIII. Index

I. Abstract.....	6
II. Resumo	7
III. Acknowledgments.....	8
IV. Methods.....	9
V. List of abbreviations	10
VI. List of Figures	11
VII. List of Tables	12
1. Introduction.....	14
1.1. Introducing core concepts and ideas	17
1.1.1. Medicine shortage.....	17
1.1.2. Parallel Trade	20
1.1.3. Commercial chain of pharmaceutical products.....	23
2. A cross-country comparison within the European Union.....	26
2.1. Portugal.....	26
2.1.1. Dealing with medicine shortages and, then, with parallel trade	26
2.1.2. The reality of parallel trade.....	34
1.1. The Netherlands.....	35
1.1.1. Shortages as a major political concern.....	35
1.1.2. Parallel trade dynamics	40
2. Discussion	43
2.1. Limitations	46
3. Conclusions.....	47
4. Bibliographic References.....	48

1. Introduction

Occasional and temporary shortages of medicines have always occurred. This was usually due to production or quality-control issues related to manufacturing, but the past couple of years have seen sustained shortages of many commonly prescribed brands and formulations. Shortages now seem to be a daily fact of the overall commercial circuit of medicines[1]. Over the past decades, drug shortages have consistently been causing considerable and worrying impact among health systems and hence to patients in the European Union (EU) and all across the world. While pointed reasons behind this phenomenon can be many (such as change of production site, problems with supply of raw materials or API (active pharmaceutical ingredient) lack of market attractiveness, disruption of supplies and supply quotes, among others)[2], it should be right to say that throughout the past decade, the economic and budgetary struggle which derived from the 2008 global crisis has been an exacerbating factor - directly or indirectly - of isolated and aggregated drug shortage events among Member States (MS) of the EU.

Shortages are widely felt both in hospital and community pharmacy context, dealing considerable impact among the different stakeholder stages[3]. Recently, a 2015 survey of community pharmacists undertaken by the Pharmaceutical Group of the European Union (PGEU) showed that 73% of shortages lasted more than two months and 87% have potentially harmed patients[4]. Recently in The Netherlands, a specific shortage event of Thyrax[5] due to production reasons, affecting thousands of people, has triggered overall social mediatisation and attention around this phenomenon, from patients to governmental bodies. Following this occurrence, a twenty-fold increase in the penalty to be paid by Market Authorisation Holders (MAH) which deliberately cause shortages of medicines was stipulated[6]. A European Association of Hospital Pharmacists (EAHP) Report from October 2014 on medicine shortages presents overall relevant data on the reality and perspectives of hospital pharmacists regarding this matter which seems to affect hospitals as well[7]. Due to supply shortages and medicines unavailability, pharmacists need to dedicate more time sourcing medicines instead of dedicating this time advising and consulting with patients. Pharmacists and other healthcare professionals within the system usually lack information about why a shortage has occurred, and regarding when the situation might be resolved, which means they are unable to give assurance of future supply, creating uncertainty and anxiety for patients. Medicine shortages also have negative effects on full-line wholesalers' capability and obligation of distributing

medicines whenever and wherever needed [1].

To bigger or lesser extent, this paradigm seems to be common to most (if not all) the EU MS, which may leave one to look at it as a European issue. However, the current overall approach to shortages seems to take place mostly on the national level, with national strategies and measures that are directly dependent of each political and juridical context, and not by assuming that it would be beneficial and even feasible to give centralised European mechanisms and structures a bigger role to play[8].

In harmony with the fundamental principle of subsidiarity instituted by the Treaty of Maastricht, national authorities retain responsibility for the regulation of supply of medicines in their own countries, and most already impose an obligation of continuity of supply of medicines on wholesalers and manufacturers. Nevertheless, data and mechanisms to better understand and handle shortages are still lacking in a considerable number of MS, which directly results in an insufficiently transparent approach within national borders and a deficient standardisation of procedural elements on the international scale. For instance, a significant number of authorities in Europe do not use a standard definition of what constitutes a medicine shortage, and this leads to delays in information about the risks of cross-border shortages[9].

Challenges in effectively dealing with medicine shortages arise both on the side of the causal component and on the side of the resolution component of these occurrences, with multiple factors and features respectively inherent. However, one specific dimension seems to raise particular interest when defying the understanding of this issue, given its potential and alleged connection with both the causal and resolution aspects: parallel trade of pharmaceuticals.

Parallel Trade (PPT) has also been recently subject of huge attention and labelled as “one of the most salient controversies that emerged as a result of the European single market for pharmaceuticals”[10] that was once envisioned and which has been in discussion for many years now.

The occurrence of the parallel import of pharmaceutical products in the European Union is common and results essentially from price differences in different countries. The first register of a product being sold through this mechanism dates back to 1975, in The Netherlands[11], and was made possible by the Treaty of Rome[12]. PPT allows wholesalers to buy products in countries with low prices and sell them at higher margins in countries with high price for the particular drug. For a normal good sold in efficient markets, the result of international price

differences and parallel trade is price convergence, which means that PPT should only be a transitory business opportunity. However, in case of pharmaceuticals, both economic, legal and political dimensions are present, meaning that prices do not simply converge overtime. In other words, pharmaceutical PT is likely to stay[13]. As for its role in society and in the pharmaceutical sector, many arguments for and against PPT have been presented, mainly involving considerations in regards to public health budgets, access to medicines and incentives to innovation through R&D[13]

Parallel trade can lead to a drug shortage when export of the product is not foreseen and cannot be anticipated. Additionally, when imported products are sold cheaper than prices valid in that country, marketing of the product by national suppliers can also be discouraged. The impact of parallel trade on drug shortages is poorly studied but heterogeneous price setting between European countries makes its role in drug shortages plausible[14], particularly and naturally in MS which present the lowest medicines prices, given the tendency to be targeted as sources of import[15]. This issue has been of substantial concern for all the stakeholders within the pharmaceutical sector throughout the world. Especially in the EU, where the issue of a Single Pharmaceutical Market has been on the table for so many years, building a consistent and efficient regulatory and economic mechanism that optimises trade of pharmaceuticals between MS is a matter of major importance for both industry and government stakeholders. From a detailed analysis of the EC 1998 Communication and the progress made to date on achieving a single EU pharmaceutical market, one can see that PPT in Europe is a major symptom of a greater problem that exists within the EU pharmaceutical market[16]. The ICH13 process and the WHO credibly attempt to introduce commonly agreed international pharmaceutical regulatory standards, but how these standards are adopted throughout the world is a major issue of concern and has not been resolved.

A strong link between production problems, drug shortages and market attractiveness is proposed and this needs to be investigated in Europe[17]. Taking on the existence of very contrasting regulatory frameworks throughout MS, this research proposal aims fundamentally to produce an incisive analysis on the current paradigm and situation regarding these two main issues in two specific countries: Portugal and the Netherlands. The intention to do so arises mainly from the fact that, while these two MS are currently facing common relevant drug shortage phenomena, the respective economic and regulatory grounds contrast in many ways. It is interesting to understand where both of them differ, how consistent are their approaches

to this issue and then, where there is room to improve.

After a summary contextualisation of the both major phenomena in discussion throughout this document – medicines shortages and parallel trade of medicines – I shall carry on further with a specific description of how these two issues have been coexisting in both countries. From the very definition of medicine shortage itself to the juridical philosophy of parallel trade applied to pharmaceutical products, this work aims to study two current national frontlines of reaction to what has clearly become a subject of public interest and concern within the commercial circuit of medicines, with the purpose of elaborating an array of conclusions that may generally fit into other contexts within the EU and that ultimately contributes to the overall discussion of this problem.

1.1. Introducing core concepts and ideas

As is the case with any other scientific approach to a subject, the first step to take should necessarily be the definition of the core elements on which this research focuses its attention. Moreover, given the fact that most of the content analysed further derives from elements of governmental national public policies – mainly concerning two different countries – and communitarian regulation documents, each with their own essence and particular juridical context, the necessity of clarifying the content which composes the very basis of the discussion is highlighted.

1.1.1. Medicine shortage

What could apparently seem to be, technically speaking, an accessible definition, is in fact the first element to raise challenges to an integrated approach to this system inefficiency, mainly by making it tough to statistically analyse and benchmark contexts of occurrences in different countries. As of today, the perspectives towards what should be considered a shortage diverge, in some cases substantially, between national regulations and documents of other nature[18]. Given the different regional regulatory paradigms (i.e. FDA and EMA), a diverging nature of concepts would not be surprising between them, but as we narrow our focus specifically to the European sphere we still come across a considerable level of contrast in the perspectives of

different stakeholders towards this subject.

For instance, while a medicine shortage is generally defined by EMA as a situation in which the supply of a concrete medicine cannot meet the needs of the patients, the European Federation of Pharmaceutical Industries and Associations (EFPIA) puts it as an interruption of supply due to any sort of mismanagement within the commercial circuit. Here we have two perspectives upon the same inefficiency, whether it immediately corresponds to a public health concern or simply reflects a punctual market limitation, even if later on other concerns come attached. In 2015, a survey elaborated by EMA and spread through the NCA of EU MS (plus Iceland, Liechtenstein and Norway) aiming to collect feedback regarding national approaches to supply problems evidenced further divergence among definitions of a shortage, depending on elements related to the length of the unavailability, the adequacy of supply and the clinical impact, leaving it clear that producing a common definition would be a goal out of range. Moreover, among the 28 answers, 18 of the entities assumed they did not rely on a domestic definition of medicine shortage, this factor contributing even more to a call for a harmonised action.

As far as centralised policy is concerned, countries that make up the European Union mostly rely on the content that derives from Directives, which they need to incorporate in their national legislation. Overall, despite particular structural differences, the field of pharmaceutical regulation finds many common pillars between MS, as could only be the case if the core intention is to sustain a unified market. When it comes to predict action upon a potential risk of shortage, the European legal framework is essentially mirrored in the Directive 2001/83/EC, which stipulates that a MAH must notify the competent authority if a given product ceases to be placed on the market of a Member State, either temporarily or permanently, and such notification shall, otherwise than in exceptional circumstances, be made no less than 2 months before the said interruption[19]. Furthermore, on the Article 81, the Directive states that “*(...) the holder of a marketing authorization for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorized to supply medicinal products so that the needs of patients in the Member State in question are covered. The arrangements for implementing this Article should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the Treaty rules, particularly*”

those concerning the free movement of goods and competition”.

To say that a shortage essentially corresponds to a failure in meeting the condition stated in the previous article is a legitimate exercise, but still somehow vague so as to reach the desired purpose of a concrete, common definition. Considering the level of awareness and impact that shortages have come to represent to society nowadays, one may be led to assume that enhancing regulatory efforts by the European Commission (EC) around the subject would comprise a beneficial strategy, at least in terms of enclosing, for public health purposes, a sort of official characterisation of what the relevant agents within the European environment should see as a product shortage.

On the EU level, the European Medicines Agency (EMA) has, in parallel to national regulations and dynamics on medicines shortages, an online centralised catalogue for shortage events registered simultaneously in more than one MS. The first and obvious consideration on this platform is that it seems to be detached from the local impact of shortages, although recommendations are provided to patients and healthcare professionals regarding due shortages.

While further central action does not happen, national authorities are left to their pro-activity and pragmatism in their duty to attenuate any suspected impact derived from shortages, which can originate from various factors along the chain, as shown in **Figure 1** below.

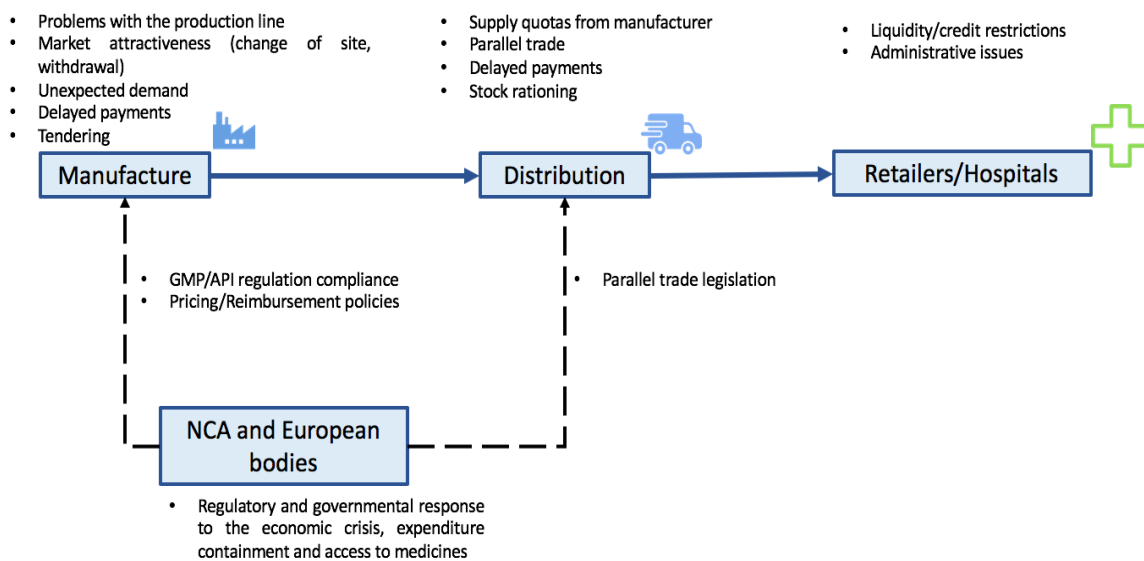


Figure 1 - Possible factors contributing to medicine shortages along the supply chain of pharmaceutical products. Source: own authorship.

And this is where we enter the reality which more strongly attracts the interest of this initiative: studying deeper within the national context the current status of approach to this phenomenon. As will be exposed further, the two national paradigms in analysis – Portugal and The Netherlands – have their own peculiarities and, overall, the interest of the comparison arises from the connection between these characteristics and each country’s specific macroeconomic, healthcare and pharmaceutical conjunctures.

For the purpose of the analysis intended with this research, one of the starting premises was to assume a medicine shortage as in fact being any occurrence in which a product cannot be obtained from a distributor or a manufacturer in the moment it is requested, hence meaning a negative impact to the patient. Other than this, surely market inefficiencies will occur but should be categorised differently once they do not constitute, intrinsically, a threat to the idealised performance of the whole pharmaceuticals commercial chain.

1.1.2. Parallel Trade

Nowadays’ reality concerning free trade of pharmaceuticals owes its core elements, in good part, to the Treaty of Rome, signed in 1957, which instituted the European Economic Community (EEC) and, as part of its foundational principles, the free movement of goods.

As stated in its original article 10, currently article 29 of the Treaty of Functioning of the EU (TFEU) “*products coming from a third country shall be considered to be in free circulation in a Member State if the import formalities have been complied with and any customs duties or charges having equivalent effect which are payable have been levied in that Member State*”[20]. This was the first step of the broader intention of creating an internal market within the Community – now European Union (EU) – that comprised the so-called four freedoms: goods, services, people and capital, as stated today in the most recent version of the (TFEU).

For all purposes, prohibitions or restrictions on imports and exports of goods may only be justified “*on grounds of public morality, public policy, public security (...) or the protection of industrial and commercial property. Such prohibitions or restrictions shall not, however, constitute a means of arbitrary discrimination or a disguised restriction on trades between Member States*”[21].

Moreover, parallel trade is made possible largely due to the existing regulations regarding

intellectual property (IP). As a member of the World Trade Organization, the European Union as a whole is obliged to define its own policy to protect intellectual property rights, as encouraged by the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement. Bearing this in mind, the 89/104/EEC Directive of the Council of the European Union formally incorporated in the single market dynamics what literature defines as the Exhaustion Principle, which essentially means that *"the trademark right shall not entitle the proprietor to prohibit its use in relation to goods which have been put on the market in one of the Member States under that trademark by the proprietor or with his consent"*[22], which basically means that once a product is sold in one of the MS, its IP rights become exhausted in all the others, hence prohibiting trade of such product by a third party.

Although in accordance with the fundamental aims of the European Project, the feature of free trade of goods has given rise to disagreement and controversy in some contexts, particularly concerning pharmaceutical products, given the unique nature of this research-based sector and also the widely noticed key factor for the density of such trade dynamics: some sort of arbitrage due to inter-state price differences. To all extent, parallel trade applied to medicines can be defined as the practice of buying branded or generic products which have been put on the market at a relatively low price with the consent of the brand owner in one country and then subsequently, without the brand owner's consent, importing these products into another country where the brand owner can also in principle claim protection and where these same products are normally sold at a higher price[23]. In 2016, parallel trade represented an estimate share of 9% of the total imports of pharmaceutical products within the EEA (European Economic Area), comprising a value of around 5,5 billion € in sales[24].

Since this mechanism was made possible and legal, a lot of polemic situations and disputes have taken place between industry stakeholders, parallel traders and the European institutions, namely the European Court of Justice (ECJ). The very first case of parallel import of a pharmaceutical product, in 1975 in the Netherlands, ended up being referred to the ECJ given the delicate conflict between the economic and political dimensions of this subject[25]. These cases have, though, been helpful in triggering adequate regulatory improvements by the institutions in charge.

In 2003, while recognizing the significant volume of parallel imports of pharmaceuticals, the EC issued another Communication specifically regarding this matter, as it had already done back in 1982, where it further clarifies the legal grounds under which parallel imports can be

done and then also defining a few conditions that should be followed by parallel traders so that commercial and industrial property of the products are protected, presented below [26]:

“To qualify for the simplified procedure, the parallel imported medicinal product must satisfy two conditions. It must:

- 1. have been granted a marketing authorisation in the Member State of origin;*
- 2. be sufficiently similar to a product that has already received marketing authorisation in the Member State of destination (the similarity between two pharmaceutical products is considered to be sufficient when the two products have been manufactured according to the same formulation, using the same active ingredient, and have the same therapeutic effects).*

(...)

The proprietor of the trademark may not oppose the repackaging of a medicinal product when the following conditions have been met:

- 3. the use of the trade-mark right by the owner contributes to the artificial partitioning of the internal market;*
- 4. the repackaging does not adversely affect the original condition of the product;*
- 5. it is stated on the new packaging by whom the product has been manufactured and repackaged;*
- 6. the presentation of the repackaged product is not such as to damage the reputation of the trademark and of its proprietor; and*
- 7. the proprietor of the trademark receives written notice of the repackaging before the new product is put on sale.”*

In 2013, the entry into force of the Directive 2011/62/EU – the so-called Counterfeit Medicines Directive – also made the whole process of importing active pharmaceutical ingredients more safe and regulated, by forcing the presentation of a declaration from the competent authority of the exporting country on how the production process of the product fulfilled European GMP requirements.

There exists a wide array of documents generated by the aforementioned European institutions in reaction to issues raised by controversial cases of parallel trade of medicines. By going through its content, we are led to conclude that there is a very robust will to preserve the core premises that since the beginning sustained the envisioned internal market of the Union, above

the risks and arguments continuously pointed out during these last decades concerning the trade freedoms extrapolated to products of such peculiar marketing conditions.

In 1998, the European Commission (EC) issued a Communication on the Single Market of Pharmaceuticals, where it highlighted the importance of this unified platform as an essential mechanism to protect the health of patients mainly by optimizing access to medicines throughout Europe and to foster innovation and industrial development. At the time, the main challenges, barriers and overall complexity that came attached to such aim were already recognised. Despite the collective progresses achieved in the meantime, the current reality is still far away from what was politically projected. In this conjuncture, thus, preserving and even fomenting parallel trade of medicines seems perhaps to be a legitimate way of strengthening the course towards what would certainly be a robust achievement for the Union.

The free trade of medicines throughout the whole EU would perhaps not raise this much concern if it were not for the unique characteristics that make up the paradigm of this market, namely its nature of utmost public interest. This leads to governmental regulatory and financial intervention and also the structural economic contrasts between each MS, from which consequently the respective pricing policies derive and that end up mostly influencing national price dynamics to a point where although it may become profitable (and beneficial[27]) to incur in such trade, an argument has also been made about this being an opportunistic approach which may in the end represent some consequences to the overall marketing chain.

1.1.3. Commercial chain of pharmaceutical products

Both shortages and parallel trade are phenomena that occur somewhere into the commercial chain of pharmaceutical products, directly and indirectly influenced by a multitude of factors. For the purpose of better conceiving and understanding how all these elements are connected with each other, it seems pertinent to produce an incisive description of this complex chain, from the manufacturing process until its sale to a final consumer – the patient.

Every organised societal system comprises, more or less defined, more or less complex, a supply chain of pharmaceutical products. In the EU, such structure has evolved over the years into a level of significant complexity, conditioned by a mixture of Community (mostly the Directive 2001/83/EC) and national regulations, these latter mostly imposing principles transposed from European Directives. This means that, although it is possible that some aspects of national supply chains differ between MS, the essence of the aforementioned provisions leave it not much likely that those divergences imply that, in this case, distinct schemes are needed to illustrate the cases for Portugal and The Netherlands. A consolidated map is shown below in **Figure 2**, whereby the regular pathway of supply is articulated with the dynamics of parallel trade.

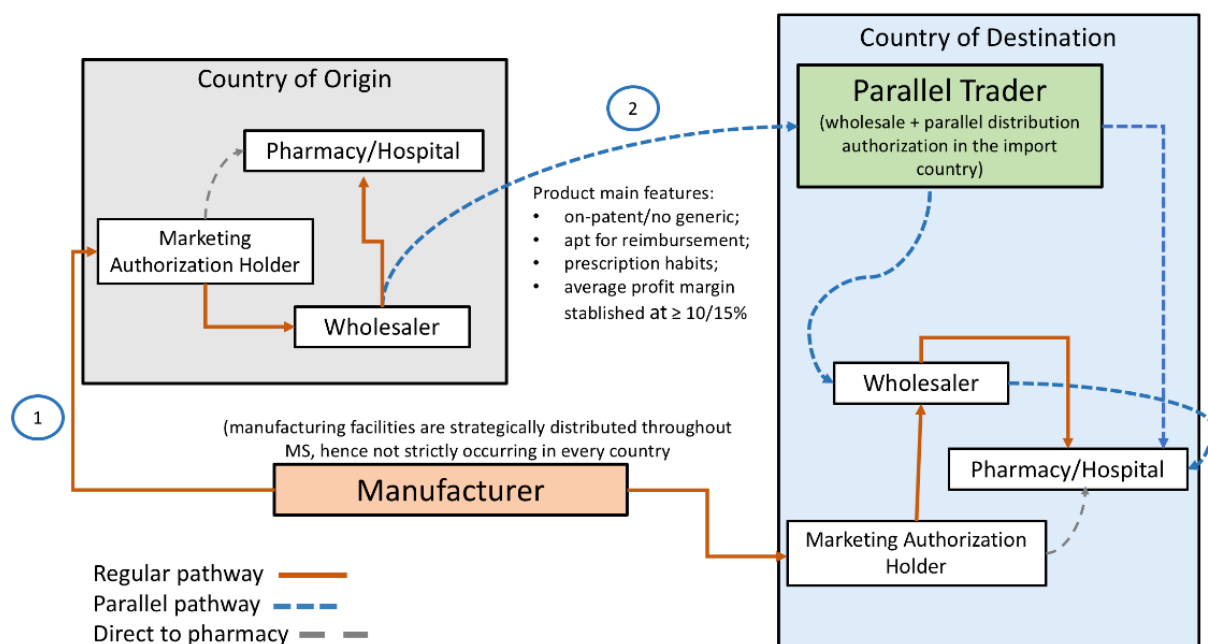


Figure 2 - General scheme of the commercial supply chain of medicines, composed by both the regular pathway and the parallel pathway. For illustrative purposes only, as of course other relevant details are missing. Source: own authorship.

The aforementioned Directive essentially structures the key elements of the supply chain in three levels: manufacturing/marketing, distribution and dispense to patient, each of the activities attached to them requiring a legal authorisation, generally granted by the due NCA. As for the marketing and distribution of medicinal products, quoted in a previous section, the Article 81 stipulates for due authorisation holders the fundamental obligation of ensuring, within the limits of their practical responsibilities, appropriate and continued supply of products under their control so as to cover the needs of the patients of the respective jurisdiction. Yet, the same Article calls for a consideration of proportionality between the

protection of public health that is behind this obligation and the compliance of the Treaty rules concerning the free movement of goods and competition, which essentially refers to the coexistence of a national market and a legitimate parallel market.

The simple picture one can retain from the essence of the daily commercial routines of medicines is that the overall levels of national units' supply is managed by the respective marketing authorisation holders, who should then channel the products to the final consumer through the various authorised distributors, who then assume the responsibility of providing pharmacies and hospitals with the daily demanded units of medicines. However, punctual flaws tend to occur, the major and perhaps most significant consequence of which is, commonly, a shortage.

Although the word “simple” was used to introduce this paragraph, the fact is that those dynamics have evolved in the recent years into a scenario that comprises variables such as product discounts, credit target prizes, plafond-specific conditions, retailer group acquisitions and commitments, among others, all of which end up causing a significant twist to what would be a certain linearity inside a chain that requires maximal efficiency. As of today, for instance, some community pharmacies are offered facilitated access to products that have a status of limited supply as a counterpart of assuming a higher monthly credit consumption from a specific distributor. This means that if it does not turn out to be commercially interesting for the pharmacy to commit to such level, pharmacists end up having to find an alternative way to what we just above assumed to be the regular channel of supply in order to satisfy a patient in need, sometimes turning the request to the marketing authorisation holder himself.

Other situations could be described, but the main intention here is to highlight the fact that we are dealing with a chain that has to, mostly financially, sustain many parts along its way and the overall economic struggle of the last decade has led each of them to be proactive in reinventing themselves. Among these, parallel trade of medicines constitutes itself a mechanism of economic arbitrage that explores this current paradigm and attempts to introduce competitive cheaper versions of existing products into the chain. The way it impacts the quality of the supply system is the main theme to which this research, over the next chapters, aims to add a reflective contribution.

2. A cross-country comparison within the European Union

Having previously put the essential aspects of the two main subjects to context, the intention of this section is now to present further evidence and practical vicissitudes related to the said issues by congregating and comparing elements that characterise two different realities influenced by and under the same political, economic and regulatory universe of rules and values. As explained before, this analytical exercise is found useful on the grounds that it explores, on the one side, the conjuncture of a MS (Portugal) which, given the lower prices of medicines, may be more appealing for parallel exports of products and thus to register a concerning causal link with shortages and, on the other, a reality which is in better position of reflecting the also broadly claimed perks that derive from parallel trade (The Netherlands). The methodology will consist of exposing characteristic elements of each conjuncture first and then moving on to the comparative analysis.

2.1. Portugal

2.1.1. Dealing with medicine shortages and, then, with parallel trade

More or less in harmony with the international wave of awareness towards the problem of supply shortages, in Portugal the concern exacerbated by stakeholders and consequent mediatisation of such occurrences began to increase around 2006 (that is, at least, the most accurate perception that derives from this investigation).

By that time, INFARMED had already implemented (since March 2005) an online platform of notification and information of punctual supply ruptures of specific products. During the following years, the pharmaceutical sector in Portugal was hit by a set of governmental measures that aimed to reduce overall national expenditure with medicines, altogether which, then conjugated with the impact of the global financial crisis, led to a progressive densification of shortages.

By 2010, INFARMED, in response to public news calling attention for the cases of supply disruption, where parallel exports were already being highlighted, kept assuring its diligent commitment to assuring the effectiveness of the distribution chain. However, collected evidence would suggest the continuous emergence of a threat demanding action beyond the

structural resources of the NCA. Nevertheless, as discussed later, to some degree the dimension of the problem would be foreseen mainly based on data that at this point is still missing to better characterise the full extent of the phenomenon.

Although no precise data could be collected to illustrate the scenario, the issue of shortages became more and more prominent over the time. From 2010 to 2012, the strategy of the national regulator seemed to point at wholesalers and pharmacies, by announcing stricter rules of minimum supply levels[28], [29]. This seemed to be the logical approach, given that a considerable amount of supply inefficiencies was being related to post-manufacturing stages of the chain and also given the outcome of a total of 82 inspections performed between 2008 and 2009 related to illegal export of medicines, from which 52 offence processes were triggered, 3 of them targeting wholesaler entities and the remaining 49 targeting community pharmacies. Out of 14 manufacturing entities inspected, none was accused of legal non-compliance[30]. Nevertheless, it was still important to address the issue holistically and consider improvements on the overall shortage notification system, which happened through the Deliberation 050/CD/2012, whereby more consistent shortage criteria were defined. These, for all purposes, make up the most accurate shortage definition elaborated by INFARMED:

Table 1 - Criteria to define a medicine shortage, as implemented by INFARMED by the Deliberation n° 050/CD/2012

Low Risk Shortage	Whenever there is an equivalent product available in the circuit (active substance, pharmaceutical form and dosage).
Medium Risk Shortage	Equivalent products are not available. Alternatively, products with the same therapeutic indication or equivalent products with a different pharmaceutical form are available.
High Risk Shortage	Any situation that is not comprised within the previous ones.
Definitely withdrawal or suspension	Obligated to notify NCA at least 3 months in advance
Temporary supply shortage	Obligated to notify NCA at least 2 months in advance

This initiative followed a year in which, despite intense awareness and regulatory concern around the issue of shortages, a considerable number of infractions (68) related to illegal exports were registered [31]. Illegal exports are defined by the NCA as those potentially compromising the national supply.

The overall situation seemed to have reached a point where shortages were assumed as an unfortunate – and sometimes out of national control - daily element of the supply chain, but particular occurrences were not being linked to a notification from the respective MAH and hence its origin would naturally be associated with the remaining possible factors, among which parallel trade seemingly played a role. Despite the context and the legal framework, concrete evidence of this causal link remained allegedly inexistent or unavailable. In 2012, Deloitte published a study requested by APIFARMA strengthening the generalised impact of medicine shortages all over the national pharmacies' network and introducing statistical estimates to support the claim of such causal link.

Further action was then consequently taken by INFARMED in order to correct these inefficiencies. In December 2012, two initiatives were implemented to promote citizen's closer interaction with their NCA: two communication channels to report shortage occurrences and an online platform displaying the network of pharmacies with attached information regarding their level of supply of medicines containing the active ingredients that altogether make up the WHO's list of essential medicines. The efficacy of such initiatives is always highly dependent on the individual's awareness and perception of reliability with regards to such mechanisms. Later on, in February 2013, the CIVIFAR platform was established, this time meant to collect shortage notifications from community pharmacies. It was not possible to access the compiled data sets that over time were collected from this platform, but this surely had the potential of complementing INFARMED's activity of monitoring shortage dynamics. Recent access to CIVIFAR's website informs the user of its deactivation since September 2017. Currently, some versions of internal management software for pharmacies allow pharmacists to notify INFARMED regarding products that are missing upon reception of daily orders. Having called INFARMED's Centre for Medicines Information (CIMI) to ask for further clarification on how is this information then processed by the institution for market monitoring purposes, I was told that due to limited resources, attention to these data sets has not been a priority.

2013 was also the year of implementation of a major (and for that reason, controversial) public policy to address more incisively the case of potentially problematic parallel exports in Portugal – SiExp. This consists of another online platform for market monitoring purposes which aims to request from all the key elements of the supply chain (MAH, wholesalers and pharmacies) information regarding all the transactions made of a specific list of products considered by INFARMED to be in a critical status of supply within the national market. In

the meantime, the said list has been updated four times as a consequence of periodic assessments of the available market evidence, the extent of which was not possible to scrutinise. It is also worth noting that, complementary to this approach, in 2014 the maximum value for the fine to apply in cases of insufficient market supply was increased from 44 891€ to 180 000€. From 2012 to 2015, a total of 689 inspection actions were taken, resulting in 109 legal offenses for infringement and a total of 1,9M€ in fines [32].

Considering the already referred terms in which MS under jurisdiction of the TFEU may legitimately apply measures to correct negative effects of free trade of goods (namely on public health), the core intention behind this specific policy, in response to the evolution of this specific context, would seemingly be comprehensible and justify the means in which it was legally published.

The European Commission (EC), however, has concluded differently. Article 258^o of TFEU concedes the EC the power to take legal action against MS that punctually incur in disrespect towards their obligations under EU Law. Within the fulfilment of such responsibility, in May 2016 the EC has urged Portugal to remove such *“unjustified and disproportionate notification requirements related to the export of medicinal products for human use”* [33], on the grounds that the criteria to determine which products would at a given moment be in risk of shortage due to parallel trade and hence be included on the list were not transparent enough, while imposing excessive reporting obligations on wholesalers. In order to avoid a further referral of the case to the European Court of Justice (ECJ), as TFEU also commands, the Portuguese authorities reacted in accordance with the recommendations, the result of which may be noted in the premises emanated from the Deliberation n^o524/2017, whereby INFARMED published the most recent version of the product export notification list together with several amendments to the general Regulation of the procedure, namely: a) inclusion of the criteria (essentially consisting of economic correlation between trade volumes and shortage reports and then also the existence of therapeutic alternative) that serve the basis of evaluation of commercial “criticality” of each product and b) a more general obligation of the terms in which the transactions made by each party should be notified, excluding for example the legal demand for specifying the entities involved in each transaction.

From February of 2016 onwards, after a localised pilot trial, INFARMED also announced the national extension of the initiative “Via Verde do Medicamento”, which consisted of a figurative fast track order mechanism. Pharmacies would be able to, by assessing a

prescription, be granted priority in ordering certain products in critical supply status at the moment, from a special stock channel of the product supplied by the MAH and delivered by one of the pharmacy’s main wholesalers [34]. Although useful, unfortunately sometimes the wholesaler fails to meet this obligation.

In parallel to the policy-making, it is relevant to evaluate how the scenario for shortages in Portugal has evolved over the last years. Data sets of shortage notifications by MAH and by pharmacists were requested to INFARMED on behalf of this research. Access was granted to shortage notifications of MAH only, for the period of 2013-May2017. Motives for each shortage were not available.

Overall, **Figure 3** and **Figure 4** display a clear increasing trend of notifications within the period in analysis, with a constant predominance of shortages among API with therapeutic indication for Nervous System (ATC code N), followed by Cardiovascular System (C), Anti-infectives (J) and Alimentary tract and metabolism (A).

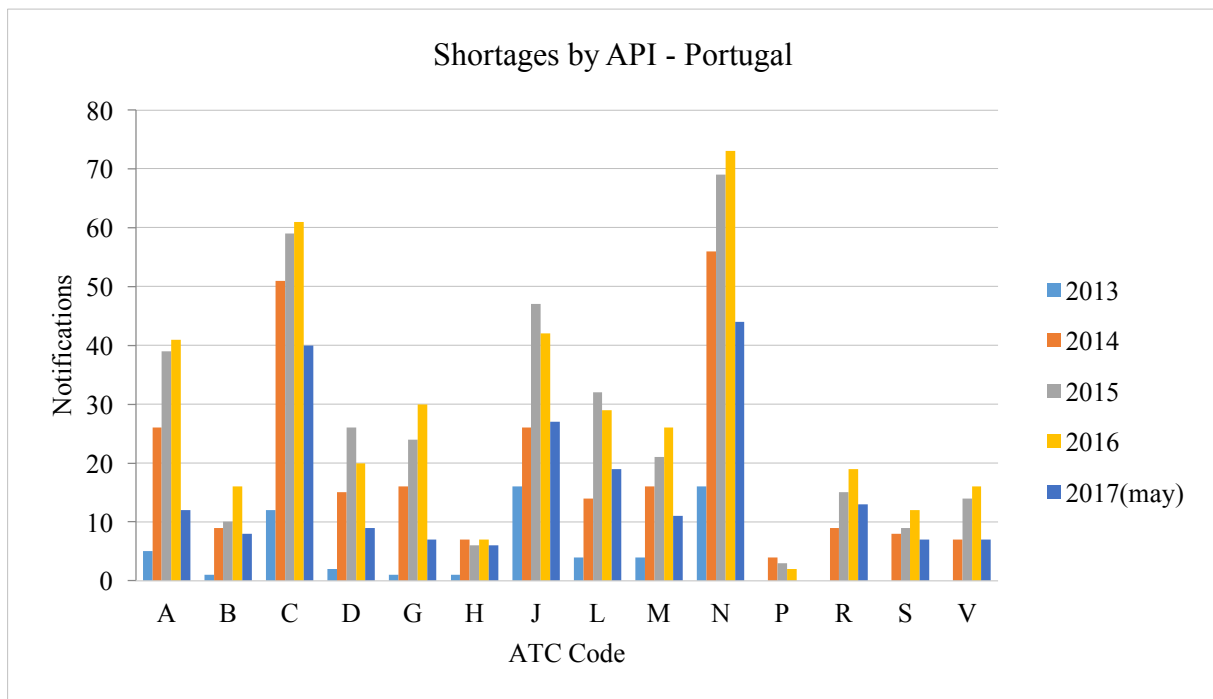


Figure 3 - Shortages by API. ATC Code Classification (2013-may 2017) Source: INFARMED, CIMI

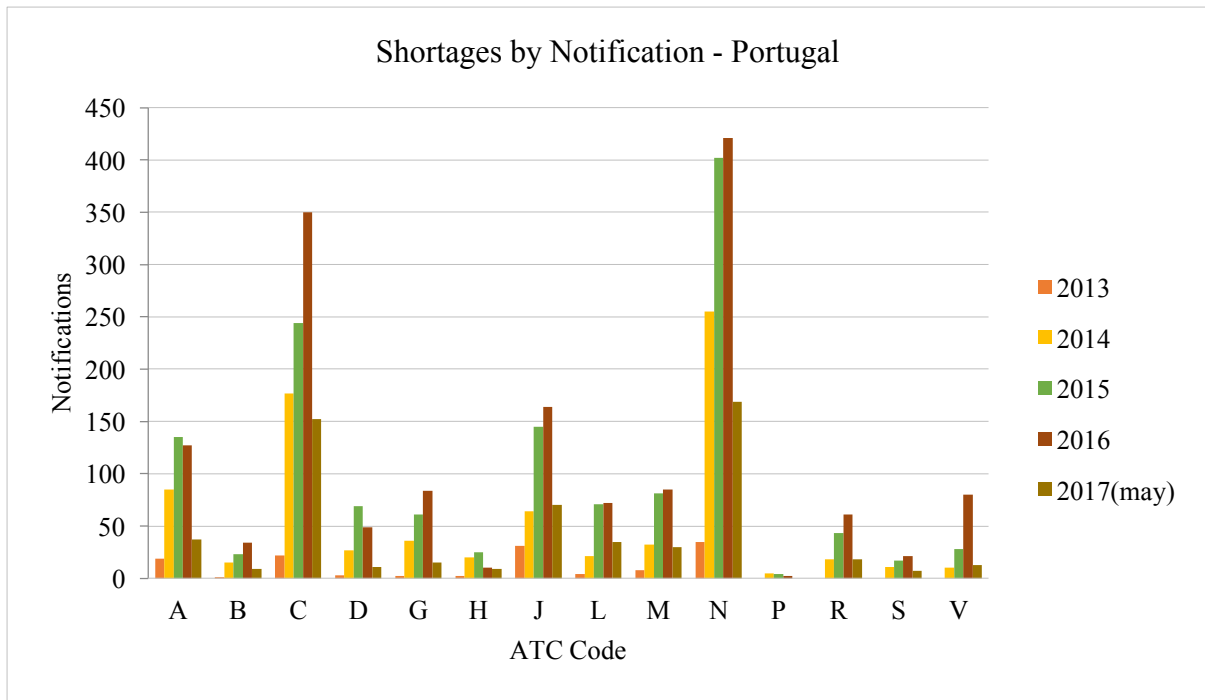


Figure 4 - Shortages by Notification. ATC Code Classification (2013-may 2017) Source: INFARMED, CIMI

(ATC Legend: A – alimentary tract and metabolism; B – blood and blood forming organs; C – cardiovascular system; D – dermatologicals; G – genito-urinary system and sex hormones; H – systemic hormonal preparations, J – anti-infectives for systemic use; L – antineoplastic and immunomodulating agents; M – musculo-skeletal system; N – nervous system; P – antiparasitic, insecticides, repellents; R – respiratory system; S – sensory organs; V – various.)

Comparison with data of shortages in pharmacies published by Deloitte in 2012 [35], 2013 [36] and 2016 [37], presented in **Figure 5** regarding the national supply market evidences some contrast between the two sides of the notifications.

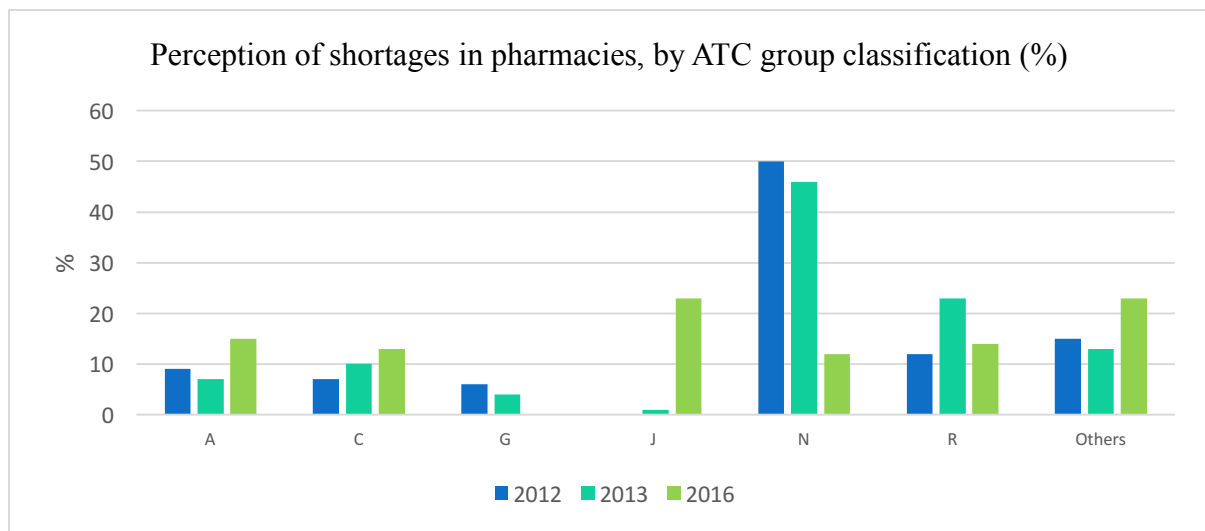


Figure 5 - Perception of shortages in pharmacies, according to ATC code criteria (2012-2016). Source: Deloitte

In CIMI's data, N products constantly achieve the highest position of notifications and keep increasing throughout the years, whereas in Deloitte's sample such products register a decreasing trend of shortage, going from highest ranked in 2013 to lowest ranked in 2016. The high level of shortages of R products published by Deloitte also finds no statistical agreement with the notifications by MAH, which remain lower in comparison to C and A product, while in the first case these assume similar levels. Although inconclusive, these discrepancies reflect the impact of factors other than those related to the manufacturer.

Moreover, in alternative to requesting data of shortages in community pharmacies to CEFAR (Centre for Health Studies and Evaluation), which was not possible, online browsing allowed for access to punctual processed list of top product shortages registered in community pharmacies by the same entity.

Table 2 - Top 20 products in shortage (Aug 2013- Jul 2014) registered in Portuguese community pharmacies. Source: CEFAR adaptation.

Top 20 shortages (Aug 2013-Jul 2014)			
Medicines	Notified by MAH	Medicines	Notified by MAH
1.Mycostatin oral susp.		11.Cymbalta caps 60mg x28	
2.Lovenox inj. 40mg/0,4mL x6		12.Cipralextab rev. tab 10mg x56	
3.Spiriva inal caps. 18mcg x30		13.Cialis rev. tab 20mg x4	
4.Varfine tab. 5mg x60		14.Risidon rev. tab 1000mg x60	x
5.Stagid tab. 700mg x60	x	15.Urispas rev. tab 200mg x15	
6.Crestor rev. tab. 10mg x60		16.Minigeste rev. tab. x63	
7.Avamys 27,5mcg/dose x120		17.Lyrica caps. 75mg x56	
8.Micardis Plus tab 80/12,5mg x28		18.Inderal-LA p.l. caps. 80mg x28	
9.Ilvico N rev. tab x20		19.Lovenox inj. 60mg/0,6mL x6	
10.Atrovent 0,25/2mL x20		20.Dolviran sup. X10	

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Table 3 - Top 10 shortages (Dec 2015) out of total shortages registered in community pharmacies, and top 10 shortages comprising products requiring export notification to INFARMED. Source: CEFAR; adaptation.

Top 10 shortages (Dec 2015)		Top 10 shortages in products requiring export notification (Dec 2015)	
Medicines	Notified by MAH	Medicines	Notified by MAH
1. Combodart caps. 0,5/0,4 x30	x	1. Avamys 27,5mcg/dose x120	
2. Polydexa sol.	x	2. Lovenox inj. 40mg/0,4mL x6	
3. Terricil	x	3. Atrovent inal. Sol. 0,25/2mL x20	
4. Ovestin cream	x	4. Humalog KwikPen 100UI/mL x5	x
5. Pneumo 23 inj.	x	5. Azopt susp. 10mg/mL	
6. Avamys 27,5mcg/dose x120		6. NovoMix Penfill 100UI/mL x5	
7. Urispas tab. 200mg		7. Lovenox inj. 60mg/0,6mL x6	
8. Lovenox inj. 40mg/0,4mL x6		8. Seretaide Inal. 25/250 mg/dose	
9. Zolofit rev. tab 50mg x60	x	9. Lovenox 80mg/0,8mL x6	
10. Minigeste rev. tab x63		10. Humalog Mix 25 KwikPen 100UI/mL x5	

The charts above show that the majority of products registering higher stock shortages in pharmacy daily practice does not find a correspondent shortage notification from MAH in the respective time range. For the list comprising products which require an export notification, the fact that manufacturing issues seem to be absent in order to possibly justify such deficiencies points, once more and although inconclusively, to delivery issues.

Although data sets for a wider range of time would allow for more consistent interpretations and conclusions around the matter, the available elements reflect the apparent weight of delivery-related inefficiencies.

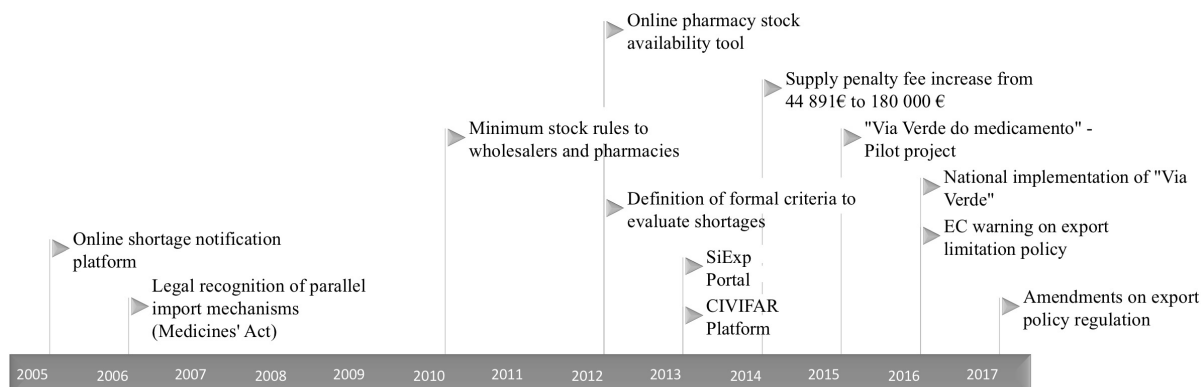


Figure 6 - Timeline of policies to address shortages and parallel trade of medicines in Portugal.
Source: own authorship

So far, the legal and regulatory elements that make up the Portuguese horizon of approach to shortages potentially related to parallel exports are described above and are compiled into the timeline of Figure 5, as well as a quantitative description of the phenomena over these last years. The term “potentially” quite reflects the challenge worth stressing at this stage, because the paradigm of the whole supply chain still puts it hard to effectively evidence the link and then target all occurrences of such nature.

2.1.2. The reality of parallel trade

But before we go there, let us also reference the legal tools that apply to Portugal as a potential parallel importer. The general idea of parallel trade being a legal way of bringing technically cheaper versions of the same product into the national market, thus leading to an eventual reduction of expenditure with medicines, be it public or out-of-pocket, puts it in a position worth exploring by governments facing more significant budgetary struggle in the healthcare sector.

Portugal is definitely no exception to this scenario, and hence the line of action towards parallel trade has essentially promoted a minimally beneficial price competitiveness (Decree-Law n° 65/2007 [38], imposing a retail price of any imported product to be at least 5% lower than the reference product) and an authorisation procedure simplification (Decree-Law n° 182/2009 [39]) attempting to stimulate requests from importers. Yet, a recent access to INFARMED’s product database (INFOMED) made on behalf of this research indicates a total of only five product presentations approved so far through a parallel import procedure plus five more with

a parallel distribution status, which applies to products that have been authorised via centralised authorisation procedure through EMA.

Table 4 - Medicines with Authorisation for Parallel Import, in Portugal (as accessed in November 4th, 2017). Source: Infomed.

Active substance /INN	Product name	Dosage, Form	Price Difference % (R/IP)
Clopidogrel	Plavix (DP GreenMed)	Revested Pill, 75mg	-
Morphine	Morfina Serra (IP)	Injectable, 10mg/mL	-
Nifedipine	Adalat CR (IP)	Prol. Release Tablet, 60mg	3,8%
Noradrenaline	L-Noradrenalina Braun (IP)	Injectable, 1mg/mL	-
Orlistat	Xenical (DP Alliance)	Capsule, 120mg	5,2%
Orlistat	Xenical (DP Euromedicines)	Capsule, 120mg	0
Orlistat	Xenical (DP GreenMed)	Capsule, 120mg	5,2%
Orlistat	Xenical (DP Tiliafarm)	Capsule, 120mg	-
Perindopril+Amlodipine	Coveram (IP)	Tablet, 10mg+5mg	-
Polyvalent bacterial lysate	Paspat Oral (IP)	Tablet, 3mg	5,2%

One of the MAH entitled to sell some of these products was contacted on behalf of this research and said that at the moment no supply of any product was being sustained, due to current lack of relevant commercial profit.

On the other hand, in 2011 an analysis of the exports market of medicines most susceptible to this practice showed that out of 343M€ of exports, more than 73M€ corresponded to the segment of parallel export [35]. Altogether, we can easily conclude that the parallel export dynamics within the national circuit is significantly more intense than that of parallel importation of medicines, even despite governmental efforts to foster the latter.

2.2. The Netherlands

2.2.1. Shortages as a major political concern

Although in different terms, shortages have also been dealing their significant share of impact to the medicines supply chain of The Netherlands. Data from KNMP – the Royal Dutch Pharmacists Association – evidence a quite significant increase in the number of shortage notifications between 2004 (91) and 2016 (625), with a major trend for densification of annual

occurrences since 2010 (see Error! Reference source not found.). Despite the significant amount of notifications, 99% of these are resolved with hard work and extra demand of resources from pharmacists. In 2016, only 7 shortages resulted in severe consequences for patients. Such data is sourced from the platform *Farmanco*, created and managed by KNMP since 2004 specifically meant to collect and publish information with respect to shortages notified by pharmacists and verified by the respective manufacturer. Daily, this online platform provides users with constant complementary details on each shortage occurrence such as reason for deficit, level of impact and possible solutions. These notifications, though, correspond only to situations where a given product is expected to be unavailable to supply for at least 14 days. As a result, it is not the most adequate mechanism to address intermittent supply inefficiencies caused, for example, by parallel exports. Nevertheless, its features seem to be proportionate to the most preponderant nature of occurrences within the national context.

Back to the impact, available sources reflect indeed a bigger and rising concern around shortages since 2010 onwards, having increased nearly four-fold in the following years, as shown in **Figure 7**.

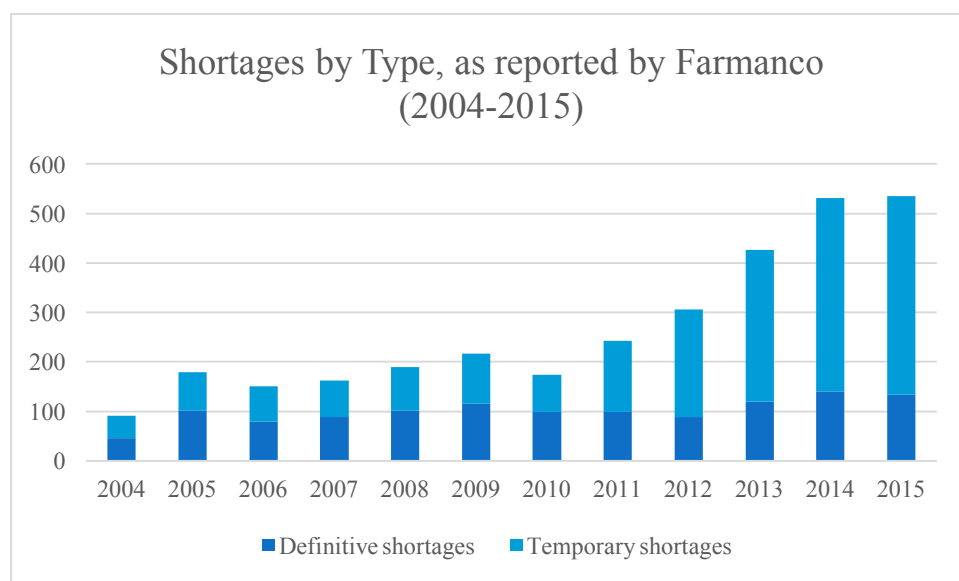


Figure 7 - Number of shortages notified to Farmanco, by type. (2004-2015). Source: Farmanco KNMP

As the concern rose around the subject, the Ministry of Health, Welfare and Sport (VWS) initiated, in the beginning of 2012 and together with the Inspectorate of Health (IGZ), the Medicines Evaluation Board (MEB) and the National Institute for Public Health and Environment (RIVM), a shared initiative to study the contributing factors and developing proper resolution strategies to approach shortages. In 2011, the Minister had already been

addressed by representatives of political parties requesting further evidence on whether the medicine pricing paradigm in The Netherlands was leading to shortages due to parallel exports. The Minister assumed a commitment to take the due diligences in order to investigate such matter, but at the time the answer was that research made by responsible entities within the (VWS) had found no evidence of such link. As was noted in Portugal, part of the problem lied on the fact that no periodic isolated commercial statistics for parallel exports are collected by national agencies [40].

In December 2012, in response to a demand for investigation and action, the Institute for Responsible Use of Medicines (IVM) published a report that resulted from a holistic research and testimonies from various entities of the sector around the topic of medicines shortages, which mainly advised for: a) even further insight regarding impact of shortages among patients; b) incentivising cooperation between governmental institutions and remaining stakeholders; c) increasing share of information that may contribute to more effective action; d) evaluate the impact of the existing policies concerning marketing of medicines, namely the preferential policy. Cumulatively, RIVM elaborated an Impact Model scheme to help entities better addressing and classifying every case of shortage as having Low, Middle or High impact according to specific criteria [41], [42].

In July 2013, few months after the outcomes of the above-mentioned report had been discussed and evaluated, the Minister addressed the due Standing Committee to reinforce her commitment and strategy towards the problem of shortages. Starting by assuming the relevance of considering international cooperation to resolve the impacts of an issue that derives from a global sector and thus transcends national boundaries, the Minister then set the research on the impact of shortages among patients as a key priority, announcing as well the creation of a Working Group composed by representatives of the many sides that are responsible for the well-functioning of the whole supply chain, which should collaborate to, among others: a) optimise the notification procedure for shortages, b) improve the communication strategy between stakeholders, c) involve prescribers in this reality, so that therapeutic evaluation is constantly paired with the current conjuncture of the supply and d) work closer with healthcare insurers to evaluate mechanisms to prevent the medicines preferential policy from originating cases of shortage [43].

Then, in 2014, a new report by the consulting firm Berenschot came public, filling some gaps on the available horizon of evidence for the impact of shortages for patients. One of the

conclusions worth highlighting was that such impact did not seem to go beyond an individual inconvenience for the patient who eventually has to deal with a switch in the presentation of a product or even switch from a manufacturing entity with which it has somehow created legitimate commercial empathy to another. These elements, although relevant, do not pose major impacts on the public health [44], bearing in mind that out of all notified shortages since 2004, cases where no alternative was found comprised only 1% of the total [45].

During this year, once again, representatives of political parties raised concerns around parallel exporting practices by wholesalers, as evidence to either confirm or dismiss suspicion around this causal link had not been collected up to the point. It seemed to have been the case, with a concrete shortage of the product Purinethol, denounced in a parliamentary debate in 2015 as being facing supply problems due to such exports. VWS took action, and in response to the situation the volume of monthly supply of the product increased by 25%, while the price of the product was also increased in order to prevent parallel trade, even though evidence of which could not be gathered [46].

The focus and continuous efforts from the working group and the involved parties did not attenuate the ascending flow of shortages. Despite national concern, the global dimension of supply inefficiencies was still heavily influencing the sector. In February 2016, after a complex process related to a production site transfer from The Netherlands to Germany, the medicine Thyrax Duotab 0,025mg became unavailable in the dutch market. An overall look into this process points for reasons of economic and production nature, from which the main conclusion taken by the IGZ is that there was an inadequate provision strategy by the MAH upon such transfer [47], which ended up dealing significant impact to more than 350.000 patients. Such episode, although peculiar, pushed even more for stricter political and regulatory action towards shortages, which led to renewed commitments from the VWS and the shortages working group [48], essentially turning out into the following actions:

- Joint Notification Centre, established in January 2017, as an optimised version that replaces the previous model which consisted of two notification centres, whereby expected shortages were reported to the MEB and unexpected shortages to the IGZ;
- A revised definition of what effectively should be seen as a shortage, based on a patient perspective, thus consisting of *“an interruption of availability of a medicinal product that is a burden for a patient and where the burden is greater than is the case for a*

generic substitution”. This intends to allow for more effective focus on cases that require action from the regulator;

- Proposal of a legislative amendment to increase maximum penalty fee from 450.000€ to 820.000€, while also increasing the standard fee from 45.000€ to 150.000€;
- Greater surveillance upon medicines considered to be clinically critical within the Dutch community. The creation of a list of critical active substances which should not by any means be in risk of supply was also considered, but had no strong support from the assigned working group as it would not essentially address the main challenges of the problem and presented practical problems [49];
- Setting up by wholesalers of an early warning system for punctual supply failures, while also committing to forego parallel exports of a product upon facing a situation of potential or actual shortage.

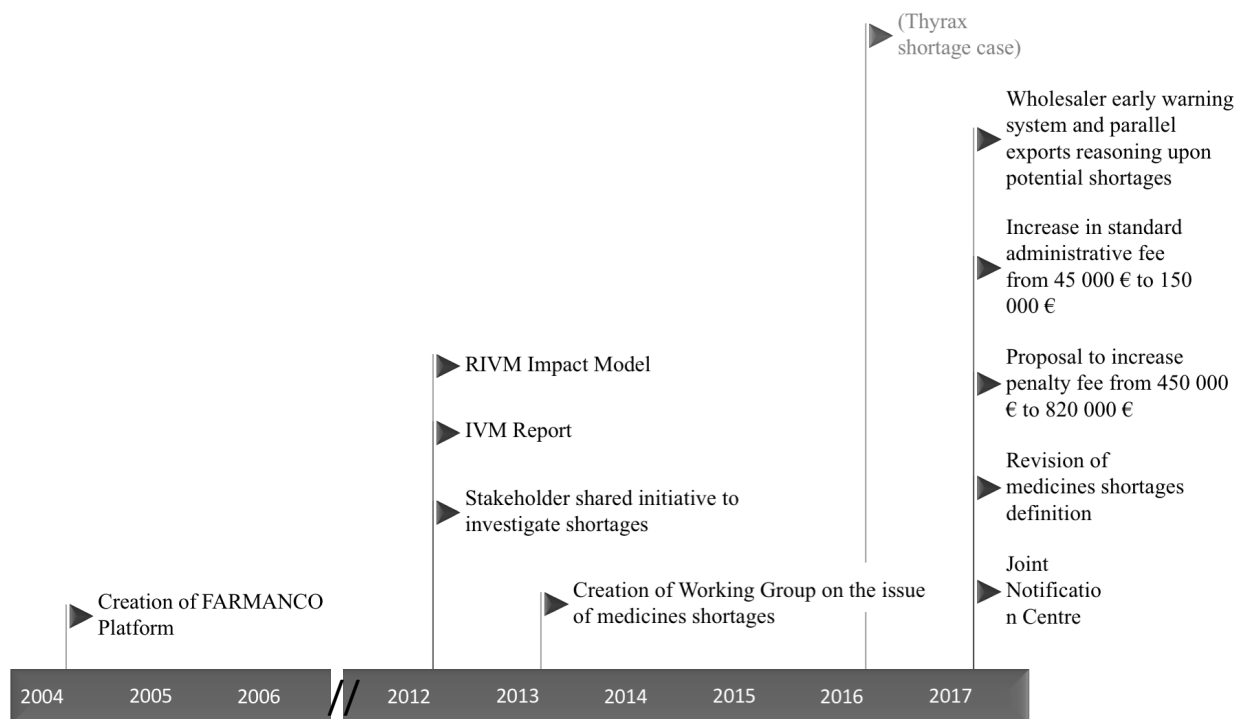


Figure 8 - Timeline of policies to address causes of medicines shortages in the Netherlands. Source: own authorship.

While further work is still ongoing by the government and the many parties that compose the sector, an overall commitment can already be reflected in these proactive steps. Having all the above-mentioned in consideration, we are led to assume that the current paradigm of shortages in The Netherlands demands for big efforts but, within the horizon of concern, parallel trade is

seemingly not being assumed as a major causing factor.

2.2.2. Parallel trade dynamics

The previous section puts the reality of shortages to context in The Netherlands, from which we can perceive that throughout the years there has been, from some parties, the assumption that parallel trade is indeed originating some of the deficiencies. This assumption, however, has not so far been matched with incisive market data to support the claim. Nevertheless, being one of the first countries to introduce this arbitrage practice and in fact one of those with a highest share of parallel imported products, it becomes interesting to see how this branch of activity has evolved in this period of major concern regarding shortages. Error! Reference

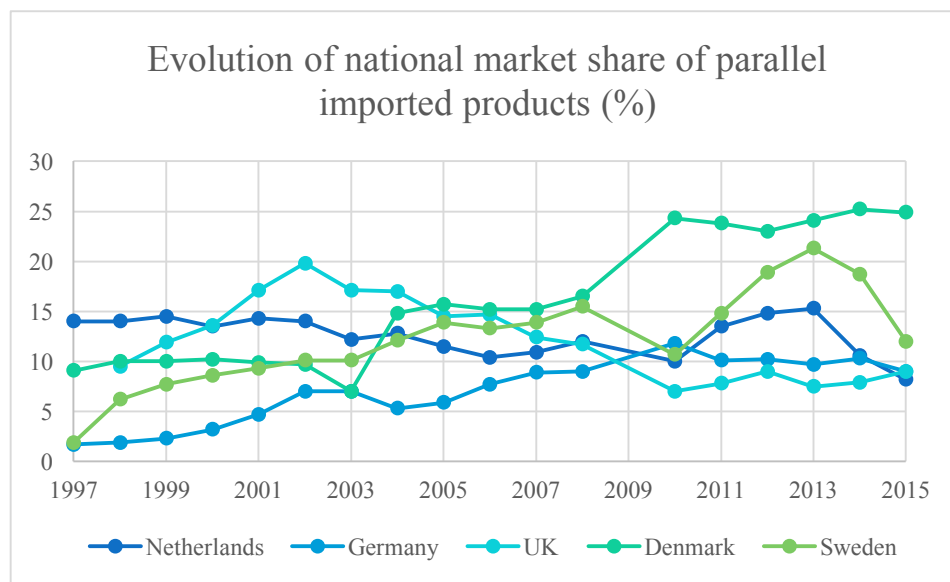


Figure 9 - Evolution over time of national market shares, in percentage (%), of parallel imported products among top importer countries. Source: EFPIA "The Pharmaceutical Industry in Figures" (1997-2015)

source not found. allows for an overview of the (estimate) trend over time of the market share (%) of parallel imported largest importers in the EU. These 5 countries combined comprised, in 2016, 81% of the total share of parallel imports of Europe, with Germany clearly leading the market with a share of 50%, followed by the UK with 20% [24].

The Netherlands accounts for the first known case – and for that matter, the first legal action – with regards to parallel trade of medicines within the European Union [25], in 1975. From the following decades up until the recent years, the country has been quite fond of this economic

arbitrage practice. In 2010, parallel imports accounted for 13,9% of the total imports of medicines into the country, which represented around 458M€ of trade volume. **Figure 10** shows the variation in number of Parallel Import Authorisations, conceded by the MEB throughout nearly the last decade.

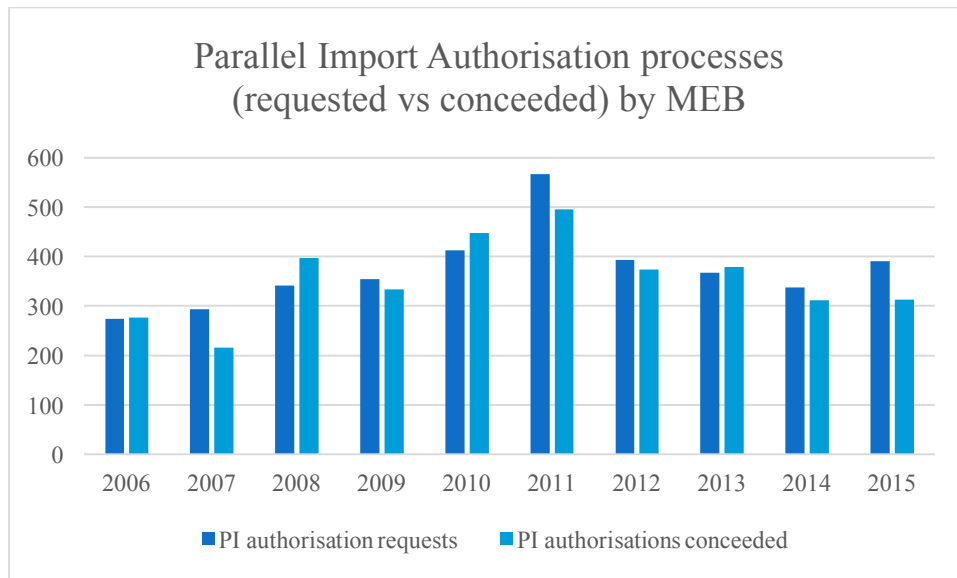


Figure 10 - Evolution of the number of Parallel Import Authorisations requested vs conceded by the Medicines Evaluation Board. Source: MEB Reports (2006-2015)

This assumption can be applied both to imports and exports. Which means that although from the figure we may perceive a recent decrease in importing activity - possibly due to a decrease in prices – this very same price reduction may foster the exporting component. Exports of pharmaceutical products in The Netherlands have significantly increased over these last years, although unfortunately methods for collection of such data do not make it possible to isolate the share related to parallel trade.

Dealing with such dynamics may comprise a sort of regulatory dilemma on the grounds that the general public interest of reducing prices for medicines may punctually be affected by the potential risk of reaching critical levels of exports for a given product, as described above with the case of Purinethol.

Beyond the commercial procurement activities performed by parallel traders, who look for profit opportunities, how imported medicines are dealt with by the respective national pharmaceutical system is also a relevant element to consider in order to weigh its influence on this practice and also to conclude on its added value to the overall supply chain. The main argument whereby parallel trade is directly beneficial for patients [27] seems to fail upon

meeting with the Dutch paradigm of access to medicines, given the broad cover of such expenses by healthcare insurers [50]. The pricing and reimbursement system makes it so that pharmacists and sick funds are the ones potentially benefiting from the competitiveness of lower prices derived from parallel imported products, together of course with the traders themselves. Moreover, such products are on average priced 3% below their reference product in the market and pharmacies, by governmental incentive, may keep one third of the difference between the parallel imported product and the reference one [50]. All in all, pharmaceutical policy in The Netherlands applied to pricing and expenditure aims to promote sales of cheaper medicines within product clusters, regardless of their nature. Even so, specific measures to incentivise preference for parallel imported products do exist.

3. Discussion

Putting the two described realities in perspective, it is clear that in both countries the number of shortages has consistently increased over the last years, which means they still face relevant challenges related to shortages, despite sustained efforts to address the problem. This comparison also does not add much to the already widely highlighted fact that shortages are in a good deal an international issue, to which consistent solutions will most likely have to arise from within shared political and technical consensus and efforts between - in the case of the social universe in analysis – the Member States of the EU. In fact, this figurative dive into these two national contexts leads to the conclusion that even despite the significant level of awareness around shortages and, for that matter, parallel trade of medicines, due national entities and stakeholders are to some extent left to their own proactivity and pressure upon coming up with measures that attempt to prevent and reduce the social and economic impact of some of these occurrences.

The overall perception we may achieve from both Portugal and The Netherlands with regards to this level of impact is that most of the situations have a technically acceptable solution (meaning an available equivalent therapeutic alternative), and hence to all purposes a supply deficiency of a product ends up being, pragmatically speaking, no more than an inconvenience. Such inconveniences should not, however, by all means, be neglected if we are to recognise the influence it may have on a patient's optimal therapeutic compliance and even on the commitment a pharmacy is supposed to sustain, every day, with its surrounding community. For this reason, notification of all sort of undesired occurrences should be fostered.

In Portugal the paradigm of under-reported supply deficiencies could be minored through the implementation of a platform similar to Farmanco, through which shortages other than those reported to INFARMED by MAH could be processed and congregated into a single spot, of easy access to pharmacists and remaining relevant parties, namely prescribers, in the process so that better perception of market dynamics could be achieved.

Complementary to this, it seems equally important to foster the involvement of the patient in the subject of shortages. Taking the wave of promotion of eHealth as a crucial element of the future of healthcare, digital tools could be built so that patients, when facing a situation of product unavailability, could also submit a simplified notification openly reporting the grounds of the inconvenient.

As to each country's adopted definition of shortage, differences can be pointed out between the two countries, although the key element to define the attached risk is common and heavily depends on the existence of an alternative. Nevertheless, while the definition of INFARMED bases the classification of shortage in this single criteria, in The Netherlands the definition of shortage itself is further complemented with more specific criteria structured in the Impact Model built by RIVM, whereby the impact assessment of each shortage is also evaluated based on the population groups the product is mainly indicated for, the estimated number of people using the product over the last 12 months and the expected duration of the shortage, among other elements.

The chronology of policies and initiatives also reflects, between the countries, a contrasting philosophy of action and responsibility-sharing on what concerns the entities involved in the process. While in Portugal INFARMED, due to statutory assignment, stands out as the centralised authority responsible for regulation and strategic planning of intervention in the face of the problem of shortages, The Netherlands relies on different assignment of roles among the existing bodies, such as the MEB, IGZ, RIVM and IVM.

As for the multifactorial origin of such inefficiencies and the way these are perceived by NCA, each causal factor naturally weighs differently *per se* and within the national context of the supply chain, hence leading to different prioritisation of action from involved parties. In Portugal, the fact that the main measures adopted recently are aimed at controlling exports of some products considered to be punctually in critical supply status reflects a significant preponderance of parallel trade as a potential inducer of shortages. In The Netherlands, despite stated and frequent concern about such link, overall strategy (in part prompted by the Thyrox case) and priority towards shortages is strongly focused on consolidating mechanisms to prevent and address cases of systemic supply deficiencies that may represent greater deal of impact, even though commitments from due stakeholders concerning a higher control of exports upon risks of shortage have been made.

Despite the contrasts, the challenges appear to be the same for both countries when this causal link is concerned: more effectively monitoring and gathering evidence to proof or disproof the said connection. The elements available make it legitimate to infer that such challenges, when public policy is concerned, are in good part due to the fact that the essence of the current monitoring mechanisms in both countries are meant to dedicate attention to occurrences that may lead to temporary (or permanent) but constant unavailability of a product over a certain

and more or less predicted period of time, while the deficient supplies that may potentially occur derived from partial batches being exported often translate in inconstant and intermittent unavailability in some cases and in supply quotas from wholesalers to community pharmacies in many others, all situations which throughout pharmacists daily practice may commonly not result in a formal notification of shortage. Moreover, the fact that a considerable number of products that make up the list of top shortages in Portugal finds no single notification from the due MAH, within the respective time range, also points for an undesired monitoring inefficiency. These situations might also be due to deficient complementarity between manufacturer supply and pharmacy consumption, which in any case should be optimised.

On this matter, there is public evidence of INFARMED's inspecting activity upon infringements derived from illegal exports and general non-compliance with the legal obligation of supplying the national market. While data of such nature could not be accessed for the Dutch reality, the recent move towards a legislative amendment to increase the maximum penalty fee for MAH that do not comply appropriately with their supply obligations up to 820.000€ mirrors a strong intention of imposing stricter sense of social responsibility within the sector. In Portugal, the recent increase of similar value to 140.000€ is also a positive sign, but concern may be raised as to whether it falls below the marginal level of interest for exporters to incur in such activity.

A well-functioning supply chain of medicines should not bear with episodes in which a wholesaler excuses himself, upon direct request, from the obligation of supplying a product that is not formally under shortage by simply justifying that such product has a "commercial quota" status, as often happens in Portugal.

In fact, it is somehow incongruent that such cases are allowed to coexist with a reality where, on the other hand, free trade of medicines is protected by the due jurisprudential bodies on the grounds of essentially preserving universal political values. The basic commitment of fulfilling the respective market's demand should be more strictly prioritised. And this may perhaps mean promoting control over parallel trade of medicines first, so that consequently manufacturers may optimise national stock calculations, hence attenuating these impacting quota mechanisms.

Parallel trade should not be perceived as a desired mechanism to foster pricing competitiveness for the sake of reducing national pharmaceutical expenditure. It may do so, but evidence seems

to be consistent in showing that, globally, the economic natural tendency is for it to be mostly beneficial for countries with higher prices, already favoured in terms of access due to interest from the pharmaceutical industry in supplying such markets, whereas low-price countries are left with shy opportunities of accumulating such perks and, as noticed, face risks of aggravated supply deficiencies, among others. Bearing these two countries in particular, it is also legitimate to infer that the portuguese pharmaceutical system framework makes it so that benefits of parallel trade are more directly passed on to the patients, even despite economic interest, while in the Netherlands the situation is nearly the opposite.

The effective solution may in the end not actually be to prevent parallel trade, but to optimise other elements of the European pharmaceutical market, namely the pricing paradigm. But that is, certainly, a discussion that fall outside the range of this analysis.

1.1.Limitations

As often applies, access to data related specifically to parallel exports of medicines seems to display a barrier to some research questions covered of utmost interest. Being no exception to the scenario, this research has suffered a considerable setback in terms of its initial objectives and expected outcomes because it was not possible to collect consistent nor official information on parallel exports of medicines from Portugal to other EU countries. In some cases, motive was basically lack of response. Monetary resources needed to access IQVIA's market database was also a significant limitation. Hence, unfortunately it was not possible to successfully fulfil the main goal of attempting to quantitatively link concrete shortages with concrete parallel traded products.

No response from CEFAR and delayed request assessment from INFARMED with regards to datasets of shortages within community pharmacy context also significantly impacted the intended analysis by impeding the cross-link of information between notifications by MAH and daily practice shortages over a broader period of time. The intrinsic need to access and study documentation and content that is originally published online in Dutch language comprised punctual difficulties to the browsing approach.

The cross-country comparison made over the document was not able to collect elements of the same exact nature for both realities, limiting somehow the holistic comparison.

4. Conclusions

The research was triggered with a basis in two main premises. On the one side, a context of great international concern towards shortages. On the other, the fact that the discussion around parallel trade still seems to be covered in arguments that partially lack real world evidence to either support or refute its effect in national supply chains. This approach aimed, thus, to complement such discussion.

Parallel trade of medicines was never, throughout this research and at least for the countries in analysis, assumed as the potential the main cause of shortages within the supply chain. Even so, it seemed worth to further explore the available practical evidence of this causal link and analyse the political and regulatory postures of two conjunctures in different positions towards this practice. The evidence within reach of this project did not allow for conclusive positions as to whether parallel trade has been, in concrete cases, the single causing factor of a shortage. However, the analysed data evidences a considerable amount of concrete supply deficiencies caused by delivery-related factors, in which this practice is included.

Nevertheless, other inferences attached to the core issue were possible. The cross-country policy-making contrast regarding parallel trade confirms the available and possible evidence, theory and assumption that such practice tends to affect long known low-price countries in Europe to a large extent, a figurative basket in which Portugal has been always included.

Throughout these last years, despite a national concern common to both countries, Portugal has been more intensely developing measures to specifically address parallel trade as a potential supply disruption factor. On this matter, the European Commission has raised concern regarding excessive and unjustified control and request of information towards trade flows of certain products authorised in the national market. In The Netherlands, although policy efforts does not exhibit this same level of priority given to potential trade-related shortages, the limited level of information to assess such suspicion has also been pointed out as an element requiring further optimisation, thus reflecting the effective need to consolidate market monitoring mechanisms. On the background, perhaps the need for a shift in the political and jurisprudential culture with regards to parallel trade of medicines should also be considered. Overall, this research recognises and subscribes the relevance of further investigation and attention around this main subject.

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