Shortages of essential cancer medicines: Who is responsible and what are possible solutions?

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Article type: Essay

Word Count: 1765

Funding: No funding.

Conflicts: None.

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Widespread shortages of essential cancer medications are increasing in the United States.[1] Currently, the U.S. Food and Drug Administration (FDA) reports cancer drug shortages are the worst in three decades. Generic medicines are particularly impacted which has resulted in a scarcity of numerous highly effective chemotherapies recommended by the National Comprehensive Cancer Network (NCCN) in the management of over a dozen cancers, such as cisplatin, carboplatin, dacarbazine, and methotrexate. Of the 40 cancer medicines currently included in the US FDA Shortages Database, nearly all are listed in NCCN guidance as category 1 or 2A treatments **(Figure 1)**, denoting a high level of supporting evidence for their efficacy and panel consensus of their essential value. Indeed, over half are listed on the WHO Model List of Essential Medicines. This situation has forced clinicians to modify or withhold cancer treatment to ration medicines with more than 100,000 patients impacted, and more patients likely to be affected if no action steps will be taken.

Drug shortages are a challenge worldwide. According to the Organisation for Economic Co-operation and Development, between 2017 and 2019, shortages of medicines across several therapeutic areas increased by 60% through Europe, Canada, and the U.S.[2] Shortages can harm patients, result in higher drug costs, and add substantial economic strain on health care systems. The generic supply chain is complex and multifaceted and varies between countries. Briefly, the clinical supply chain often begins with several (often overseas) companies that produce the active pharmaceutical ingredients (APIs), manufacture, and package the final product, for the generic sponsor or brand owner. Regulatory bodies approve the drug application and hospitals procure the medicines for patients that receive the medicines through prescriptions from their health care provider **(Figure 2)**. There several factors related to each step along the complex interaction between manufacturing, regulatory, purchasing, and reimbursement bodies that can increase the likelihood an severity of shortages. However, there are key dynamics in the US that exacerbate cancer drug shortages compared to other countries in Europe. Given that generic medicines account for over 90% of U.S. prescriptions[3], drastic steps must be taken to increase the security of these medicines. Who is responsible and what are possible solutions?

While shortages also occur to brand name medicines, generic sterile injectables, including many essential chemotherapies, are disproportionately impacted, often due to quality issues.[4] Indeed, it is widely reported that the current cisplatin shortage can be traced to quality control failures from one manufacturer in India which supplied over 50% of the cisplatin to the U.S.[5] Sterile injectables

only comprise of a third of the entire generic market, yet represent 57% of all drug shortages in the U.S.[6] In Europe, where prices are comparatively higher, the proportion of generic sterile injectable shortages is much lower, ranging from 17 to 31% across countries.[6] Furthermore, cytotoxic medicines are more costly to manufacture given their hazardous nature and requirement for specialized facilities. For this reason, cancer medicines are among the most impacted therapeutic classes by shortages. The current US market is so concentrated that prices are pushed unsustainably low which disincentivizes manufacturers from investing in robust quality management systems that include contingency plans for supply interruptions. One optimistic prospect is the current development of a rating system by the FDA to evaluate the robustness of manufacturing facilities —the quality management maturity (QMM) program.[7] This would provide greater transparency into current standards and, most importantly, financially incentivize manufacturers towards quality production rather than solely low prices.

Healthcare professionals and patients are most impacted by cancer medicine shortages.[8] In a survey conducted by the NCCN, 20% of oncologists reported the need to reduce doses of carboplatin and cisplatin or switch patients to alternative regimens due to the current shortages.[9] Given the severity of the current cisplatin and carboplatin shortage, much of the focus has been on these drugs. However, there are other shortages of high-value chemotherapy drugs that will disproportionally affect some malignancies more than others. Examples are patients with classical Hodgkin's lymphoma which are impacted by shortages of dacarbazine and the discontinuation of several presentations of bleomycin — two components of ABVD, a commonly used frontline regimen at NCCN member institutions. A similar situation is observed in the management of gestational trophoblastic disease, a highly curative cancer, with methotrexate shortages. Four manufacturers of this important cancer drug are reporting shortages due to increased demand, meaning that its usage is being restricted to high-risk disease or patients unresponsive to dactinomycin. This is likely compounded by increased use due to shortages of cisplatin given methotrexate shortages were reported a month after cisplatin. Providers are being forced into making difficult decisions to substitute medicines where appropriate based on efficacy, safety, and availability. This is recognised by professional associations, such as the NCCN, American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO), who have produced new clinical guidance to help and advice oncologists to manage shortages and provide essential monitoring of this situation. Clinical guidance ought to be timely with multiple alternatives updated in real time given the interconnected relationship whereby shortages of one generic chemotherapy results in shortages of

others due to replacement use. Furthermore, ethical frameworks could be developed to aid clinical treatment decisions and minimise the impact of cancer drug shortages, such as those developed in pediatric oncology.[10]

Countries worldwide increasingly dependent on the relatively few pharmaceutical companies that market generic drugs and manufacture raw materials. More than 60% of the APIs worldwide are sourced from a handful of manufacturers within Asia, predominantly from India and China.[3] Currently, the FDA has information about the finished product and APIs but not about the quantities the manufacturers can produce, nor which suppliers provided the raw materials which complicates monitoring efforts. Since the COVID-19 pandemic exposed many vulnerabilities of overseas dependence for manufacturing medical supplies, there has been legislative incentives to increase onshore manufacturing capacity, such as President Biden's American Jobs Plan which included proposals to strengthen supply chains, onshore APIs and promote innovation, among other plans.[11] One notable example to attempt to re-shore generic production is Civica Rx, an American-based, non-profit generic manufacturer founded in 2018 by seven health systems and three philanthropies to address drug shortages.[12] Furthermore, the Senate Committee on Health, Education, Labor, and Pensions has proposed measures to map the pharmaceutical supply chain through disclosure about the source of APIs, risk management plans, manufacturing volumes and improved notification of supply interruptions to federal agencies. However, these measures have not yet been adopted. Additional transparency into the supply chain or re-shoring pharmaceutical manufacturing would be central to identifying vulnerabilities and preventing future shortages. Lastly, the US, among other countries, could focus on a list of essential cancer medicines to increase the feasibility of reforms, such as medicines included on the "The Medicare High-Value Drug List" or the WHO Model List of Essential Medicines.

Procurement practices exacerbate cancer drug shortages in the US. Cancer medicines are subject to highly competitive procurement practices by a handful of large health care intermediaries, such as group purchase organizations (GPOs). According to an estimation from the Healthcare Supply Chain Association, 98% of US hospitals use at least one GPO.[13] These organisations negotiate contracts on behalf of a group or consortium of health care facilities, such as hospitals, to leverage purchasing volume that facilitate discounts with manufacturers by economies of scale.[13] However, the market is heavily concentrated — four large organisations account for >90 percent of the market for medical supplies. This extent of purchasing power is unique to the US and drives prices even lower, resulting

in small profit margins which disincentivizes pharmaceutical manufacturers from entering and remaining within the market. An example of this is the recent announcement by Teva Pharmaceuticals to consolidate their portfolio on 'high-value generics',[14] which may explain why nearly half of the cancer drugs included in the FDA drug shortages database are discontinuations from this company. Furthermore, GPOs are except from the Anti-Kickback Statute as part of the safe harbor exemption which allows these organisations to increase their profits through various strategies, such as charging manufacturers fees to be included in vender catalogues or to become the sole supplier.[15] Taken together, one large region may be dependent on the supply from one manufacturer therefore increasing the risk for shortages. When quality issues arise, the market is slow to respond given limited alternatives. Currently, policy makers do not have transparency into these agreements, and it is therefore difficult to assess their impact on the market. In addition to other previously discussed solutions that address systemic issues, policy makers could repeal the safe harbour exemptions to promote fair market competition.

Effective solutions to cancer medicine shortages must be implemented nationally due to the structure of the pharmaceutical industry and international trade rules. However, given that over half of the cancer drugs in the current shortage database are listed on the WHO Model List of Essential Medicines, international organisations, such as the WHO, could re-invest resources to convene countries to develop strategies to manage and prevent shortages. WHO has begun this work in response to the World Health Assembly (WHA) resolution WHA69.25 "Addressing the Global Shortage of Medicines and Vaccines"[16], which requested the development a technical definition, identification of root causes, and monitoring mechanisms for essential medicines frequently at risk for shortages. One report published after the WHA found over 56 definitions of shortages and stockouts across countries[17], highlighting substantial variation between countries which increases the difficulty for global monitoring. However, developing a common definition could be a low risk, high yield intervention to improve country alignment. Indeed, key steps outlined in ESMO's Call to Action was the development of a common definition between European countries.[18,19] ASCO could join these efforts to harmonise efforts between Europe and the US. Furthermore, WHO could fast track approvals of new generic medicines though the WHO Prequalification Program — a program that invites manufacturers to supply certain priority medicines and prequalifies them based quality in as little as three months. WHO has programmes for essential antimicrobials, such as the Global Antibiotics Research & Development Partnership, that monitor clinical study pipelines, and convene countries, academics, public and private sectors

to facilitate multi-sectoral solutions for priority diseases. These initiatives could serve as inspiration for generic oncology medicines which suffer the same fate in pharmaceutical market.

The problem of excessive prices has been at the center of the deliberations on access to cancer medicines, especially in the US. However, recurrent shortages demonstrate how patients are also deprived of lifesaving, inexpensive generic cancer medicines too. Effective solutions will require a diversity of global stakeholders to take preventative measures to ensure sustainable access to essential cancer medicines for patients.

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