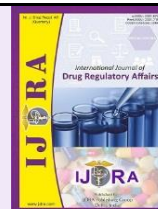




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### Short Communication

## Drug Shortage - Impact on the supply of critical drugs

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### Abstract

In the United States (US), drug shortages have been a particularly prevalent issue, especially concerning generic drugs and biologics. These shortages affect treatments for a wide range of diseases, from mild to moderate conditions to severe life-threatening illnesses. The scarcity of oncology-related drugs is particularly concerning, as these medications play a crucial role in cancer treatment and have a direct impact on human lives. In this article, we will discuss two such drugs, Cisplatin and carboplatin, examining their causes of the current shortage and exploring potential solutions that could help alleviate these drug shortages.

**Keywords:** Carboplatin, Cisplatin, FDA, Cancer, critical drugs, CBER, CDER, GMP

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### 1. Introduction

In circumstances where the demand for essential goods, materials, or medicines surpasses the available supply, consumers may be left waiting for the product to return to stock or be compelled to seek alternative options. For many everyday items, finding substitutes can be relatively simple.

However, in regard to the highly regulated industry of pharmaceutical drugs and biologics, the situation becomes more critical as patients rely on these products for their health and well-being. In cases where there is a shortage of medicines designed to treat various diseases, patients may have limited alternatives, or the available alternatives may have side effects and eventually might be forced to wait until their required medication is available again. This issue becomes even more complicated for life-threatening illnesses such as cancer, where timely treatment is crucial to addressing the disease effectively. In this context, we will explore the current drug shortage affecting cisplatin and carboplatin, two chemotherapy medications used in oncology treatments.

The scarcity of these essential drugs has significant implications for patients battling cancer and underscores the importance of addressing such shortages in the healthcare industry.

### 2. Drug Shortage in the US

In the US, the Food and Drug Administration (FDA) is responsible for regulating medicines intended for human use. According to the FDA, a drug shortage is defined as a period of time when the demand or projected demand for the drug within the US exceeds the supply of the drug. (1)

From a drug and biologics standpoint, the FDA's drug shortage program is led by two distinct centers: the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), with each center focusing on specific product types. The scope of this article concentrates on products regulated by CDER, which include prescription and generic drugs as well as CDER-regulated biologics. (2) The figure below illustrates the drug shortage information provided by the FDA.

The management of drug shortages for CDER-regulated products falls under the purview of the Drug Shortage Staff within CDER. These shortages are documented in a publicly accessible drug shortage database, which provides comprehensive information on current and resolved shortages, discontinuations, and other relevant details. As of June 27, 2023, the database shows that 138 CDER-regulated drugs are currently in shortage, while 70 shortages have been resolved. Among the 138 drugs, 14 are oncology medications, including cisplatin and carboplatin, both of which are currently listed as being in short supply. (3)

# DRUG SHORTAGES:

We know it can be frustrating when you can't get a medicine you need. That's why FDA works closely with the pharmaceutical industry and stakeholders to prevent drug shortages and to lessen the impact on patients anytime there is a delay in the availability of the medicines you need. Ensuring there are as few disruptions to patient care as possible is one of our top priorities.

- Several factors, that are outside of our control, can cause or contribute to drug shortages. Sometimes manufacturers have an unforeseen breakdown in manufacturing lines affecting their production. Other times, shortages are caused by product quality problems, a manufacturer discontinuing a product, or unexpected surges in demand brought on by things like seasonal illnesses.
- In many instances, companies can eventually meet the demand allowing consumers to get the medicines they need.

## How FDA helps prevent and resolve shortages

**FDA can:**

- Expedite reviews of new production lines or material sources to increase production quickly,
- Extend product expiration dates, if it is safe to do that,
- Import medicines to the U.S., if they meet our safety and effectiveness criteria.

**FDA cannot require a pharmaceutical company to:**

- Make a drug, even if it is a medically necessary drug,
- Make more of a drug,
- Change how much and to whom the drug is distributed.

## How the pharmaceutical industry can help prevent drug shortages

Drug companies must notify FDA about manufacturing interruptions or product discontinuances and create a risk management plan for their product supply chain. Early notification from drug companies of any issue that could lead to a potential disruption in supply is critical to preventing or lessening the impact of drug shortages.

For more information visit:  
[www.fda.gov/drugshortages](http://www.fda.gov/drugshortages)

**FDA U.S. FOOD & DRUG ADMINISTRATION**

Figure 1. Drug shortage information (4)

Cisplatin and carboplatin are both generic chemotherapy medications widely utilized in the treatment of various forms of cancer. Acting as alkylating agents, these drugs

work to inhibit or halt the growth of cancer cells by causing breaks in DNA. (5-7)

Per the FDA's drug shortage database, the table below provides the date the shortage was posted for these two drugs:

**Table 1.** Reported date of drug shortage per FDA database (8, 9)

Product	Date first posted on FDA's drug shortage database
Cisplatin Injection	10-February-2023
Carboplatin Injection	28-April-2023

The situation with cisplatin became critical when the FDA inspected a facility responsible for producing 50% of the supply of cisplatin in the US. The inspection resulted in several observations and a Form 483 notice, leading to an import alert on various products manufactured by Intas Pharmaceuticals. Notably, this did not include the drugs in shortage, cisplatin and carboplatin, which were not restricted from importation. However, following the inspection conducted by the FDA in late 2022 and the ensuing observations, Intas Pharmaceuticals voluntarily halted the manufacturing and export of products to the US. This action significantly contributed to the limited supply of these vital drugs and subsequently increased demand from other manufacturers.

The shortage of cisplatin indirectly affected the availability of carboplatin as well. Since carboplatin can be a substitute for cisplatin, its shortage was also influenced by the scarcity of cisplatin, contributing to ongoing drug supply issues. (10-12)

### 3. Discussion

Several factors contribute to the occurrence of drug shortages, including but not limited to: (3, 13-15)

**Profitability Issues:** The commercial viability of generic drugs is often low, which can deter manufacturers from continuing production. If these manufacturers decide to reduce or cease production, it can lead to a shortage. In cases where a manufacturer shuts down operations entirely, other manufacturers producing the same product will have increased demand and may not have the necessary infrastructure to keep up.

**Quality Control and Regulatory Compliance:** The FDA mandates that all approved manufacturers adhere to specific regulatory requirements and current Good Manufacturing Practices (cGMP). If there are concerns regarding compliance and product quality, the FDA may require manufacturers to rectify these issues, which can impact production capacity and potentially cause a shortage.

**Unexpected Shifts in Demand:** Unforeseen events, such as the recent COVID-19 pandemic, can drastically alter the demand for specific drugs and products. This sudden surge in demand can result in temporary shortages.

**Supply Chain:** Any changes or disruptions in the supply of raw materials, active pharmaceutical ingredients (APIs), or any other components required for the

production of finished drugs have the potential to lead to a shortage.

### 4. Potential Solutions

There are few strategies that could be implemented to mitigate drug shortages, each tailored to the specific circumstances causing the shortage:

**Importation of Unapproved Products:** As a temporary measure, the FDA may allow the importation of unapproved forms of a drug to increase supply. For instance, recently, the FDA allowed the importation of non-US labeled unapproved cisplatin injection from China, manufactured by Qilu Pharmaceuticals, to address a shortage illustrating this approach.

However, there is still a need to leverage this strategy in the short term, and the FDA may need to exercise its enforcement discretion to allow the importation of both cisplatin and carboplatin from other unapproved sources. This will help to alleviate the shortage.

**Intermarket Reliance and Harmonization:** The harmonization of Good Manufacturing Practice (GMP) inspections across different markets can reduce the time taken for each agency's inspection. If regulatory agencies collaborate on GMP inspections of manufacturing sites, they could potentially expedite the process based on shared evaluations.

**Incentives for Generic manufacturers:** Long-term solutions could include offering tax breaks or other economic benefits to encourage more generic manufacturers to increase their production capacities.

**Promoting Domestic Manufacturing:** Encouraging more manufacturing within the US can reduce shipping and inspection times, leading to quicker product availability and distribution. This becomes particularly beneficial during natural disasters or pandemics when exports from international markets may be reduced or halted, making reliance on domestic manufacturers more important.

Considering the factors causing drug shortages and the proposed solutions to address them, it is clear that these shortages can stem from a number of factors and that their onset may be unpredictable. Nevertheless, establishing and implementing both immediate and long-term strategies to combat these shortages is crucial, particularly for medicines used in oncology or other fields where the treatments are lifesaving. Prioritizing this issue is essential to ensure continued access to critical medications. (13-17)

### 5. Conclusion

From the discussion, it is clear that quality concerns are the primary cause of supply shortages, leading to heightened demand from other manufacturers who may lack the capacity to scale up production. This situation poses a significant challenge, particularly for patients battling life-threatening conditions. While the FDA's mitigation strategy allowing the importation of unapproved but essential drugs from countries such as China does offer temporary relief and access to necessary medicines, it is evident that more long-term

solutions are required to prevent such circumstances in the future.

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### Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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