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Evaluating Oncology Drug Shortages: Strengthening Active Pharmaceutical Ingredient Supply Chain Vulnerabilities in the United States

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: This study seeks to identify the root causes of these shortages and evaluate the fragilities within the oncology supply chain that obstruct efforts to enhance drug availability. The United States is experiencing significant drug shortages that critically impact patient care, especially for oncology patients.
Study Design: We utilized publicly accessible cross-sectional data on drug shortages documented by the US Food and Drug Administration between 2023 and 2024.
Methodology: Descriptive statistics and bivariate correlational analysis were employed to examine drug availability and its associations across multiple influencing factors. These variables are the rationale behind shortages, current status, updates, and therapeutic classifications.

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Results: The most common reason for drug shortages is increased demand (12.1%), followed by a shortage of an active ingredient. While the proportion of drugs impacted by shortages is higher in non-oncology therapies, the estimated proportion of shortage remains significant in oncology medication (9.2%, $p<0.001$)
The descriptive statistics indicate that complying with Good Manufacturing Practices (GMP) led to 92.3% of cases being unavailable. The shortage of an API contributed to 54.4% limited availability/supply and 39.2% unavailability. The oncology drugs are less likely to be with reported shortage causes. However, there is a moderate correlation to unresolved statuses($r = 0.358$, $p<0.001$), as seen in the bivariate correlation.
Conclusion: The persistent unavailability and limited supply of certain drug products underscore the systemic inefficiencies in the supply chain that necessitate targeted interventions. While oncology drugs comprise a smaller fraction of the overall drug shortages, their availability is crucial for promoting pharmaceutical care in cancer therapies. Shortage of active pharmaceutical ingredients and non-adherence to Good Manufacturing Practices significantly exacerbate the issue of drug unavailability. These demonstrated supply chain challenges persist, specifically for oncology therapies. Domesticated API productions and advanced technologies for routine inspection are potential strategies for overcoming the unavailability of oncology therapies.

Keywords: Drug shortage; supply chain; pharmaceutical active ingredients; availability information; oncology therapies.

1. INTRODUCTION

In 2023, drug shortages in the United States (US) have reached an alarming point with remarkable effects on patient care and therapeutic outcomes, particularly among patients diagnosed with cancer (Plackett 2023, Tucker et al. 2020). The recent shortages of essential drugs may underscore vulnerabilities in the logistic supply of active pharmaceutical ingredients, necessitating strategic interventions to promote the consistent availability of different categories of therapeutic medications (Nelson & Faquin2024). According to the US Food and Drug Administration (FDA), a drug shortage occurs when the total supply of drugs is less than the current demand for commercially available drug products nationally. Reasons attributed to the shortage vary from manufacturing disruptions, competitive market landscape, issues with quality control, and delays in regulatory affairs to discontinuations (US Food and Drug Administration 2024, McBride et al., 2022, Socal et al. 2023)

Drug shortages, amongst other factors like regulatory processes and off-label usage practices, influence the availability of oncology and non-oncology therapies in the US healthcare market (Shah 2023, Sharma et al. 2022). For instance, approximately 63% of oncology drugs evaluated in recent trials were available as off-protocol therapy at trial initiation (Green et al. 2016). Additionally, the oncology market was projected to exceed $32 billion by 2005, driven by high demand exceeding the bioactive ingredient supply for almost a decade (Booth et al. 2023). The high demand indicates that drug shortages may be related to an economic issue that affected other European countries, such as Belgium and France, about a decade ago (Bogaert et al. 2015). Furthermore, the limited approval of oncology drugs has created challenges in bringing new therapies to market (Booth et al. 2003).

However, increasing localized production of active pharmaceutical ingredients (APIs) in the US significantly benefits the pharmaceutical supply chain and overall patient care. The positive outcomes of enhancing local manufacturing of these therapeutic compounds are eliminating the dependency on suppliers overseas, fostering advanced technologies for precision medicine, and stimulating local economies coupled with job creation (Miller et al. 2022, Mitchell,2024, Adak 2024). The overall consequences involve mitigating the risk of drug logistics interruption (Adak 2024). Enhancing healthcare and ensuring an uninterrupted supply of bioactive compounds for disease eradication to strengthen national drug logistics systems (Aronson et al. 2023).

Despite the FDA's efforts to mitigate supply disruptions, drug shortages remain a significant drawback in the US healthcare system. Disparities in availability across oncology and non-oncology therapeutics highlight a need for more resolution to systemic issues (Adak 2024,

Nelson& Faquin 2024). The FDA actively oversees the dynamics of drug shortages and regularly disseminates updates regarding market conditions, particularly the capacity of domestic manufacturers to fulfill demand (US Food and Drug Administration 2024). However, gaps persist due to the limited availability of API from production within the US. This inconsistency in supply reinforces a critical research gap in interpreting the factors contributing to these shortages and the effectiveness of current mitigation strategies. The primary issue is the lack of targeted approaches to address therapeutic-specific shortages, such as those anticancer medications, resulting in unequal access to safe and effective medications. This study seeks to analyze the root causes of drug shortages, focusing on the vulnerabilities within the supply chain that diminish the effectiveness of current interventions to enhance drug availability. The mainstay of this study would inform the development of more robust and equitable strategies to address the ongoing problem of the drug supply chain system.

2. METHODOLOGY

2.1 Data Description

The publicly available cross-sectional data were obtained from all drug shortages recorded between 2023 and 2024 and were extracted from the US Food and Drug Administration (FDA) drug shortage list (https://dps.fda.gov/drugshortages). This study did not involve direct human subjects' investigation; therefore, approval from the institutional review board (IRB) was not required.

2.2 Dependent and Independent Variables

The dependent variable utilized in this analysis is the availability of information regarding drug shortages. Categories of information available about drugs include available or estimated availability, limited availability, limited supply, unavailable, discontinued, and others (out of stock, pending approval). The different levels of independent variables utilized in this study include reasons for drug shortage (delayed shipping, demand increase for the drug, discontinuation of the manufactured drugs, regulatory delay, requirements related to complying with GMP, and shortage of an active ingredient), Type of update on drug shortage (new, reverified, and revised), status of shortage(resolved and unresolved), therapeutic categories (Oncology and non-oncology therapeutics)

2.3 Statistical Analysis

The descriptive statistics in this study explore the distribution pattern of the variables expressed in percentages and cross-tabulation to explore the relationship between independent and dependent variables. The frequency distribution of variables examines the number of occurrences of the levels of factors used to assess drug shortages. The cross-tabulation was used to investigate drug availability information outcomes across different levels of factors used to evaluate drug shortages. Chi-square tests were performed to determine differences in the characteristics of the dependent variables across each category of independent variables. A 2-tailed t-test and $\chi 2$ tests were implemented using IBM SPSS, version 29, and the significance level was set at 2-sided $P < .05$.

The bivariate correlational analysis examines the relationship between different levels of drug availability information and various reasons for drug shortages, the status of drug shortages, updates on drug shortages, and therapeutic categories.

3. RESULTS AND DISCUSSION

Table 1 displays the pattern of drug shortages, indicating that a combined 26.8% of drugs are either unavailable or have limited availability. Specifically, 12.6% of drugs are reported as having limited availability, while 14.2% are entirely unavailable. The primary reason for drug shortages is the increased demand for the drug, which accounts for 12.1%. This high demand is followed by a scarcity of APIs. More than half (54.2%) of the updates regarding drug shortages are in the re-verification stage. Additionally, about 30% of these shortages are undergoing revision, indicating ongoing changes to the information on drug availability due to supply disruptions or shortages. Almost all of the ongoing shortages—about 93.6%—are unresolved, while just a small portion, only 6.4%, have been resolved. Among the drugs impacted by shortages, 90.8% are non-oncology therapies, and only 9.2% are oncology therapies.

The descriptive analysis summarizing the drug availability information and other variables of drug shortages from Table 2 underscores the critical role of demand surges as the leading cause of shortages. Manufacturing and supply chain issues also contribute to significant unavailability. For instance, requirements related to complying with Good Manufacturing Practices

(GMP) led to 92.3% of cases being unavailable. A shortage of an API contributed to 54.4% limited availability/supply and 39.2% unavailability. Delays in drug shipping accounted for 45.8% of cases with limited availability/supply, and 50.8% of cases were classified as unavailable. Updates on reverified drugs: 71.2% were reported as available, 11.4% had limited availability, and 16.1% were unavailable.

The unresolved status of shortages accounted for 63.6% of available drugs and was disproportionately represented in cases with limited availability (16.5%) and unavailability (18.7%). Notably, no resolved shortages were reported across all availability categories, highlighting the persistent challenges in addressing shortages. Therapeutic non-oncology agents have more issues with availability, with about 13.1% being only limited availability and 14.9% not available at all. Conversely, the availability of oncology therapies is relatively high, with approximately 7.4% partially available and 8% completely unavailable. A substantial proportion of cancer therapies, approximately 34.9%, are classified into other categories based on their availability of information. Overall, all analyses from the Chi-Square test revealed significant differences across the variables in the descriptive analysis.

The correlational analysis in Table 3 uncovers a compelling trend: drugs with unresolved shortages are more likely to face limited availability or complete unavailability. Even oncology drugs, less associated with reported shortage causes, show a moderate link to unresolved statuses ($r = 0.358$, $p<0.001$). However, there is no significant association between different categories of drug availability information and oncology therapies ($r = 0.025$, $p = 0.274$). The result shows that reasons for shortages have minimal impact on information on drug availability trends, with a slight but statistically significant relationship ($r = 0.081$, $p= 0.049$, 95% Confidence Interval 0.000, 0.160). Demand fluctuations or manufacturing delays may significantly be linked to different categories of information on drug availability.

Table 1. Description of variables for assessing drug shortage

Variables	Number of Occurrence	Percent Occurrence
Drug Availability Information		
Available/Estimated Availability	923	48.30%
Discontinued	9	0.50%
Limited Availability/supply	240	12.60%
Unavailable	272	14.20%
Others	466	24.40%
Reasons for Shortage		
Delay In Shipping Of The Drug	59	3.10%
Demand Increase For The Drug	232	12.10%
Discontinuation Of The Manufacture Of The Drug	31	1.60%
Other	130	6.80%
Regulatory Delay	3	0.20%
Requirements Related To Complying With Good Manufacturing Practices	13	0.70%
Shortage Of An Active Ingredient	125	6.50%
Update on Shortage		
New	329	17.20%
Reverified	1036	54.20%
Revised	545	28.50%
Status of Shortage		
Unresolved	1787	93.60%
Resolved	123	6.40%
Therapeutic Categories		
Non-Oncology therapies	1735	90.80%
Oncology therapies	175	9.20%

Table 2. Descriptive analysis of drug availability information to estimate characteristic drug shortages

							Pearson Chi-Square Tests
Variables	**Categories of Variables**	**Available/Estimated Availability(%)**	**Discontinued(%)**	**Limited Availability&supply(%)**	**Unavailable(%)**	**Others(%)**	**Value (P-Value)**
Reasons for Shortage	Delay in Shipping of the Drug	1.7	0	45.8	50.8	1.7	266.22 (<.001)
	Demand Increase for the Drug	22	0	34.5	42.2	1.3	
	Discontinuation of the Manufacture of the Drug	0	29	35.5	22.6	12.9	
	Other	3.1	0	39.2	56.9	0.8	
	Regulatory Delay	0	0	33.3	66.7	0	
	Requirements Related to Complying with Good Manufacturing Practices	0	0	7.7	92.3	0	
	Shortage Of An Active Ingredient	6.4	0	54.4	39.2	0	
	%Total	10.8	1.5	40.3	45.9	1.5	
Update on Shortage	New	2.7	0	2.4	0	94.8	1314.569 (<.001)
	Reverified	71.2	0.7	11.4	16.1	0.6	
	Revised	32.3	0.4	20.9	19.3	27.2	
	%Total	48.3	0.5	12.6	14.2	24.4	

Status of Shortage	Unresolved	63.6	0.5	16.5	18.7	0.7	1848.48 (<.001)
	Resolved	0	0	0	0	0	
	%Total	48.3	0.5	12.6	14.2	24.4	
Therapeutic Categories	Non-Oncology therapies	48.3	0.4	13.1	14.9	23.3	19.8(<.001)
	Oncology therapies	48.6	1.1	7.4	8	34.9	
	%Total	48.3	0.5	12.6	14.2	24.4	

Table 3. Bivariate Correlational Analysis to Determine Factors Associated with Drug Availability Information of Drug Shortages

		Reasons for Shortage	Status of Shortage	Types of Availability Information	Therapeutic Categories
Reasons for Shortage	Pearson Correlation	1	.a	.081*	-.088*
	Sig. (2-tailed)		.	0.049	0.031
	N	593	593	593	593
Status of Shortage	Pearson Correlation	.a	1	.358**	.235**
	Sig. (2-tailed)	.		<.001	<.001
	N	593	1910	1910	1910
Types of Availability Information	Pearson Correlation	.081*	.358**	1	0.025
	Sig. (2-tailed)	0.049	<.001		0.274
	N	593	1910	1910	1910
Therapeutic Categories	Pearson Correlation	-.088*	.235**	0.025	1
	Sig. (2-tailed)	0.031	<.001	0.274	
	N	593	1910	1910	1910

** Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed); a Cannot be computed because at least one of the variables is constant.*

The unavailability, limited availability, or supply of drug products reflects persistent supply chain inefficiencies that require intervention. A previous investigation demonstrated a shortage of cisplatin and carboplatin, chemotherapeutic products while proposing importation and promoting local medication production to strengthen the US pharmaceutical supply chain (Shah 2023). Conversely, the correlational analysis in our study showed that reasons for shortages are less likely to be reported regarding oncology therapies. Although oncology therapies represent a smaller proportion of total shortages, their availability remains a high-priority concern due to their clinical importance.

Furthermore, there are chances of unresolved supply chain issues, specifically regarding oncology drugs. Effective resolution strategies are crucial, as medications with unresolved shortages are more likely to face limited availability or complete unavailability. Another drawback is the re-verification process of updating drug logistics, which may lead to shortages, signaling that active efforts are required to track and manage availability. However, many updates require revision, indicating ongoing instability in supply chains. There is a clear need for more decisive interventions to resolve shortages, as current measures are insufficient.

While spikes in drug demand are the leading cause, active ingredient shortages and GMP compliance are significant causes of drug unavailability. Reasons for drug shortages have minimal impact on availability trends, indicating that other factors, such as demand fluctuations, regulatory processes, or manufacturing delays, may play a more prominent role. These factors are critical for exploring targeted interventions that alleviate shortages of API and promote GMP compliance.

Previous studies have suggested tailored strategies to address API shortages and deviation from GMP adherence. Approaches that harness the supply of APIs include incentivizing domestic production, adopting advanced technologies like blockchain, and collaborating with government stakeholders in the healthcare industry (Bilal et al. 2024, Nonzee & Luu 2019, Adak, 2024). Weaknesses in data integrity have demonstrated deviations from current GMP standards, which are remedied by frequent audits, responsive inspections by regulatory authorities, and access to information through ICT. These approaches to ensuring GMP compliance have built resilience in the supply chain (Katsaliaki, et al. 2022, V. M. and G. G. N. K., 2020). Overall, stabilizing the availability of oncology and non-oncology therapies in the US presents a viable solution for reducing drug shortages. Stable availability is vital to strengthen the API supply chain and support effective GMP compliance.

The implications of our findings underscore the urgent need for robust interventions addressing shortages of API, which pose a substantial public health threat in the United States. These identified drivers of drug shortages compromise medication safety for cancer patients, often necessitating therapy substitutions. For instance, alterations in medication regimens can lead to suboptimal clinical outcomes and diminished quality of life, resulting in increased toxicity, reduced therapeutic efficacy, and an elevated risk of medication errors in patients diagnosed with cancer (Nonzee & Luu 2019).

4. CONCLUSION

Although surges in demand are the primary drivers of drug shortages, shortages of active pharmaceutical ingredients (APIs) and issues related to Good Manufacturing Practice (GMP) compliance also play critical roles. Current supply chain challenges are particularly concerning for oncology medications. Additionally, the factors contributing to shortages of oncology therapies are often underreported, complicating efforts to address these issues effectively.

5. LIMITATION

One study's drawback is the limited information on the specific reasons for API shortages. Sufficient information was unavailable to determine the available drugs' resolution status. However, this study reveals the post-pandemic trends of drug shortages, which was one of the limitations of a previous study. Furthermore, correlation to demonstrate factors related to drug availability information of drug shortages does not establish causation. A significant correlation does not necessarily indicate a direct causal relationship, as other confounding factors may be involved, or the correlation may be coincidental. It is essential to conduct further analysis to determine the nature of the relationship between the variables.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare(s) that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

Appendix Table 1. Pearson correlation coefficients and confidence intervals for variables

Confidence Intervals				
Bivariate Correlation of Variables	Pearson Correlation	Sig. (2-tailed)	95% Confidence Intervals (2-tailed)b	
			Lower	Upper
Reasons for Shortage - Status of Shortage	.a	.	.	.
Reasons for Shortage -Availability Information	0.081	0.049	0	0.16
Reasons for Shortage - Therapeutic Categories	-0.088	0.031	-0.168	-0.008
Status of Shortage - Types_of_Availability	0.358	<.001	0.318	0.397
Status of Shortage- Therapeutic Categories	0.235	<.001	0.192	0.277
Availability Information -Therapeutic Categories	0.025	0.274	-0.02	0.07
a Cannot be computed because at least one of the variables is constant.				
b Estimation is based on Fisher's r-to-z transformation.				

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