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Medicine Shortages in Cyprus: Perceptions on Causes and Ways of Supply Chain Management

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Abstract. Drug shortages are a global phenomenon which over the last decade seems to be deteriorating and affecting all healthcare systems in Europe and other countries around the world. Shortages of medicines constitute a growing problem with a significant impact on public health and, if not addressed effectively, could lead to a global crisis in the provision of pharmaceutical care to patients. This research aims to investigate the main causes of drug shortages in Cyprus, the extent of the problem locally and the stages of the downstream pharmaceutical supply chain where shortages are most likely to occur. The research is conducted through semi-structured face-to-face interviews with a number of stakeholders from the local pharmaceutical supply chain followed by qualitative analysis of the gathered data. The findings of the study indicate that drug shortages in Cyprus are mainly located at the production and importation stages of the pharmaceutical supply chain. They originate from multifactorial causes and they are both supply and demand related. Cyprus, as a small country, has always confronted problems with shortages of medicines. The peculiarities of its market make Cyprus particularly vulnerable to shortages, but the extent of the problem does not seem to differ compared to that observed in other small European countries. The study findings are anticipated to shed light on the causes of shortages and to strengthen the efforts being made to address the problem nationally especially at a time where the healthcare system of the country is under reform.

Keywords: drug shortages, medicine shortages, supply chain, pharmaceutical supply chain.

1. Introduction

Drug shortages are a global phenomenon which over the last decade seems to be deteriorating and affecting all healthcare systems in Europe and other countries around the world (European Medicines Agency (EMA), 2019). Shortages of medicines constitute a growing problem with a significant impact on public health and, if not addressed effectively, could lead to a global crisis in the provision of pharmaceutical care to patients (European Cooperation in Science and Technology (eCOST) Action CA15105: Medicines Shortages in Europe, 2018).

Drug shortages are a complex and major problem for global public health as they do not only affect those involved in the supply chain but they also have a significant impact on patients, health professionals and healthcare systems (Truong et al., 2019). In particular, drug shortages may have serious consequences including treatment delays or inability to provide the most appropriate treatments to patients, the use of less effective or more expensive treatments and to increase the likelihood of medication errors or side effects (World Health Organization (WHO), 2016).

Shortages occur for both innovative products and for drugs for which generics are also available. All therapeutic categories are prone to shortages. Those most commonly reported include anti-cancer medications, antimicrobial agents, anesthetics and analgesics (European Association of Hospital Pharmacists (EAHP), 2019; Pharmaceutical Group of European Union (PGEU), 2019; WHO, 2016).

The causes for which shortages occur are multidimensional and multifactorial as they arise through the context of a complex global supply chain (International Pharmaceutical Federation (FIP), 2019). The causal factors that contribute to the occurrence of drug shortages vary and they relate both to supply problems and changes in demand (WHO, 2016). They are mainly related to production and quality problems, natural disasters, market disruptions as well as difficulties arising from various legal, commercial and pricing frameworks (eCOST, 2018; Lyengar et al., 2016).

International recommendations for mitigating the problem of shortages mainly focus on practices to promote effective supply chain management, good cooperation between stakeholders, optimization of regulatory procedures, procurement and pricing practices, and establishment of national reference systems (Lyengar et al., 2016; The Economist Intelligence Unit, 2016; WHO, 2016).

2. Background of the Project

2.1. The pharmaceutical market in Cyprus

The main characteristic of the pharmaceutical market in Cyprus, until 1 June 2019, was the absence of a universal national healthcare system. This made Cyprus the only country in the European Union which did not have in place a universal healthcare insurance scheme for the whole population (Petrou, 2014).

According to the provisions of the General Healthcare System (Amending) Law of 2017, a new GHS was introduced and implemented in two stages. The first stage began on the 1st June 2019 and provides the introduction of outpatient healthcare. The second and final stage of GHS implementation, beginning June 1st 2020, included introduction of all the remaining healthcare services.

Before 1st June 2019, the pharmaceutical market in Cyprus was divided in two sectors:

a. The public sector, the beneficiaries of which constituted around 80% of the population and had free access to pharmaceuticals from public pharmacies after presenting a prescription from a public sector physician. The purchase of pharmaceuticals for the needs of the public sector was done exclusively via tenders. With the exemption of products with no alternative in the same therapeutic class, most of the tendering procedures led to the purchase of a single product – the one offering the lowest bid price. Most of the times, this product had the whole public market exclusivity for 2 years (Petrou, 2014).
b. The private sector, which constituted around 20% of the population, and was relying on private health insurances and out-of-pocket payments for access to health services and pharmaceutical products (Petrou & Vandoros, 2015).

Cyprus' pharmaceutical market is perceived to be a non-attractive as it accounts for less than 0.3% of EU corresponding pharmaceutical market (Petrou & Vandoros, 2015). The long-lasting fragmentation, its small size, the necessity to use the national language, coupled with the geographic location of the island, have erected as a barrier to uninterrupted supply of medicines to Cyprus (Petrou, 2014).

Prior to the introduction of the GHS, two parallel market existed, and while this feature disrupted the health care equity, it was a remedy for shortages since patients visited private pharmacies in case of shortages in the public sector and vice versa. The unification of the market and the abolishment of tendering, which provided market exclusivity for a period of two years and allowed proper planning - which is not the case in the current competitive market - calls for strict monitoring of this issue.

This particularity of the healthcare system, combined with other challenges the country is facing such as the small market size, the economic crisis and the possible consequences of the UK's withdrawal from the European Union (Brexit) (EMA, 2019), indicate an urgent need for action to ensure the uninterrupted supply and adequacy of all necessary medicines in the Cypriot market.

2.2. The pharmaceutical supply chain in Cyprus

The legal downstream pharmaceutical supply chain in Cyprus constitutes of the authorized local manufactures (local manufacturing companies of generics), the multinational research and development pharmaceutical companies operating in Cyprus or their local representatives, importers, wholesalers, distributors, hospital

and community pharmacies and, ultimately, patients.

The central public warehouse is responsible for the purchase and supply of pharmaceuticals to all the public hospital pharmacies whereas the three main private warehouses are responsible for supplying the private sector (community pharmacies). All warehouses purchase their stock from local importers, wholesalers and distributors. In addition, the central public warehouse can purchase and supply the public sector with unlicensed products for which there are certain medical needs. These products are sourced via special procedures from warehouses abroad.

2.3. Aim and Objectives of the research project

It is evident that is of utter importance to cast light on shortages in Cyprus, its pillars and potential potent approaches to proactively mitigate their impact.

The main aim of the project is to investigate and analyze the main causes for drug shortages in Cyprus, the extent of the problem locally and the stages of the downstream pharmaceutical supply chain where shortages are most likely to occur.

Secondary the study aims to draw conclusions on the interpretation of the concept of 'drug shortages' by the various stakeholders, to investigate the flow of information among the supply chain stakeholders regarding local shortages, to investigate the history, current situation and trends of drug shortages in Cyprus and any measures taken by the industry in recent years so as to contribute in any way to addressing the problem. Moreover, the study aims to draw conclusions on the main constraints faced at the local level for resolving the problem and to investigate possible ways of dealing with the problem based on the particularities of Cyprus.

The project is focusing on analyzing the problem and causes of drug shortages in Cyprus during the implementation of the previous, non-universal, healthcare system. Nevertheless, references are made to the current situation in the context of the new GHS but without thoroughly analyzing the causes.

3. Methodology

The research design of the study is a qualitative analysis which was conducted through semi- structured face-to-face interviews with a number of stakeholders from the local pharmaceutical supply chain.

The aim of this research design was to gather the required information through in-depth investigation, collection and recording of participants' views on the subject under study.

The semi-structured questionnaire consisted of open-ended questions that allowed the participant to deepen and freely develop his / her answer. Participants' responses were recorded in notes on the electronic interview forms. Interviews took place at a predetermined time and place. With the grouping technique, the

confidentiality of participants' anonymity and the safeguarding of their personal data ware ensured.

In total, 14 people were invited and accepted to participate in the interviews. 13 of the participants were representatives of the various stages of the legal supply chain in Cyprus and 1 participant represented the National Competent Authority (medicines regulatory authority) of Cyprus (Figures 1a and 1b).

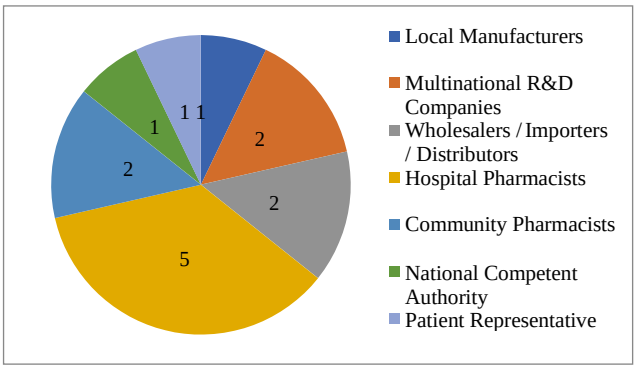


Fig. 1a: Number of interviewees representing the different levels of the national downstream pharmaceutical supply chain.

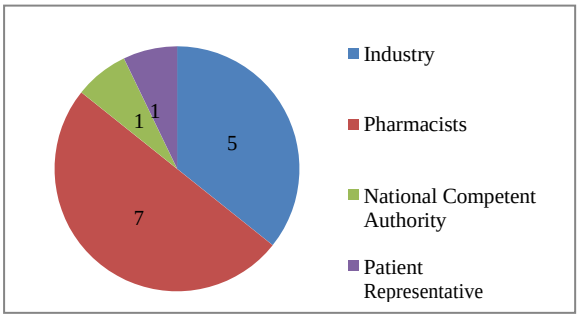


Fig.1b: Number of interviewees representing the different levels of the national downstream pharmaceutical supply chain.

4. Results

4.1. Current status

RQ: In your experience, how often do shortages occur?

Half of the interviewees agreed that drug shortages before the implementation of the GHS were not a serious or a frequent problem in Cyprus.

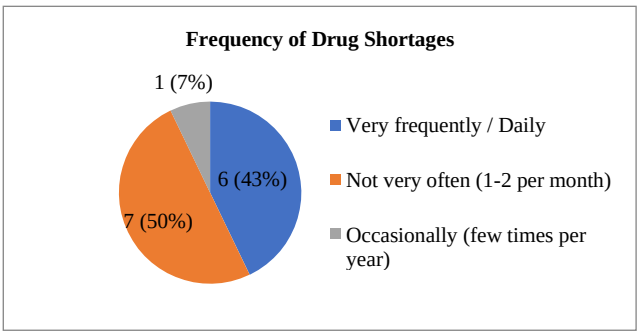
Six (6) of the interviewees (3 hospital pharmacists, 2 community pharmacists and 1 research company) agreed that shortages occurred very frequently or on a daily basis.

Two (2) hospital pharmacists and the patient representative answered that drug

shortages occurred once or twice a month.

The local manufacturer and the NCA representative answered that the frequency with which shortages occurred did not differentiate from the average number of shortages in other European small countries.

One (1) research company stated that shortages of their own products occur occasionally in Cyprus (approximately 4 times a year) and usually they are of short duration. This happens because of the country's small market size for which relatively small quantities are required and which, therefore, allows precise



forecasting and forward planning on their part.

Fig. 2a: In your experience, how often do shortages occur?

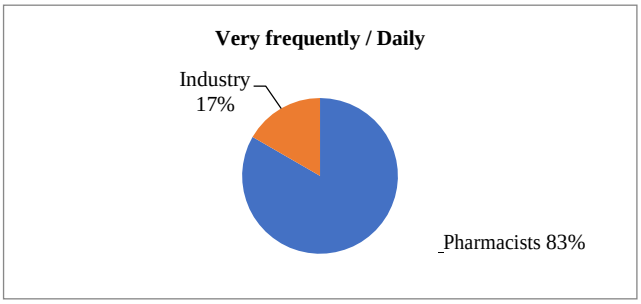
Fig. 2b. In your experience, how often do shortages occur?

RQ: How would you describe the flow of information between the different stakeholders in the pharmaceutical supply chain?

Eight (8) interviewees (all pharmacists and the patient) answered that there is no information regarding drug shortages or the flow of information is problematic.

Six (6) interviewees (all industry and NCA) believed that there is satisfactory flow of information between the various stakeholders.

4.2. The problem



RQ: How would you define a medicine shortage?

All hospital pharmacists and one (1) community pharmacist agreed that the definition of a drug shortage is: not being able to purchase from the warehouse a medicine that a patient needs leading in search of alternative medicines, postponement or cancellation of drug treatments.

The NCA representative defined the problem as the absence from the Cypriot market of any stock of a certain active ingredient at a given pharmaceutical form for a time period of more than two weeks approximately. One (1) community pharmacist agreed that a shortage is defined as the absence from the market of any stock of a certain active ingredient at a given pharmaceutical form.

According to one (1) wholesaler and one (1) research company representative, a drug shortage is the absence of a certain pharmaceutical product from the market and its non-availability to patients.

According to one (1) distributor, a drug shortage is the temporary or permanent non availability of stock of a certain pharmaceutical product at their warehouse.

One (1) research company representative stated that a drug shortage exists when, for a specific time period, there is not available stock to meet the demand of a patient or a healthcare professional – hence the demand is greater than the supply.

According to the local manufacturer drug shortages occur when:

i. A product is missing from the market because it is not registered,
ii. A product, although registered, it's not marketed for various reasons such as pricing, small market size or because of the manufacturer's inability to supply the market (e.g. quality or regulatory issues),
iii. A registered marketed product is not available for a specific period of time.

From the patient's perspective, a shortage occurs when a specific pharmaceutical product which has been prescribed to a patient is not immediately available at pharmacy level.

4.3. History

RQ: When did it begin and is this a recent phenomenon?

All of the interviewees answered that drug shortages are not a recent problem in Cyprus. Shortages of medicines always existed, as this is a worldwide phenomenon, however they have not been a serious problem for the local market.

Two (2) of the interviewees (1 pharmacist and the patient representative) stated that before the implementation of the GHS, shortages occurred mainly in the public sector while the problem is now more prevalent in the private sector. However, this was attributed to unforeseen shifts in clinical practice in the context of the new healthcare system and it was estimated that – with time and system facilitation - the problem will mitigate.

4.4. Shortage Occurrence

RQ: To the best of your knowledge, which stage of the supply chain are shortages most likely to occur?

One (1) pharmacist working at the private sector answered that shortages occur more often at the manufacturing level while one (1) other community pharmacist and the NCA representative answered that shortages of locally manufactured generic products occur at the production level while shortages of products manufactured outside Cyprus may occur at the importation level.

Besides manufacturing problems that may result in serious global shortages, hospital pharmacists working at the public sector agreed that drug shortages in Cyprus are likely to occur at the level of the central warehouse e.g. from the wholesaler to the warehouse and from the warehouse to hospital pharmacies. The reasons for these shortages were attributed mainly to procedural, bureaucratic and regulatory issues.

The two (2) research companies and the two (2) wholesalers responded that shortages are most likely to occur at the production / manufacturing level. One (1) research company and one (1) wholesaler added that when shortages at the manufacturing level are of long duration, they may consequently affect the downstream stages of the supply chain (importation, distribution).

According to the local manufacturer, shortages in Cyprus occur when a certain pharmaceutical product cannot be manufactured or imported to the country. Because of the country's small size, once the product is available at national level then it's directly distributed to warehouses and pharmacies.

According to the patient representative, besides the global problem of shortages occurring at manufacturing level, the next most common and important stage for shortages in Cyprus is importation.

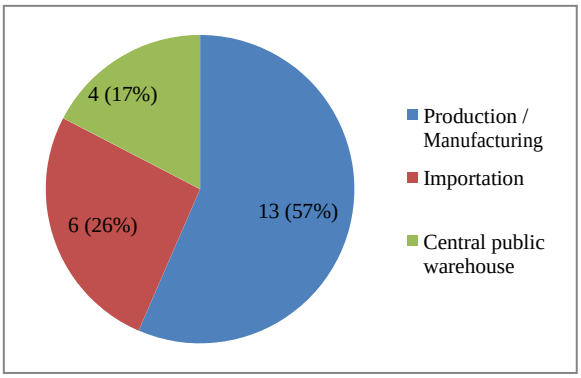


Fig.3: Where in the supply chain are shortages most likely to occur?

4.5. Main causes

RQ: What do you believe is the main cause?

Although the majority of the stakeholders listed manufacturing and importation as the main stages in the supply chain where shortages are most likely to occur, the reasons behind these shortages were quite varied.

Manufacturing problems. Almost all of the interviewees (except one pharmacist) answered that problems in the manufacturing process are a main cause of drug shortages, both globally and nationally.

Reported reasons leading to shortages at the manufacturing level were quality problems such as defective batches or machines (answer from 3 pharmacists and 1 wholesaler), scarcity of raw materials (answer from the NCA representative and 2 pharmacists), the limited number of API manufacturers (answer from 1 pharmacist) and financial problems - such as taxes on APIs - leading to reduced production (answer from the local manufacturer and 1 pharmacist).

Legislative and Regulatory requirements. Legislative and regulatory requirements and restrictions were listed as one of the main causes for shortages from six (6) interviewees.

According to one (1) research company, one (1) wholesaler and one (1) pharmacist, the small size of the Cypriot market in combination with specific regulatory requirements such as for the packaging and the PIL of the medicinal products to be in Greek language, or in Greek and English language, affects supply and may lead to shortages.

In addition, one (1) research company and the local manufacturer stated that drug shortages were recently reported because of the almost simultaneous implementation of new EU Regulations relating to FMD and BREXIT.

From one (1) wholesalers' perspective, changes in regulatory and legislative frameworks are one of the main causes of serious shortages in Cyprus.

Changes in demand. Six (6) interviewees (2 pharmacists, 1 research company, 1 wholesaler, the local manufacturer, the NCA representative) answered that unexpected changes in demand of pharmaceuticals can lead to shortages. According to the NCA representative, changes in demand can be attributed to changes in prescribing practices, changes in pricing or because of an unexpected increase in demand e.g. outbreak of an epidemic.

According to the research company and the local manufacturer, the implementation of GHS in Cyprus formed a new environment regarding prescribing behaviors. This new environment led and may lead to future shortages because of unpredictable changes in demand.

Small market size. While stating that medicines shortages are a very complex problem, the local manufacturer attributed the problem in Cyprus mainly to the

small market size, and thus to the small needs, making the market unattractive for MAHs to introduce their products. The small market size was also listed as a main cause of shortages in Cyprus from one (1) research company, one (1) wholesaler, one (1) hospital pharmacist and the patient representative.

On the other hand, one (1) research company answered that the small market size is a favorable factor for their company due to small quantities required to meet market needs, thus allowing a more accurate forecast.

Pricing. According to four (4) interviewees (1 pharmacist, the local manufacturer, 1 wholesaler and the patient representative), reductions to the prices of pharmaceuticals may lead to shortages as these products become unprofitable especially in a small market. A small market forcing down prices on pharmaceuticals (as part of economic crisis measures or as a measure to reduce costs) constitutes an unattractive market for manufacturers and MAHs either to introduce their products to the market or to continue supply the market with their products.

According to the wholesaler, pricing reductions can be the cause of shortages as they may lead to the withdrawal of products from the market. These shortages can be very serious in cases where the products are innovative and no generic equivalent exists.

Geographic location. Four (4) of the interviewees (1 pharmacist, 1 research company, 1 wholesaler and the local manufacturer) responded that a number of national shortages is attributed to the fact that Cyprus is an island largely depending on air connections and shipments for pharmaceutical importations.

Others. Other reasons such as complicated and time-consuming administrative procedures related to ordering and supply from the central state warehouse (3 pharmacists), understaffing (1 pharmacist and the local manufacturer), limited number of parallel importations and lack of alternative importation procedures e.g. via a state mechanism other than the one already existing for emergency needs for non-registered products (patient representative) were listed as causes of drug shortages in Cyprus.

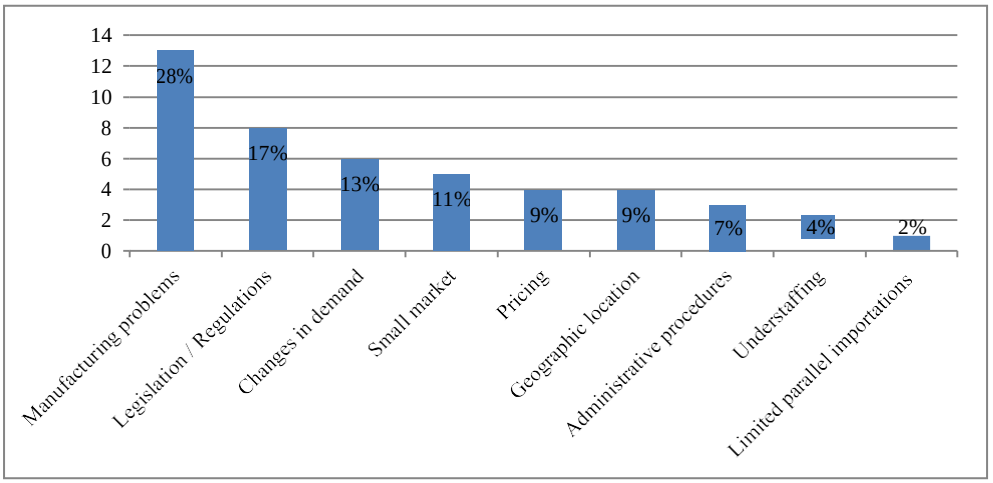


Fig.4: In your experience, what is the main cause of medicines shortages?

4.6. Trends

RQ: Has the problem been improving or getting worse over the last decade?

All of the interviewees answered that the problem of drug shortages in Cyprus worsened with the implementation of the GHS. However, the stakeholders stated that these shortages are attributed to the unpredictable change of prescribing practices in the new system and that the problem is expected to mitigate in time.

Beyond that, most of the interviewees felt that the problem was stable in the last decade.

Two (2) of the interviewees answered that the problem has improved in the last decade. The NCA representative stated that the problem has improved because of advancements in transportation and importation of medicines and because of improvements in the communication of shortages between the stakeholders. One (1) hospital pharmacist stated that the problem has improved because of the increase in the availability of alternatives i.e. generics, biosimilars and new substances.

One (1) hospital pharmacist felt that the problem got worse over the past decade and one (1) community pharmacist felt that the problem got worse in the last two years.

RQ: How has the industry evolved over the last 10 years in any way to contribute to medicines shortages?

Five (5) of the interviewees (4 pharmacists and the patient representative) didn't know if the industry had evolved in any way to contribute to shortages.

Nine (9) of the interviewees (all industry, the NCA representative and 3 pharmacists) felt that during the last decade the industry has evolved in a positive way to contribute to drug shortages.

Seven (7) interviewees answered that the industry uses better logistics and focuses on better forecasting. One (1) hospital pharmacist added that the industry has evolved in a way to use risk assessment as a preventive measure of shortages. The manufacturer and one (1) community pharmacist stated that there is an increase to the portfolio of the local pharmaceutical industries and an increase to the number of local representatives and local companies – therefore there is an increase in the availability of alternatives options. One (1) research company felt that the use of shared packs of medicinal products has contributed positively to the management of shortages.

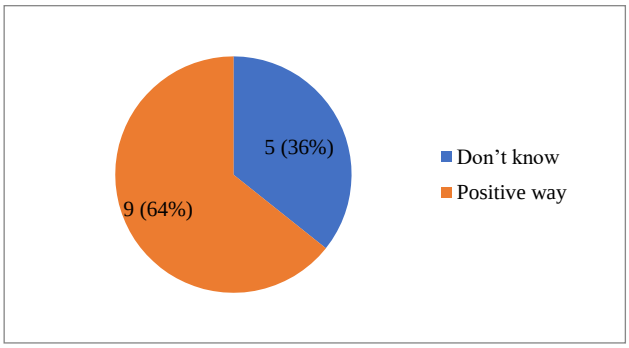


Figure.5a: How has the industry evolved over the last 10 years in any way to contribute to medicines shortages?

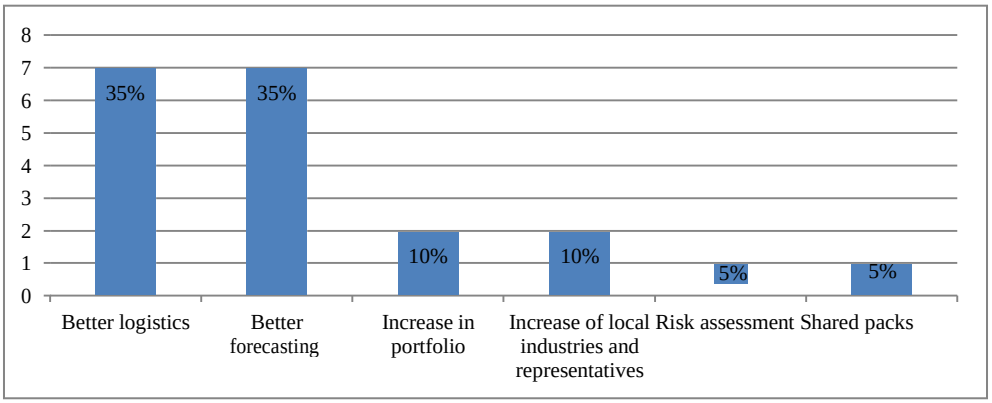


Fig.5b: How has the industry evolved over the last 10 years in any way to contribute to medicines shortages?

4.7. Measures & constraints

RQ: What measures have been or should be taken to resolve the issue in Cyprus?

The interviewees believed that the consolidation of the market with the implementation of the GHS is a step forward to alleviate the problem of shortages in Cyprus.

One (1) research company answered that, regarding their own organization, good collaboration with their distributor exists so that there is always stock available in Cyprus. Moreover, for life saving medicines efforts are made so that there is always stock available both at the level of manufacturing abroad and in Cyprus. The company added that systemic forecasting is performed based on the peculiarities of Cyprus so that the manufacturing factory is prepared for the needs of the Cypriot market. Cold chain products, specifically, are imported more frequently and in small quantities for better supply control.

One (1) other research company positively noted that patients in Cyprus have access to alternative pharmaceutical products since parallel importations are allowed, and different products with common indications are registered and marketed.

On their behalf, the NCA representative stated that good collaboration among EU member states exists on European level in order to establish and implement universal guidelines for the effective management of medicines shortages.

Beyond these, the interviewees suggested the below measures in order to tackle the problem of shortages in Cyprus.

Enhancement of collaboration. Eight (8) of the interviewees (6 pharmacists, 1 research company and the patient representative) stressed the need for enhancement of collaboration between all supply chain stakeholders.

They suggested the set-up of a transparent mechanism governed by legislation that will ensure better forecasting, regulation and management of shortages. The participants suggested that all relevant authorities should collaborate to establish a national drug shortages management team with supervisory and steering role so that immediate and bilateral information exists between all stakeholders.

Legislative and Regulatory flexibility. The two (2) wholesalers suggested that the state should consider the implementation of more flexible legislative and regulatory strategies to exceptionally allow, for a specified time period, importations of non-registered medicinal products or packages in different language in order to supply the market with the drug in shortage.

Financial incentives. The local manufacturer mentioned that the problem of shortages is global and not easy to handle. For the alleviation of the problem he suggested the provision of financial incentives from the state to local pharmaceutical industry and the consideration of the possibility of non- regular pricing updates. In his opinion, this measure would provide financial security for pharmaceutical companies to place their products on the Cypriot market.

He also suggested that efforts should be made to increase shipments and air connections so that imports of pharmaceuticals are more frequent.

Other measures. According to one (1) pharmacist, the importation of products with a longer shelf life would avoid minimizing the stock at the level of the importer / wholesaler.

The patient representative stated that Cyprus is a small country with limited bargaining power, especially for innovative products. One possible way to enforce access to medicines would be by collaborating and entering into price agreements with other European countries. One other possible way, according to the patient representative, would be for the state to try and resolve the problem on a national level in collaboration with pharmaceutical companies though e.g. managed entry agreements.

RQ: What is the largest constraint to resolving the issue in Cyprus?

The majority of the interviewees (2 hospital pharmacists, 2 community pharmacists, 2 research companies, 2 wholesalers and the patient representative) noted that the largest constraint to resolving the problem nationally is the geographic location and small market size of the country while one (1) research company and the two (2) wholesalers added that non- flexible legislative and regulatory procedures to exceptionally allow importations of non- registered products in cases of shortages negatively contribute to the problem.

5. Discussion on main findings

The findings of the study indicate that medicine shortages are not a recent phenomenon in Cyprus. Whilst with the implementation of the GHS drug shortages were occurring more often, the overall extent of the problem does not seem to greatly differ in comparison with other small European countries.

The majority of pharmacists (5 out of 6) - both hospital and community professionals - reported that medicines shortages are a very frequent problem. Pharmacists emphasized that drug shortages may have major impacts including postponements or cancellation of treatments e.g. chemotherapy sessions, substitutions with or changes to alternative treatments, and they can result in very stressful situations for both healthcare professionals and patients.

These findings are consistent with the results of the EAHP's 2019 Medicines Shortages Survey (EAHP, 2019) according to which 95% of participating hospital pharmacists reported that medicines shortages is a current problem in EU hospitals and that the types of impact medicines shortages have on patient care are: delays in care or therapy, cancellation of care, suboptimal treatment or increased length of hospital stay.

The findings are also consistent with the findings of the PGEU's Medicine Shortages Survey 2019 according to which the unavailability of medicines continues to rise in Europe and has a tremendous impact on patients and pharmacy practice (PGEU, 2019).

The manufacturing level for both local and international pharmaceutical products was listed as the level of the supply chain where shortages are most likely to occur. As stated from the participants, manufacturing is the main and most important stage of the supply chain because shortages occurring at this level are often more serious and of longer duration. These shortages may consequently lead to shortages to occur at the stage of importation to the country. However, because of the country's small size, once the product is available at national level then it's directly distributed to warehouses and pharmacies.

In addition, legislative and regulatory frameworks as well as pricing policies were listed as main causes for shortages in Cyprus.

The participating wholesalers and importers, given the small market size, stressed the need to balance aggressive pricing policies with availability concerns. Notably, the decreased level of product introductions in small markets with low prices has been well described in the literature with a number of studies showing that the smaller the market and/or with tighter pricing policy, the lower the availability of innovative drugs (Birgi, 2013). Regulatory requirements are in place to ensure safe and well-regulated markets for medicines. During a medicine shortage, when a manufacturer needs to adapt its production to changes in demand or supply, the time taken to meet these regulatory requirements and gain approval can delay the mitigation of the shortage (The Economist Intelligence Unit, 2016). Regulatory authorities worldwide have been urgently forced to implement strategies in order to prevent and mitigate drug shortages (Dill & Ahn, 2014).

The implementation of more flexible legislative and regulatory strategies to exceptionally allow, for a specified time period, importations of non-registered medicinal products or packages in different language in order to supply the market with the drug in shortage was also raised as a suggestion from the wholesalers and importers perspective.

The study also revealed that there is a lack of common perception among the different stakeholders concerning the definition of drug shortages.

In Cyprus there is no official definition established for medicines shortages. The need for the existence of such a definition is deemed necessary as the lack of such an adopted definition within a national healthcare system, as well as diversity of definitions in the same system, or incomparability and inconsistency of definitions, can negatively affect reporting, communication, and comparative analyses of the problem (Bochenek et al, 2018).

In addition, the lack of a European-wide definition for shortages as a factor for hampering a harmonised European-wide approach to managing shortages has been identified during the HMA/EMA workshop on availability of authorised medicines in 2018 (EMA, 2019). In 2019, HMA/EMA proposed the following definition for the purpose of notification and detection of shortages by MAHs: 'A shortage of a

medicinal product for human or veterinary use occurs when supply does not meet demand at a national level' (HMA/EMA 2019).

In Cyprus, the legal obligations of all local entities that manufacture or import and distribute pharmaceutical products are outlined in the provisions of the national Law of Medicines for Human Use (Quality, Supply and Price Control). The legal obligations at the pharmacy level are outlined in the national Law of Pharmacy and Poisons. These provisions set clear and strict obligations for all stakeholders in the supply chain who should ensure the uninterrupted supply and access of patients to necessary treatments within the limits of their responsibilities.

A significant finding of the study is that all pharmacists and the patient representative agreed that they do not receive sufficient information regarding current and upcoming shortages. Although there is relatively good flow of information about current and upcoming shortages between the industry, the NCA and the state's central warehouse, there seems to be lack of communication of this information to pharmacists and patients.

The pharmacists and the patient stressed the need for enhancement of collaboration and they suggested the establishment of a national drug shortages management team with supervisory and steering role so that immediate and bilateral information exists between all stakeholders.

The need for good collaboration and communication with stakeholders for good management of shortages and the need for public communication / improvement of access to information on availability issues has been also proposed by the HMA/EMA (HMA/EMA, 2019).

The development of a system that ensures transparency around medicine shortages at national level has also been proposed as an approach to prevent shortages and mitigate their impact by various bodies and researchers (Acosta et al., 2019; Medicines for Europe, 2017; Musazzi et al., 2020; The Economist Intelligence Unit, 2016).

Finally, particularly important is the finding that 64% of the participants consider that the industry has evolved in many positive ways during the last years in order to alleviate the problem, whereas no one from the participants stated that the industry has evolved in a negative way so that to contribute to the problem.

6. Conclusions

Drug shortages are a global and increasing phenomenon. Efficient and rational management of the pharmaceutical supply chain, from the manufacturer to the patient, is a fundamental pillar of any healthcare system in terms of effective access of patients to medicinal products.

The main objective of the study was to investigate and analyze the main causes for drug shortages in Cyprus and the stages of the downstream pharmaceutical

supply chain where shortages are most likely to occur. The results of the study confirm previous findings in the literature according to which drug shortages originate from multifactorial causes and they are both supply and demand related.

The findings of the study are that shortages are most likely to occur at the manufacturing and importation stage of the local pharmaceutical supply chain. Manufacturing problems seem to be the leading cause of shortages in Cyprus followed by legislative and regulatory issues, unexpected changes in demand, the small country size, pricing policies and the country's geographical location.

The results of the study suggest that with the implementation of the GHS drug shortages are occurring more often because of the unexpected change in clinical practice and demand of pharmaceuticals. However, the prevailing perception is that the overall extent of the problem in Cyprus does not differ in comparison with other small European countries.

Another significant finding of the study is that there is a lack of a common perception of the term 'drug shortages' as well as a lack of communication and coordination among the various stakeholders affected. While a good communication among the industry, the NCA and the state's central warehouse exists, there seems to be insufficient flow of this information to pharmacists and patients.

Moreover, most of the interviewees felt that during the last decade the industry has evolved in a positive way establishing a number of initiatives aiming at preventing and mitigating drug shortages. However, various constraints still remain in order to effectively tackle the problem on a national level with the small market size of the country, combined with its geographical location, to constitute the largest barriers.

A number of possible measures and approaches were suggested in order to mitigate the impact of shortages including the enhancement of collaboration via the establishment of a national coordinating body, the permission of regulatory flexibility and the provision of financial incentives.

This is the first study conducted to specifically collect data and present perceptions on causes of drug shortages in Cyprus. Its aim is to add knowledge in terms of the current situation, to identify the main obstacles and propose measures to effectively tackle the problem. It is estimated that this research will serve as a building block in the effort to compound the problem in Cyprus whose attributes are a hotbed for shortages.

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Abbreviations

EMA – European Medicines Agency

FMD - Falsified Medicines Directive

GHS – General Healthcare System

MAH – Marketing Authorisation Holder

NCA – National Competent Authority

PIL – Patient Information Leaflet

RQ – Research Question