

The impact of medicines shortages on pharmaceutical practice

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ABSTRACT

Access to medicines is a fundamental human right and is a vital element of health care.

Over the last 10 years, there has been a tendency for the global discontinuation of drug supply to become a major problem, with an increasing exacerbation of this phenomenon in the European Union, with a potential negative impact on patient health care due to multiple causes (manufacturing problems, drug pricing policy, parallel export etc.).

National Agency for Medicines and Medical Devices of Romania (NAMMDR) argues, in full agreement with European Medicines Agency, that in this situation effective collaboration between the various stakeholders and regulators is required, and also a good communication between manufacturers, distributors and authorities. It is a point of view that NAMMDR supported in the working meetings with the representatives of the marketing authorization holders/manufacturers, wholesale distribution, patient associations. According to pharmacists, situations have been reported in which patients tend to stock up on medicines, and this puts additional pressure on existing stocks.

In this work, we intended to draw attention to the medicine shortages issue which has a huge impact on national health systems, on patients' safety, on public health and healthcare professionals.

Keywords: drug discontinuities, impact on patient, short-term strategies, long-term strategies

The lack of insulin products on the market (after its discovery in 1922) was the first known medicines shortages. Subsequently, other drugs were reported missing from the market, thus many countries were affected by medicines shortages over time. Medicines shortages appears when the supply becomes limited or the demand increases, meaning that there is an excess demand for a period [1]. Every medicines shortages affect healthcare and pharmaceutical care, lead to adverse events for patients and also affect the cost of treatments.

According to the Food and Drug Administration (FDA), a discontinuity is a situation where the total supply of all clinically interchangeable versions of a regulated drug is inadequate to meet current or user-designed demand. The European Medicines Agency (EMA) defines the medicines discontinuities as the lack of medicines for human or veterinary use that occurs when supply does not meet national demand. The International Pharmaceutical Federation (FIP) states that discontinuities of drugs are a supply problem that needs a change, it have an impact on patient care and requires the use of alternative agents. As we can see there are

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several medicines shortages definitions vary from each other depending on some parameters and give different reporting criteria [2].

In the United States of America (USA) medicines shortages negatively impacted the quality of health care. There were reported 70 medicines with supply discontinuities in 2006, 450 medicines had supply discontinuities in 2012 and in 2020 only 129 medicines had supply discontinuities [1,3-5]. Drug shortages cost USA hospitals more than 450 million dollars. In order to solve this problem FIP conducted a series of consultations with specialists in 2013 in an attempt to stop this phenomenon. The World Health Organization (WHO) established a series of solutions and approaches in December 2015, which proved to be effective globally, not only for the USA market. As a result of the implementation of the solutions established by the WHO, a decrease in drug discontinuities was observed, which led to the reporting of only 129 drugs shortages in 2020 on the American market [5].

In terms of drug shortages in the European Union (EU), it has increased in recent years with a negative budgetary impact. In 2019 a survey performed by the European Association of Hospital Pharmacists (EAHP) among 39 countries reported that medicines shortages is a current problem for 95% of hospital pharmacists, and 81% of these pharmacists experience more than three times shortages with products from one manufacturer [6].

Most medicines shortages (Figure 1) on the European market are addressed at national level by the competent national authorities, but the European regulators work with the national regulators to prevent drug shortages [7,8].

Drugs that have been frequently reported as discontinuities are Piperacillin/ Tazobactam, Cephalosporins, Gentamicin, Amoxicillin/Clavulanic Acid, Hepatitis B Vaccine, Pneumococcal Vaccine, Tuberculosis Vaccine, Tetanus Vaccine and Hepatitis A Vaccine. In latest years, a number of alarms have been issued at European level (Table 1) regarding the limited access of patients to some essential treatments, the causes being mainly associated with the existence of growing shortages of medicines, generics or innovative [7,8].

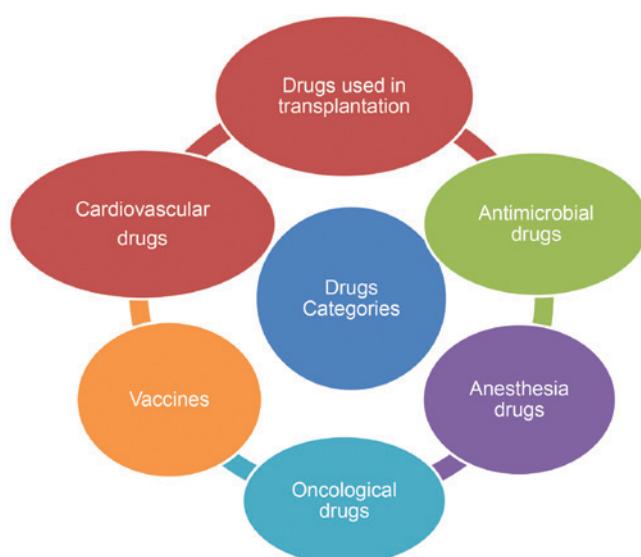


FIGURE 1. Drugs categories for which discontinuities are most commonly reported

TABLE 1. European countries that have frequently reported medicines shortages

Original (patented) medicines	Generic drugs (including brand name generics)
Belgium	Denmark
Spain	Netherlands
Austria	Portugal
Slovakia	Croatia
Bulgaria	Germany
Ireland	Hungary
Switzerland	Latvia
Italy	Turkey
Norway	Macedonia
France	Serbia
Poland	United Kingdom

CAUSES OF MEDICINES SHORTAGES

Many shortages are caused by various factors, such as natural disasters, regulatory issues, supply and demand issues etc [1]. The 2019 EAHP survey revealed that the manufacturing problems and supply chain issues were the leading factors for the medicines shortages. Many other studies identified causes of medicines shortages [5,9,10], so the main causes could be:

1. Manufacturing issues which include competing priorities (there is a lower motivation for manufacturers to produce medicines with low profitability compared with those with higher profitability);
2. Logistic issues (transportation issues and poor drug supply chain management);

3. Business problems (low profit margin, small market size, high raw material costs, production capacity constraints, low procurement ability, absence of maintenance);
4. Quality issues (leading to voluntary recall due to defects identified in the pharmaceutical forms after releasing to patients; infringements of Good Manufacturing Practice also lead to quality problems);
5. Lack of raw materials (India and China are major suppliers of active substances and excipients - any political unrest, armed conflicts, pandemics, trade disputes negatively affect the supply of raw materials);
6. Drug smuggling (which lead to implementation of drug serialization in EU);
7. Demand issues (irrational use of medicines, lack of patients' education, prescribing practices lead to a greater risk of drug shortages);
8. Regulatory issues (inflexibility in regulatory processes, lack of coherent policies, unavailability of communication between stakeholders, lack of implementation of essential drug lists);
9. Government fiscal policies (limited budgets for health, extremely high prices for patented medicines, low prices for generic medicines);
10. Lack of an advanced warning system.

For Romanian market, a worrying element for patients but also for pharmacists and doctors is the continuous process of giving up the holders of marketing authorizations to market some medicines in Romania, a process reported by the specialized institutions. Thus, according to National Agency for Medicines and Medical Devices of Romania data, 723 drugs were notified with temporary or permanent discontinuity starting with June 2016, of which 498 for commercial reasons and 185 for manufacturing reasons, none of them being discontinuous for safety reasons, respectively pharmacovigilance or parallel export. Between 2016 and 2019 a number of 129 medicines were permanently withdrawn from the Romanian market, for 83 temporarily deficient medicines the marketing was resumed in 2019. Periods of temporary discontinuity vary between 2 months and 3 years, with no information available to ensure sufficient stocks during these periods [11,12].

THE IMPACT OF MEDICINES SHORTAGES

Economic impact. Additional costs are incurred (purchase of more expensive alternative medicines; excess stockpiling; need for additional labor). There is an increase in the price of medicines, an increase in the payment made by the patient - more expensive alternative medicines, a prolonged period of therapy, prolonged hospitalization, on-line purchase. Thus, there is an economic burden on governments due to the import of medicines. For example, the economic impact in the US is over 200 million dollars for the purchase of more expensive drugs and an increase of over 350 million dollars for additional labor [5,13].

Clinical impact. It is the most important effect of medicines shortages, which was reported all over the globe. It include increased patient monitoring, suboptimal treatment using alternative medicines, treatment changes, delayed or refused treatment, transfer to other institutions, increased length of hospitalization, hospitalization due to adverse reactions/treatment failure/relapse/drug interactions, cancellation surgery due to lack of medication, and may lead to an increasing risk of mortality [14,15].

Impact on patient quality of life. The impact on quality of life aims to reduce patient satisfaction, but also to decrease the satisfaction of health professionals. Patients complain of frustration, anger, dissatisfaction, anxiety and many other psychological effects. Many studies reported a decrease adherence to treatment and loss of confidence in health professionals [16,17].

Impact on health professionals quality of life. There were observed a decrease in the satisfaction of physicians, who are dissatisfied, stressed, exasperated, threatened by patients, forced to select patients and treatments, forced to make extra efforts and consume more time [15-17]. Pharmacists also are dissatisfied, stressed, exhausted, forced to put in extra effort in managing discontinuities through extra work for the purchase of alternative medicines. Additional work to inform specialists/patients about discontinuities, to identify and access increased budgets (another provider, higher drug prices), and the lack of timely information on discontinuities prevents pharmacists from carrying out effective work [18].

STRATEGIES TO FACE MEDICINES SHORTAGES

Given that the reporting of supply discontinuities increased 3 times compared to 2014, pharmacists reported that they are affected by the lack of medicines weekly/daily / monthly/occasionally and that the average additional time needed to manage the lack of medicines is more than 5 hours/week. Thus, policies have been developed to improve access and to reduce medicines shortages by implementing several strategies to combat discontinuities, both in the short and long term (Table 2) [6,19,20].

CONCLUSIONS

Medicines shortages is a complex problem caused by multiple factors that affects all countries by reducing patient access to drugs. Drawing attention to drug shortages may encourage international regulatory authorities to work together and to collaborate in order to develop viable solutions, such as a comprehensive recovery plan.

Considering that it is impossible to predict a drug shortage, early and proper information on discontinuities and their duration are important for effective problem management. There is a need to develop and applied effective policies to build a robust supply chain and to manufacture medicines with

TABLE 2. Short-term and long-term strategies to handle drug discontinuities

Short-term strategies	Long-term strategies
Making buffer stocks	Granting credit facilities
Establishing restrictions on the use of current stock	Increasing the number of generic drug manufacturers
Reallocate available stock	Accelerating drug approval
Creating teams of experts (pharmacists, doctors, nurses) to proactively manage drugs discontinuities	Introducing legal liability for manufacturers to report future drugs discontinuities
Effective communication of pharmacists with other healthcare professionals, patients, but also with national and international regulators	Reviewing of public procurement practices
Implementing a system for reporting and tracking discontinuities, including period, drugs involved, frequency, duration, causes, impact, management strategies	Existence of a European database on advance notification system for medicines shortages, including information of duration of the disruption and available drugs alternatives

higher risk of shortages. Also, by training health professionals and by educating patients, the negative impact of drug discontinuities will be minimized.

But with all the efforts of pharmacists in order to minimize the impact on patients, solving the problem it is not just in their hands.

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