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# Periodic Drugs Shortage in Hospitals and in the Community: Causes, Consequences and Possible Solutions

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## Abstract

The aim of this article is to describe and analyze the principal aspects of a phenomenon that periodically affects medicines and medical devices all around the world in all contexts of the hospitals and the community, i.e. their shortage. Recently in Italy there has been a prolonged shortage of some medicines such as antibiotics, symptomatic remedies for fever and pain, pediatric medicines and inhalers but the phenomenon is not rare. We want to analyze some causal aspects, the principal practical consequences and also some possible strategies to remedy the problem. Technical pharmacological aspects of the individual classes of drugs mentioned will not be taken into consideration.

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## Introduction, Definitions and Approach to the Problem

The periodic shortage of drugs and medical devices has been a fairly frequent problem in all hospitals and territories for years worldwide and has recently been accentuated by the phenomenon of the SARS-CoV 2 pandemic for some classes of drugs in particular. <sup>[1]</sup>There is a lack of a standardized definition of drug shortage globally; it varies from one regulatory authority to another. Some of them define it by their level in the drug supply chain (whether low supply or increased demand), and others based on the time period or duration, for example, not giving a patient in a specific moment. Two possible reasons could contribute to the above event. First, different authorities representing various stakeholders define

drug shortages according to different criteria.<sup>[2]</sup> Second, there is a lack of high-quality scientific research on drug shortages to provide a widely accepted definition. The global standard definition is needed because the different definitions used by different countries, which define medicines shortages at different scales, make it impossible to estimate and analyze medicines shortages internationally on the demand side, have been developed by consensus and have been added some footnotes for future refinements of the definition of drug shortage.<sup>[3]</sup> On the supply side, a shortage occurs "when the supply of medicines, health products and vaccines identified as essential by the health system is considered insufficient to meet the needs of public health and patients". While on the demand side, a shortage occurs "when demand exceeds supply at any point in the supply chain and can eventually create a shortage at the point of providing adequate patient service if the cause of the shortage cannot be resolved readily to the patient's clinical needs". Typically, demand-side shortages may not be supply-side shortages, while supply-side shortages would ultimately cause a demand-side shortage.<sup>[4]</sup>

#### IMPORTANT DEFINITIONS

The "**shortage**" of a medicinal product, understood as difficulty or impossibility for the patient in finding it, is a phenomenon that can be temporary or permanent and can be determined by various problems, all attributable to the Marketing Authorization Holder, such as, for example, the 'unavailability of the active ingredient, problems related to production, regulatory measures, an unexpected increase in requests for a particular medicine, or health emergencies.<sup>[5]</sup>

By "**unavailable**" we mean a medicine for which the difficulty of finding it is not related to production problems, but to dysfunctions in the distribution chain. Unavailability, unlike shortages, generally does not occur uniformly throughout the country and is due to market distortions often linked to the dynamics of the distribution circuit. Therefore, in these cases the medicinal product, although present in the deposits of the MA holder, is not available in some regional deposits and/or pharmacies.<sup>[6]</sup>

European legislation does not contain a harmonized definition of the terms "shortage" and "unavailability" of medicines. The two phenomena actually refer to two situations of a different nature:

- shortcomings related to business problems are generally due to contingent production difficulties, but can also be related to the decision to stop marketing "dated" or low-cost drugs with limited profitability;
- the unavailability generated by market distortions can be traced back to the "parallel trade" phenomenon, which exploits the differences in the price of drugs on the various markets.<sup>[7]</sup>

In 2019, the joint EMA and HMA task force released the first harmonized definition of "shortage" for all EU countries, defined as "a shortage of a medicinal product for human and veterinary use occurs when supply does not meet national demand".<sup>[8]</sup> The overall causes of drug shortages are numerous, but can be generally grouped into supply issues, demand issues, regulatory issues, and combinations of these factors. Raw material or active pharmaceutical ingredient access may be uncertain in the global supply chain.<sup>[9]</sup> Quality issues may arise during a manufacturing run or medicine shipment. Unanticipated demand may spike due to unforeseen medical issues, such as with COVID-19. Emerging regulations may impact medicine production or efficiency in the supply chain until organizations adjust their operations. Perhaps more importantly, these underlying causes create major impacts on the participants of the supply chain.<sup>[10]</sup> These include, but are not limited to:

- Lack of visibility by manufacturers into product consumption and potential supply chain signals, which may indicate emerging supply constraints or outright drug shortages.

- Lack of early warning signals for pharmacies and hospitals about potential drug shortages, thus preventing them from taking proactive measures.
- Lack of insight for pharmacies and hospitals into the intensity and duration of current drug shortages as reported by authorities such as the FDA and ASHP, thus limiting the scale, scope, and effectiveness of mitigating actions that are taken.

Fundamental lack of getting the right information to the right people at the right time at multiple points across the supply chain to positively impact an impending supply/demand imbalance.<sup>[11]</sup>

## Main Types of Drugs and Formulations Involved

Nearly all types of drugs have been reported in shortage, including antibiotics, antiretroviral drugs, anti-protozoal, antineoplastic agents, cardiovascular medicines, analgesics.<sup>[12]</sup> Different countries or areas encounter different drugs in shortage depending upon health conditions. However, essential medicines and emergency medicines are more liable to shortage than other medicines. For example, based on the data collected by MoH, between 2013 and 2015, 677 DS notifications were received: 191 in 2013, 240 in 2014 and 246 in 2015. In the US, 117, 44 and 44 DSs were tracked in the years 2012, 2013 and 2014, respectively. The FDA helped to prevent 282 DSs in 2012, 170 shortages in 2013 and 101 shortages in 2014.<sup>[13]</sup> These shortages included sole supplier drugs for various medical conditions, including tranexamic acid tablets and injection, cefotaxim sodium injection, fluphenazine decanoate injection, metolazone tablets, ipatropium bromide respiratory solution, nitroprusside solution, clomifene citrate tablets, oral midazolam, acyclovir ophthalmic ointment, alfacalcidol drops, barium sulfate suspension for radiography, morphine injections, lidocaine injections, midazolam injections, melphalan injections, adrenalin injections, etc.<sup>[14]</sup>

Too few studies in low-middle income and low-income countries are found to depict the complete picture; only some research studies focus on the affordability/availability and shortage of some essential medicines. Almost all classes of medicines were in short supply in high-income countries.<sup>[15]</sup> Antimicrobial agents are the most affected class by drug shortage, along with oncology drugs. Benzathine Penicillin G shortage occurred in the United States (2014), and the reason reported by ASHP was a delay in manufacturing. Many oncology drugs were reported in shortage in the US, for example, Mechlorethamine, Leucovorin, Daunorubicin, PEGylated liposomal Doxorubicin etc. Cardiovascular Drugs like Labetalol and Metoprolol, Methyldopa and pindolol are found in the United States FDA drug shortage list (Administration UF, 2020). Adrenaline has repeatedly been reported in short supply by Therapeutic Goods Administration Australia, caused by commercial changes and unexpectedly increased demand-affect critical patients. Shortages of analgesics were also reported.<sup>[16]</sup> Currently, the United States FDA shortage drug list still includes Ketoprofen. Stock-out of antiretroviral drugs (ART) occurred many times in African countries. The Shortage of antimalarial drugs was seen in many low and middle-income countries and acute shortage of antimalarial drugs (Artemether /Lumefantrine was found in Kenya, Sub-Saharan Africa, and Uganda due to the delayed procurement process which led to an increased mortality rate. Shortage of Chloroquine and Sulfadoxine/Pyrimethamine was also found in the public and private sector of Pakistan, creating a gap in effective malaria control.<sup>[17]</sup>

## Causes and Principal Consequences of Drug Shortage

There are various reasons for drug shortages; overall, drug shortage causes can be classified as supply issues, demand issues, or regulatory issues. For example, manufacturing problems, financial pressures, shortage of raw materials, and just in time inventory are found as essential causes of medicines shortages in developed countries of the EU, United States, Saudi Arabia, and developing countries like Pakistan. [18] Supply issues mean manufacturers are unwilling or unable to produce enough medicines to satisfy the demand. It can be classified into manufacturing problems, unavailability of raw materials, business reasons (economic reasons like low-profit margin, low market size, cost raise of raw materials, capacity constraints), and logistic problems (supply chain issues). [19] In high-income countries, these causes have been controlled to some extent, but in the low and middle-income countries, financial burden affects manufacturing quality and capability, medicines availability, affordability, and drug supply chain quantification. Drug shortages may occur when there is a problem in the supply of raw materials. It could be a shortage of active pharmaceutical ingredients (API), excipients, or packaging materials. India and China are the important active pharmaceutical ingredient suppliers for almost all economic levels. Unavailability of raw materials could be due to political turmoil, armed conflicts, animal disease, trade disputes, environmental conditions, degradation during transport, or low plant yield as a source of material from the source country. Other causes are business issues, logistics and demands. [20] The impact of drug shortage is very high because the drug shortage affects all stakeholders, especially patients/consumers, in economic, clinical, or humanistic aspects. Drug shortages usually result in an extra cost or budget for different stakeholders, especially patients, at all economic levels. In high-income countries, the stakeholders are aware of drug shortages, and the suppliers have to manage unavailability of raw materials through additional operations. [21] The retailers have to purchase many short-supplied drugs with increased prices or purchase expensive alternative brands, start compounding or logistic modifications. The hospitals have to put extra costs to manage the shortage, such as purchasing costly brands, excess inventories, and awareness programs to deliver staff knowledge. On the other side, medicine prices increase after a drug shortage, especially for lower-priced generics, medicines with a solo manufacturer, unapproved medicines, and orphan drugs. An increase in medicine price is also an illegal practice in the gray market that stocks up a large share of medicine in advance and provides them at a higher price to customers in short supply. [22] The out-of-the-pocket cost of patients increased as they have to purchase costly brands, expensive alternatives, costly compounded medicines, pay more for a prolonged duration of therapy, extended hospital stay, and compromised treatment. Drug shortages also lead to online purchasing from illegitimate vendors that are difficult to differentiate for the consumers. In addition, such purchasing increased the financial burden for patients as they are available at increased prices than in pharmacies. Clinical outcomes of drug shortage have been reported in the majority of studies in developed countries. It included alterations in treatment, inferior treatment, prescription inaccuracies, dispensing errors, administration errors, delayed or denied treatment, prolonged hospitalization, adverse drug interactions. [23]

### DRUGS SHORTAGE IN ITALY: THE ROLE OF AIFA

AIFA, the Italian drug agency, is the regulatory body in charge of supervising and regulating all activities relating to medicines including production, supervision, distribution and methods of access for patients. On its website there is a web page (<https://www.aifa.gov.it/farmaci-carenti>) which is periodically updated where it constantly monitors, through specific procedures, the temporary unavailability of medicines on the national market, in particular those indispensable for treatment of certain diseases.<sup>[24]</sup> AIFA constantly updates and publishes a list of temporarily deficient drugs on this page of the institutional portal, which contains the following information:

- commercial name of the missing drug, active ingredient, pharmaceutical form, packaging and name of the company that holds the MA;
- start date and presumed end date of the shortage;
- existence or otherwise of equivalents;
- reasons that led to the shortage;
- suggestions and/or measures adopted by AIFA;
- possible notes.

The list is fed by the information submitted by the marketing authorization holders and on the basis of the reports received and verified by the Office. In addition, an extract from the list is published with the temporarily lacking drugs for which AIFA issues the authorization to import to healthcare facilities for analogues authorized abroad or has issued the Import Determination to the MA holder. The Agency also publishes the list of decisions with which the companies holding the MA of the deficient drugs have been authorized to import similar drugs from abroad. Finally, AIFA publishes the list of medicines that cannot be removed from distribution and sale, in order to guarantee a sufficient supply of medicines to meet the treatment needs throughout the national territory.<sup>[25]</sup>

## Strategies for Mitigate the Problem

There are several strategies proposed to manage the problem of shortages; we will limit ourselves to reporting some of them, the most realistically feasible in all hospital and territorial contexts. In hospitals, the health care team uses following strategies managing drug shortages:

- informing prescribers and recommending them alternative agents,
- contacting other suppliers for the short medicine,
- investigating supply restoration and planning,
- substituting the prescribed medication and
- updating the formulary.

However, in the community pharmacies, community pharmacists and working staff use to manage the drug shortages by adopting strategies:

1. management of current shortages,
2. contacting the authorized supplier,
3. contacting other pharmacies, and
4. suggesting an alternative treatment to the patient.

When there is a limited supply of some medicines in a medical institution and no supplies for an unknown period, the institution should limit the supply to specific patients. priority should be given to patients on reparative therapy, pediatric patients, cancer patients with no available alternatives, patients in clinical trials, and patients on treatment regimens with genuine survival benefits. Products with minor defects such as particulates, vital substances, can be used after proper handling in the event of a shortage.<sup>[26]</sup> The US FDA adopted the strategy and allowed the use of medicines with

inadequate packaging, labeling defects, glass particles in an injectable (filter before use), and unregistered medicines after risk assessment or proper manipulation to overcome the shortage. When a shortage occurs, drugs with close expiration dates can be used by extending the printed expiration date.<sup>[27]</sup> In a drug shortage situation, the manufacturer is responsible for distributing the currently available supply consistently among different areas or different institutions. Good communication and transparency among stakeholders with an adequate reporting system are necessary to achieve an efficient and fair redistribution of the available amount of deficient medicines. It is important to make good use of drugs, especially those in widespread use such as antibiotics, analgesics, applying the principles of appropriateness of use and de-escalation as soon as possible, limiting long-term prescriptions for drugs such as benzodiazepines, psychotropic drugs, opioids etc... The use of generics should be increased and the pharmaceutical companies themselves should increase their production, both to reduce the marketing price and to increase the availability of the same product on the pharmaceutical market. Another interesting aspect concerns the diffusion of the practice of galenics in pharmacies, still little practiced in Italy today, which would make it possible to produce pharmaceutical forms even in the event of a shortage of the corresponding medicinal specialties for formulations such as all oral ones, many injectables, eye drops, topical skin preparations, etc. As regards hospital medicines, certainly measures such as the introduction of prescription monitoring registers, the limitation in terms of reimbursement and access to certain drugs, especially high-cost ones, and the implementation of joint tables among pharmacists, clinicians and representatives of pharmaceutical companies it is one of the best strategies both for early monitoring of shortages and for preventing them, guaranteeing access for the most needy patients to high-cost drugs and monitoring prescribing appropriateness and limiting abuses and waste.<sup>[28]</sup>

## Declarations

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## References

1. <sup>^</sup>Shukar S, Zahoor F, Hayat K, Saeed A, Gillani AH, Omer S, Hu S, Babar ZU, Fang Y, Yang C. *Drug Shortage: Causes, Impact, and Mitigation Strategies. Front Pharmacol. 2021 Jul 9;12:693426. doi: 10.3389/fphar.2021.693426. PMID: 34305603; PMCID: PMC8299364.*
2. <sup>^</sup>Shuman A, Unguru Y. *Drug Shortages: The View Across an Ocean. Oncologist. 2020 Apr;25(4):274-276. doi: 10.1634/theoncologist.2019-1010. Epub 2020 Feb 6. PMID: 32027068; PMCID: PMC7160395.*
3. <sup>^</sup>Clark SL, Levasseur-Franklin K, Pajoumand M, Barra M, Armahizer M, Patel DV, Wyatt Chester K, Tully AP. *Collaborative Management Strategies for Drug Shortages in Neurocritical Care. Neurocrit Care. 2020 Feb;32(1):226-237. doi: 10.1007/s12028-019-00730-7. PMID: 31077080; PMCID: PMC7222107.*

4. <sup>^</sup> Poulsen JH, Dieckmann P, Clemmensen MH, Nørgaard LS. Drug shortages in hospitals: Actors' perspectives. *Res Social Adm Pharm.* 2022 Apr;18(4):2615-2624. doi: 10.1016/j.sapharm.2021.05.001. Epub 2021 May 13. PMID: 34020898.
5. <sup>^</sup> Traynor K. Drug shortages worsening, pharmacists say. *Am J Health Syst Pharm.* 2022 May 6;79(10):713-714. doi: 10.1093/ajhp/zxac090. PMID: 35411372.
6. <sup>^</sup> Rinaldi F, de Denus S, Nguyen A, Nattel S, Bussièrès JF. Drug Shortages: Patients and Health Care Providers Are All Drawing the Short Straw. *Can J Cardiol.* 2017 Feb;33(2):283-286. doi: 10.1016/j.cjca.2016.08.010. Epub 2016 Aug 17. Erratum in: *Can J Cardiol.* 2017 Jun;33(6):829. PMID: 27923583.
7. <sup>^</sup> Lipworth W, Kerridge I. Why drug shortages are an ethical issue. *Australas Med J.* 2013 Nov 30;6(11):556-9. doi: 10.4066/AMJ.2013.1869. PMID: 24348871; PMCID: PMC3858608.
8. <sup>^</sup> Decamp M, Joffe S, Fernandez CV, Faden RR, Unguru Y; Working Group on Chemotherapy Drug Shortages in Pediatric Oncology. Chemotherapy drug shortages in pediatric oncology: a consensus statement. *Pediatrics.* 2014 Mar;133(3):e716-24. doi: 10.1542/peds.2013-2946. Epub 2014 Feb 2. PMID: 24488741; PMCID: PMC3934344.
9. <sup>^</sup> Fox ER, Sweet BV, Jensen V. Drug shortages: a complex health care crisis. *Mayo Clin Proc.* 2014 Mar;89(3):361-73. doi: 10.1016/j.mayocp.2013.11.014. PMID: 24582195.
10. <sup>^</sup> Mazer-Amirshahi M, Pourmand A, Singer S, Pines JM, van den Anker J. Critical drug shortages: implications for emergency medicine. *Acad Emerg Med.* 2014 Jun;21(6):704-11. doi: 10.1111/acem.12389. PMID: 25039558.
11. <sup>^</sup> Wiggins BS, Nappi J, Fortier CR, Taber DJ. Cardiovascular Drug Shortages: Predominant Etiologies, Clinical Implications, and Management Strategies. *Ann Pharmacother.* 2014 Sep;48(9):1177-1186. doi: 10.1177/1060028014539142. Epub 2014 Jun 10. PMID: 24915735.
12. <sup>^</sup> Mazer-Amirshahi M, Fox ER, Nelson LS, Smith SW, Stolbach AI. ACMT Position Statement on Prescription Drug Shortages. *J Med Toxicol.* 2020 Jul;16(3):349-351. doi: 10.1007/s13181-020-00775-7. Epub 2020 Apr 15. PMID: 32297150; PMCID: PMC7320088.
13. <sup>^</sup> Sabogal De La Pava ML, Tucker EL. Drug shortages in low- and middle-income countries: Colombia as a case study. *J Pharm Policy Pract.* 2022 Jun 13;15(1):42. doi: 10.1186/s40545-022-00439-7. PMID: 35698240; PMCID: PMC9189796.
14. <sup>^</sup> Drug shortages are likely to continue. *Gastroenterol Nurs.* 2012 May-Jun;35(3):231-2. doi: 10.1097/SGA.0b013e3182562de3. PMID: 22647805.
15. <sup>^</sup> Dill S, Ahn J. Drug shortages in developed countries--reasons, therapeutic consequences, and handling. *Eur J Clin Pharmacol.* 2014 Dec;70(12):1405-12. doi: 10.1007/s00228-014-1747-1. Epub 2014 Sep 18. PMID: 25228250.
16. <sup>^</sup> Oncology Drug Shortages Persist. *Cancer Discov.* 2020 Jan;10(1):6. doi: 10.1158/2159-8290.CD-NB2019-134. Epub 2019 Nov 20. PMID: 31748199.
17. <sup>^</sup> Nystrom EM, Bergquist WJ, Wieruszewski PM, McMahon MM, Barreto EF. Parenteral Nutrition Drug Shortages: A Single-Center Experience With Rapid Process Change. *JPEN J Parenter Enteral Nutr.* 2019 Jul;43(5):583-590. doi: 10.1002/jpen.1538. Epub 2019 Apr 8. PMID: 31531869.
18. <sup>^</sup> Donnelly KA, Zocchi MS, Katy TA, Fox ER, Pines JM, van den Anker JN, Mazer-Amirshahi ME. Prescription Drug Shortages: Pediatric Emergency and Critical Care Medications. *Pediatr Emerg Care.* 2021 Nov 1;37(11):e726-e731.



doi: 10.1097/PEC.0000000000001773. PMID: 30829846.

19. <sup>^</sup>Hvisdas C, Lordan A, Pizzi LT, Thoma BN. *US Propofol Drug Shortages: A Review of the Problem and Stakeholder Analysis*. *Am Health Drug Benefits*. 2013 May;6(4):171-5. PMID: 24991355; PMCID: PMC4031712.
20. <sup>^</sup>Wilson D. *Deepening drug shortages*. *Health Aff (Millwood)*. 2012 Feb;31(2):263-6. doi: 10.1377/hlthaff.2012.0030. PMID: 22323154.
21. <sup>^</sup>Cameron EE, Bushell MA. *Analysis of drug shortages across two countries during pre-pandemic and pandemic times*. *Res Social Adm Pharm*. 2021 Sep;17(9):1570-1573. doi: 10.1016/j.sapharm.2020.12.001. Epub 2020 Dec 11. PMID: 33323334.
22. <sup>^</sup>Li E, Subramanian J, Anderson S, Thomas D, McKinley J, Jacobs IA. *Development of biosimilars in an era of oncologic drug shortages*. *Drug Des Devel Ther*. 2015 Jun 24;9:3247-55. doi: 10.2147/DDDT.S75219. PMID: 26150698; PMCID: PMC4484646.
23. <sup>^</sup>Calleja K. *Drug Shortages and Group Purchasing Organizations*. *JAMA*. 2020 Aug 25;324(8):808-809. doi: 10.1001/jama.2020.9055. PMID: 32840589.
24. <sup>^</sup>Stolar MH. *Drug shortages*. *Science*. 1976 Apr 9;192(4235):94. doi: 10.1126/science.192.4235.94. PMID: 17792425.
25. <sup>^</sup>Why drug shortages occur. *Drug Ther Bull*. 2015 Mar;53(3):33-6. doi: 10.1136/dtb.2015.3.0316. PMID: 25765598.
26. <sup>^</sup>Biedermann F. *New Dutch regulations to alleviate drug shortages*. *Lancet*. 2022 Jul 30;400(10349):349-350. doi: 10.1016/S0140-6736(22)01421-0. PMID: 35908565.
27. <sup>^</sup>Drug Shortages Lead to Rationing, Treatment Delay. *Am J Nurs*. 2020 Apr;120(4):14-15. doi: 10.1097/01.NAJ.0000659952.01971.15. PMID: 32218027.
28. <sup>^</sup>Pall R, Gauthier Y, Auer S, Mowaswes W. *Predicting drug shortages using pharmacy data and machine learning*. *Health Care Manag Sci*. 2023 Mar 13:1–17. doi: 10.1007/s10729-022-09627-y. Epub ahead of print. PMID: 36913071; PMCID: PMC10009839.