DRUG SHORTAGES

The Dimensions of a critical problem

EXTRACT

We must emphasize that the “phenomenon” of drug shortages has a dramatic impact on the health of patients, as well as on the practice of medicine by health professionals. Indeed, Drug Shortages may lead to: (I) significant delays in the treatment, (II) in unsatisfactory treatment (III) or even in non-treatment.

Dimitris Pantazis

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Introduction

We know very well that the problem of “Drug Shortages” is not a current one. It is also well-known that drug shortages are a worldwide problem, although their manifestations vary among different countries. Based on the existing reports we can say that developed countries, like countries of Europe and North America, can be characterized mainly by shortages of drugs for cancer, arthritis, cardiovascular or hormonal diseases, as well as for diseases of the nervous system, like epilepsy. It is important also to mention that this problem started about ten years ago and became much more frequent and critical during recent years.

At this point, we should clarify that, in this article, the term “drug shortages” does not concern the shortcomings of medicines stemming from parallel trade which have an impact on specific countries (like Greece for example) which mainly are countries in which parallel trade happens. In this article, we refer to Worldwide shortages of essential medicines that concerns all countries, but vary in intensity, frequency and extend between different countries, the causes of which are not related to parallel trade.

Especially talking about Europe, we can say that the intensity and the extent of the problem have only recently come to light thanks to a survey carried out by the European Association of Hospital Pharmacists (EAHP), which was sent to 600 hospital pharmacies across 36 countries In May 2014.

According to this survey, hospital pharmacies across Europe are reporting difficulties in getting hold of a range of commonly used cancer drugs, including 5-fluorouracil, carboplatin, cisplatin, doxorubicin, etoposide, melphalan, methotrexate, oxaliplatin, and vincristine. Medicines used for pain relief, including morphine are also reported to be in short supply in some countries.

Finally, we must underline that the “phenomenon” of drug shortages has a dramatic impact on the health of patients, as well as on the practice of medicine by health professionals. Indeed, Drug Shortages may lead to (I) significant delays in the treatment, (II) in poor treatment (III) or even in non-treatment.

As noted by Esmo (leading European professional Organisation for Medical Oncology) in its letter of 9 April 2019 to the European Commission, shortages of critical anticancer drugs have a direct negative result on patients throughout Europe. But the “damage” generated by drug shortages has not only a negative impact on patients. Drug shortages also cause significant negative results in the cost of treatment at a time when all states are trying to rationalize pharmaceutical spending. To appreciate better this dimension (the cost dimension), we cite the research published by "The New England Journal of Medicine" in December 2013.

The Survey showed that “of the 214 physicians surveyed, 82.7% were unable to prescribe the preferred chemotherapy agent because of shortages at least once during the previous six months”. In the same survey is also mentioned that: “Despite the prevalence of scarcities, 69.6% of the oncologists reported that their cancer centers or practices lacked formal guidance for making decisions regarding allocation of drugs. Of the physicians who encountered shortages, 59.2% reported substituting a more expensive brand-name drug such as Xeloda (capecitabine) for cheaper generic drugs such as fluorouracil. ***This***

substitution makes one cycle of treatment for colon cancer 140 times more expensive and further adds to the increasing cost of care for patients with cancer"[1].

But also in a more recent report published on 15 January 2019 on behalf of American Hospital Association, Federation of American Hospitals and American Society of Health-System Pharmacists, among many others, the following are underlined : "Continued rising drug prices, as well as shortages for many critical medications, are disrupting patient care and straining hospitals' budgets and operations" (page 2). "The budget pressures resulting from increased drug spending can have negative impacts on patient care with hospitals being forced to delay infrastructure investments, reduce staffing, and identify alternative therapies. Hospitals also continue to struggle with pharmaceutical shortages, which increase costs by disrupting typical work patterns and patient care and often require significant staff time to address" (page 3). "***Almost 80 percent of the surveyed hospitals indicated that drug shortages resulted in increased spending to a moderate or large extent***" (page 17).

The causes of the problem

ESMO (the leading European professional organisation for medical oncology) considers that shortages of inexpensive essential medicines have complex and multifactorial causes.

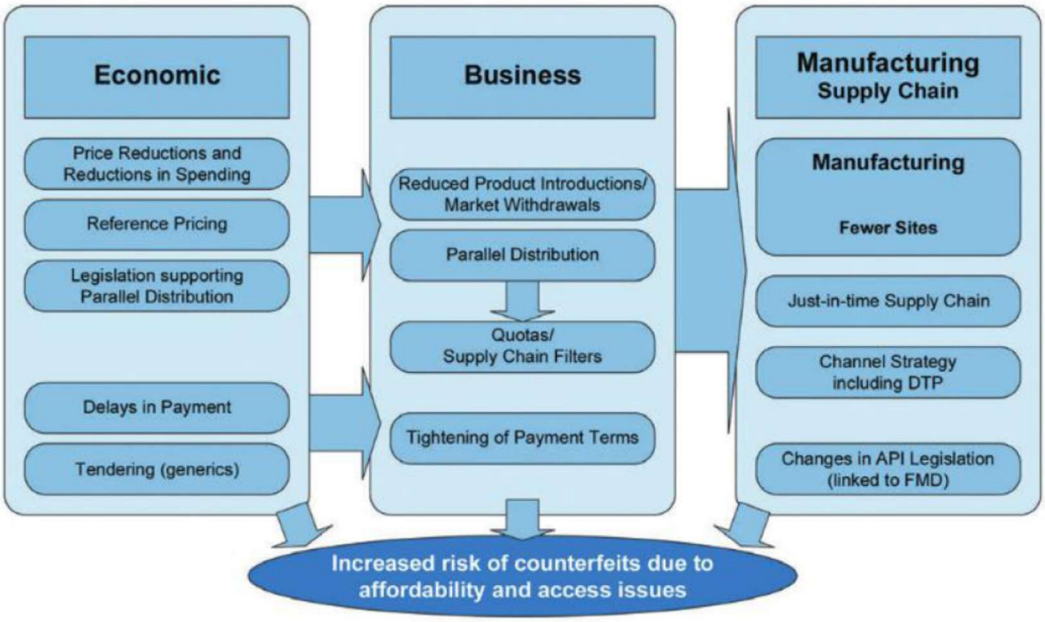
According to a study titled "Addressing Medicine Shortages in Europe," published by "The Economist Intelligence Unit Limited" in 2017, the leading causes, which are responsible for the deficiency of medicines, fall into three categories (see the Figure 1).

Figure 1: Causes of Drug Shortages

In another study published by ISPE (International Society for Pharmaceutical Engineering) in October 2014, the reason for shortages were also summarized in three main categories (see image 1 below).

[1] Survey of Oncologists about Shortages of Cancer Drugs The New England Journal of Medicine, n engl j med 369;25 December 2013 Keerthi Gogineni, M.D. Katherine L. Shuman, B.S. Ezekiel J. Emanuel, M.D., Ph.D.

Image 1: Causes of Drug Shortages



Source: ISPE - Drug Shortages Prevention Plan –October 2014

Finally, according to FDA, the underlying factors to drug shortages are multiple. According to what is stated on the website of the valid and internationally prestigious organization, in the chapter entitled "Frequently Asked Questions about Drug Shortages," "a significant reason for these shortages has been quality/manufacturing issues. However, there have been other reasons such as production delays at the manufacturer and delays companies have experienced receiving raw materials and components from suppliers. Discontinuations are another factor contributing to shortages. ***FDA can't require a firm to keep making a drug it wants to discontinue. Sometimes these older drugs are discontinued by companies in favor of newer, more profitable drugs***" [2].

Taking all these into consideration, we could conclude that, ultimately ("at the end of the day"), the leading cause of these shortages is reduced profitability. Indeed, we could safely conclude that all individual subcomponents mentioned above, contribute decisively to drug shortages, but they are not the root cause.

The operative event causes for drug shortages

As M.E. Markowski from Harvard Law School writes in an article published on "Harvard Library – office for scholarly communication", "some causes effectively impose price caps which prevent manufacturers from charging a free-market price for their products. Other causes create cost floors which stymie cost-cutting efforts by manufacturers. Whether by elevating costs or reducing prices, these contributors dampen profits, and without profits, incentives to produce evaporate"[3].

[2] LINK: https://www.fda.gov/drugs/drug-shortages/frequently-asked-questions-about-drug-shortages#q4

[3] Drug Shortages: The Problem of Inadequate Profits, M.E. Markowski, Harvard Law School, April 2012.

We must underline that the “causes” mentioned by Markowski in his article regards measures taken by governments in their effort to rebalance the pharmaceutical market. Indeed, pharmaceutical market is characterized by a high degree of complexity, and at the same time it is a strictly regulated market. Thus, ***the intensity of competition*** facing a medicinal product can change over time and not only depends on the availability of substitute ***products but is largely influenced by existing regulatory mechanisms and in particular those related to pricing and reimbursement***.

But we believe that the issue of reduced profitability, as Markowski puts it, is not as simple as it seems. On the contrary, it is much more complex and requires a better understanding of the external environment and its forces that shape the modern pharmaceutical market (PESTEL analysis). Certainly, we cannot make an in-depth analysis of the pharmaceutical market within the limited framework of this article. But we think it is worthwhile highlighting some key points that will allow us to understand better the dimensions of the problem, and also will help us understand the strategies of companies aimed at preserving and enhancing their profits, which in turn are probably linked to drug shortages.

Talking about profitability we must underline that the global pharmaceutical industry was (during the golden era – 1980s, 1990s) one of the most profitable business activities. During the 1980s the average growth rate of the pharmaceutical market was 10%, when the average rate of economic growth was around 4% [4]. Pharmaceutical companies, during the “golden age” (1980s and 1990s) grew rapidly and their profits skyrocketed. According to Fortune magazine (26 July 1993 – p. 72), the global pharmaceutical industry, in the year 1993, based on profits, was ranked first with a 19.7 billion profit, and followed by the oil refineries with 18.6 billion dollars, the Food industry with 16.5 billion dollars, the electronics and electrical equipment industry with 12 billion dollars, while in the 5th place was the beverage industry with 4.2 billion dollars. In the 10th place was the tobacco industry with 2.3 billion dollars net profits.

In order to better understand the "dynamics" of this sector, within the time period of the last 30 years, we would like to cite the following data regarding its economic performance. Thus, the six largest pharmaceutical companies in the year 2007, namely: Pfizer, Merck, Eli Lilly, Schering-Plough, Bristol-Myers Squibb, and Abbott Laboratories presented (all together) revenues exceeding ***137 billion Dollars***, while their profits amounted to ***31 billion dollars***. These companies, therefore, within a time period of 25 years presented a capital increase (market capitalization-stock value) from 25 billion dollars in 1982 to 525 billion dollars in 2006[5]. In other words, multinational pharmaceutical companies were the "goose that creates the golden eggs" that created huge profits and even higher stock market value, and it is no surprise that a bank such as J.P. Morgan Chase was so closely associated with the pharma industry.

However, in the years that followed the “Golden Age” substantial changes have occurred which significantly influenced the economic performance of these companies. Some key changes regard:

[4] Scrip Review , issue 1989, page. 7

[5] Value Line, 08 July 2007 <http://libproxy.library.unt.edu>. Yahoo Finance, 30 July 2007 <http://finance.yahoo.com>.

- Regulatory interventions by governments aiming to control prescription and limit drug expenditures. In general, we can say that the regulatory environment was getting more rigorous and pharmaceutical cost controls set by government reimbursement agencies, in many countries, have affected the direction and profitability of the pharmaceutical industry.
- Patent expiration for a number of important products and the erosion of profits by generic products. As was written in a report of pwc, "Between 2012 and 2018, generic erosion will wipe about $148 billion off pharma's revenues"[6] . In a more recent report of Evaluate Pharma it is written: "Sales at risk between 2019 and 2024 due to patent expiries - $198bn"[7] .

It is not surprising then, that the pharmaceutical industry cannot rely on its usual and old methods in order to maintain its dominant position in the market, in terms of profitability, if it (the pharmaceutical industry) does not try to take "better" advantage from any market segment of the whole pharmaceutical market. We believe it makes perfect sense for pharmaceutical companies to try to adopt a "strategy mix" (i.e., different strategies for each market segment in different countries) in order to maximize their profits.

The following are two examples, regarding the "strategy mix" adopted by big multinational companies. We cite the two cases as described on the relevant CPI website (Competition Policy International) in January 2019[8].

1st case: *UK – Pfizer / Flynn*

"In 2017, the UK's CMA[9] adopted an excessive pricing decision regarding an out-of-patent anti-epileptic drug, Epatunin, whose cost is reimbursed by the UK's National Health Service. This drug is subject to a principle of continuity of supply, which meant that patients who were stabilised on Epatunin were advised by the relevant UK health regulator to remain on this specific formulation. Up until 2012, Pfizer sold Epatunin as a branded drug under an applicable price regulation scheme. In 2012, Pfizer sold Epanutin's UK marketing authorisation (i.e. the right to sell this product) to Flynn Pharma. As a result, Pfizer became an upstream manufacturer of the drug under an exclusive supply agreement, but granted distribution rights to Flynn Pharma. Flynn Pharma then obtained approval in the UK to sell the product as a generic, rebranded it, and started marketing it under a new name. As a consequence of a regulatory gap, this meant that the rebranded generic version of Epatunin was not subject to any price regulation. Pfizer increased the price it sold the drug to Flynn Pharma, which also increased the retail price significantly – the retail price of a pack of 84 capsules of 100 mg increased from GBP 2.83 to GBP 67.50".

"The CMA concluded that Flynn and Pfizer explored a regulatory loophole (παραθυράκι) which allowed: (i) Pfizer to sell Epatunin to Flynn at prices 8 to 17 times higher than previous NHS prices; (ii) Flynn to then re-sell the drug at prices 25 to 27 times higher than previous retail prices. Applying the framework for excessive pricing developed by the EU courts, the

[6] Pwc: From vision to decision - Pharma 2020, page 6
[7] World Preview 2019, Outlook to 2024 – EvaluatePharma
[8] https://www.competitionpolicyinternational.com/excessive-pricing-in-pharmaceutical-markets/
[9] Competition and Markets Authority (CMA). CMA work to promote competition for the benefit of consumers, both within and outside the UK. Our aim is to make markets work well for consumers, businesses and the economy.

CMA found that the prices applied by Pfizer and Flynn were both excessive and unfair. On appeal, the Competition Appeal Tribunal found that the CMA did not correctly apply the legal test for excessive pricing, *inter alia* by incorrectly relying on a cost-plus approach and by failing properly to assess the possible impact of meaningful comparators when determining whether Pfizer and Flynn's prices were unfair".

2nd case: *Italy – Aspen*

"Generics company Aspen bought Cosmos drugs' trademark and marketing rights from GlaxoSmithKline. Cosmos drugs are out-of-patent cancer medicines for the treatment of specific categories of patients (namely old people and children) that are essential and non-substitutable. These drugs are reimbursed by the Italian health service and their price is subject to negotiations with the Italian regulator ('AIFA')".

"In 2013, Aspen started negotiations with AIFA and insisted that the Cosmos drugs should be categorized as non-reimbursable, which would mean the drugs would no longer be subject to price regulation. Aspen also threatened to withdraw the Cosmos drugs from the market, and deliberately caused a shortage of Cosmo drugs in the Italian market during price negotiations. This aggressive conduct by Aspen – in a situation where the Cosmos portfolio comprised lifesaving and irreplaceable drugs – led AIFA to agree to price increases of up to 1,500%. In 2016, the Italian competition authority condemned this price increase as excessive pricing, a decision since confirmed by the Italian First Grade Administrative Court".

Solutions to the problem of drug shortages

There is a range of measures proposed (at international level) to respond to Drug Shortages problem. National organizations like FDA, the 'Public Health Agency of Canada,' etc., elaborate, propose and implement various measures aiming to tackle this critical problem. These measures are in their great majority common and concern the prevention and mitigation of the effects of drug shortages on patients. Here are some examples in the table below, which concern some of the most important measures taken at a global level and aim to prevent or mitigate the problem (see table 1 below).

Table 1: *Preventive and Mitigation Solutions to Drug Shortages*

Preventative Measures	Mitigating Solutions
• **Creation and maintenance of Essential Medicines Lists (EML)** • **Study and control of the appropriate price** for generic drugs • **Forcing manufacturers to respect the "duty to supply"** clause of their licences. • **Encouraging more competition**.	• **Advance reporting** of future shortages • **Alternatives and Substitutes** • **Fast tracking approvals of substitutes** and "sole-source" products

Many developed countries implement these and other similar solutions in their effort to tackle this crucial problem.

"In the European Union (EU), most medicine shortages are dealt with at national level by the national competent authorities"[10]. "However, EMA can be involved in certain situations, for example when a medicine shortage is linked to a **safety concern** or **affects several Member States"**[3]. We must emphasize at this point that medicine shortages ***are linked to "a safety concern" and affects the majority of member states*** (especially for some important and "irreplaceable" drugs).

As in the relative website of EMA is written: "EMA and the Heads of Medicines Agencies (HMA) created an HMA/EMA Task Force on the Availability of Authorised Medicines for Human and Veterinary Use ***in December 2016*** to provide strategic support and advice to tackle disruptions in supply of human and veterinary medicines and ensure their continued availability.

Its key priorities include:

- looking at ways to minimise supply disruptions and avoid shortages by facilitating approval and marketing of medicines using the existing regulatory framework (for example by work sharing and reduced timetables when possible);
- developing strategies to improve prevention and management of shortages caused by disruptions in the supply chain (for example developing guidance for companies on reporting of shortages);
- encouraging best practices within the pharmaceutical industry to prevent shortages;
- improving sharing of information and best practices among EU regulatory authorities to better coordinate actions across the EU;
- fostering collaboration with stakeholders and enhancing communication of supply problems to EU citizens.

Of course, all these measures are indispensable and gives healthcare providers time to mobilize in each crisis, but they do not address the root causes of the problem and cannot resolve it.

Drug Shortages in Greece – the role of IFET S.A

IFET S.A. (Institute of Pharmaceutical Research and Technology) is a publicly owned company, subsidiary of the National Drug Organization (EOF). IFET S.A. imports any product if a drug shortage is established by the competent national authorities (EOF) and after a verified control of the necessity and utility of the medicine to protect and promote public health.

These medicinal products are mainly imported from other European countries and from the United States and they fall into three main categories:

- Medicines that have been approved but have been discontinued and are not available in the Greek market. Generally, these are generic and non-patent medicines.
- Medicines intended for the treatment of ultra-rare or rare diseases.

[10] Source: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/medicine-shortages

- New medicinal products which have not yet obtained state approval (license of free circulation / price). In this case IFET S.A. acts as an “early access scheme” system.

Medicinal products imported by IFET S.A. are divided into those intended for hospital cover, medicines distributed directly to patients through pharmacies (micro parcels) and, finally, products imported to cover emergency needs (emergency cover).

As we mentioned above these medicines are imported from a large number of selected and accredited suppliers from European Countries and USA (Pharmaceutical Industries and Pharmaceutical Distributors). The aim of IFET S.A. is the import of medicinal products at the lowest possible cost.

Indeed, once a drug shortage has been identified, and the competent national authorities have recognized the necessity of the medicinal product for the treatment of a particular disease, IFET SA is authorized to act accordingly for the introduction of the medicinal product concerned in Greece. In the last three years only, IFET S.A. has covered a vast number of shortages, as shown in the table below.

We believe that the "model" of IFET SA is an effective tool that can also effectively contribute to preventing and mitigating the impact of drug shortages in our country. IFET SA, in close co-operation with the EOF, can coordinate on behalf of hospitals, private clinics as well as individual patients, all the actions required, from the market research, to delivery to the corresponding healthcare provider the medicine that is considered necessary for a disease, but is not available in the Greek market***. Particularly for small countries, like Greece, the IFET "model" may be the only practical solution to mitigate the serious problems caused by drug shortages***.

Some thoughts for a permanent European Solution

The measures mentioned above can alleviate the problem, but they cannot resolve it definitively. We strongly believe that a more radical solution is necessary on the European level and such a solution could be an analog solution to that applied in the US with the creation of the “Civica.” Of course, such a solution demand for more cooperation between European countries under the surveillance of the European Commission.

Talking about Europe, we must understand that the problem of drug shortages (especial for essential drugs) cannot be resolved by any European country alone. Europe needs a coordination center that will be responsible, in close cooperation with the respective national centers, to monitor drug shortages in any country strictly. Taking into consideration that economic and market dynamics are a primary driver of this problem, the European Coordination Center must implement a package of measures such as:

1. The creation of an Essential Medicines list. Such a list can be the work of a European professional body, which must include health experts on this issue, responsible for evaluating the therapeutic value of each essential medicine on short supply. More specifically, the work of this professional body could define:
    a. Medicines for which there is no other therapeutic alternative and whose deficiency could pose a risk to public health.
    b. Medicines covering exclusively hospital needs for serious and life-threatening diseases.
2. Development of methods to anticipate the demand for the categories of medicines mentioned above, based on data such as market trends, new therapies, changes in therapeutic guidelines, new treatment regimens (at a European level).
3. The creation of a new pharmaceutical entity, similar as those to Civica. The new company must not be burdened by the same profit pressures of typical drug manufacturers.

At this point, we believe that it may be worth presenting some key points regarding this new company created in the USA at the end of 2018. The following text is based on the material taken by the website of the company.

Civica is a ***non-for-profit*** USA company and "it was founded by seven leading hospital systems concerned about generic drug shortages and three philanthropic members passionate about improving healthcare".

"Civica will focus first on providing 14 much needed medications, mostly sterile injectables such as anesthesia medications, antibiotics, and pain medications and expects to deliver these products this year. Best case scenario is that we surpass these expectations. We have enlisted the support of ***a Drug Selection Advisory Committee***, which includes health system pharmacy experts, to prioritize the medicines we make and the order in which we make them. So far, the Committee's input has reflected incredible alignment on the most urgent medication needs". "Civica ***will offer one transparent, single price to all customers***".

"***What makes Civica different from other generic drug companies is our commitment to transparency***, a one-price-for all model regardless of hospital size, and a membership structure that is open to all. We are pro-competitive and are committed to eliminating uncertainty in the generic drug supply chain, in part by entering long-term contracts with both our health system partners as well as with multiple manufacturing partners in multiple locations, allowing us to set the demand and ensure that we have dedicated manufacturing capacity for the drugs we need to deliver".

"Civica is not burdened by the same profit pressures of typical drug manufacturers. ***This will allow Civica to invest excess revenue to improve our ability to meet patient needs by supplying additional critical drug products to the market at affordable prices***, while continuing to reduce overall costs".

We don't believe that the thoughts mentioned above, about the crucial problem of drug shortages, represent an integrated proposal that can lead definitively to its solution. But we think that should be reason enough to start an in-depth dialogue among Health professionals and member states in Europe, to seek to fix solutions to this problem.

Dimitris Pantazis

CEO - IFET S.A.