



CONVERSATION WITH
THE CANCER LETTER

Richard Pazdur discusses root causes of cisplatin and carboplatin shortage and what can be done to alleviate it

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Richard Pazdur, MD

*Director, FDA Oncology Center of Excellence,
Acting director, FDA Office of Oncologic Diseases*

Today's critical shortage of cisplatin and carboplatin occurred because manufacturers failed to invest in enhancing production capacity, Richard Pazdur, director of the FDA Oncology Center of Excellence and acting director of the Office of Oncologic Diseases, said to *The Cancer Letter*.

In a wide-ranging interview, Pazdur addressed the immediate problem of shortages of platinum-based drugs as well as the underlying causes of shortages that have been plaguing oncology for over a decade.

The shortage of platinum-based drugs is causing oncologists all over the U.S. to ration the drugs that are used to treat as many as 500,000 new cancer patients per year. As cisplatin and carboplatin are being rationed at clinics nationwide, this often means that only patients who stand a chance of being cured are prioritized to receive these off-patent, inexpensive treatments (*The Cancer Letter*, [May 26](#), [April 7, 2023](#)).

"The current cisplatin shortage followed an inspection and subsequent identification of quality issues at a single company's manufacturing facility," Pazdur said. "The company shut down the production line, leading to the current shortage. As a result of the cisplatin shortage, a ripple effect was observed leading to an increased demand for carboplatin and the manufacturing challenges in meeting an increased carboplatin demand.

"To restore supply of cisplatin, FDA has continued to offer assistance to all five manufacturers on anything they can do to increase supply. In addition, we are exploring temporary importation to help meet patients' needs during the shortage. FDA has also requested that manufacturers submit data to support additional expiration dating for lots already in distribution that are approaching their labeled expiration."

Pazdur said FDA's ability to manage shortages is limited.

"Based on current laws, FDA *cannot* require a manufacturer to report an increase in demand that may lead to a drug shortage," Pazdur said. "Appropriately, we *cannot* require a company to manufacture a drug.

"We *cannot* require a company to make greater quantities of the drug—specifically, to step-up production. We *cannot* require a distributor to report on the quantities that are distributed and specific purchasers who may be given priority.

"In addition, FDA *cannot* require that essential drugs, such as cancer therapeutics, have diversified supply chains such that there is not overreliance on a single facility or country for an active pharmaceutical ingredient (API) or key starting materials. However, even when there is more than one manufacturer for a drug, most facilities are operating near capacity and are unable to rapidly fill the void if a manufacturer ceases production due to a manufacturing quality issue," Pazdur said.

Pazdur mentioned a proposal to set up a stockpile of critically important cancer drugs, but stopped short of endorsing the proposal (*The Cancer Letter*, [April 28, 2023](#)). Government officials are precluded from advocating for legislation.

"Discussions in the oncology community have focused on the proposal that the government contract with manufacturers to produce a 'buffer stockpile' of 'essential' oncology drugs," Pazdur said. "The drugs would include those administered in the front-line setting, in potentially curative settings and in clinical situations where substitutions with other drugs are not feasible or practical.

"For example, this proposal for stockpiling may involve drugs used in pediatric oncology and the reserve may be a six-

month supply that would be rotated periodically into the commercial market. This rotation of stock would avoid drug expiration and waste.

"Since these same drugs may also be used in adults, sufficient quantities would need to be available to avoid competition for limited supplies that may foster ethical dilemmas regarding drug rationing. In addition, economic incentives have been discussed aimed at fostering robust U.S. domestic manufacturing to avoid supply chain problems due to any geopolitical, natural, or pandemic disruptions," Pazdur said.

Pazdur spoke with Paul Goldberg, editor and publisher of *The Cancer Letter*.

Paul Goldberg: Why do drug shortages occur and what can the FDA do to address them?

Richard Pazdur: We define a drug shortage as a time period when the demand for a drug exceeds the U.S. supply. Drug shortages occur for a variety of reasons, including manufacturing and quality problems, delays, increased demand, and discontinuation of drug production.

Shortages are often due to interruptions in manufacturing and may be due to natural disasters or geopolitical events that may curtail operations, but more often are attributed to manufacturing quality issues requiring remediation. Sterile injectable products are most commonly vulnerable to shortages, because their manufacturing processes are more complex than for small molecules in solid dosage formulations.

A failure to invest in newer equipment, processes, or management practices that can prevent quality-related manufacturing breakdowns is often a root cause and appears to be tied to the economics of producing low-cost, older

sterile injectables where profit margins are increasingly squeezed.

FDA has consistently worked closely with manufacturers to address identified problems. We can advise, assist, and expedite inspections and reviews. Although we can take these actions, the manufacturer is ultimately responsible for addressing the problems.

Under the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA has the authority to require the drug's manufacturer to notify FDA of supply disruptions, delays, and discontinuations in manufacturing. Manufacturers are also required to notify us of certain manufacturing changes, such as a new production process, equipment, or facility.

What are the limits of FDA's authority regarding drug shortages?

RP: FDA's authority to intervene is derived from laws passed by Congress. As noted above, manufacturers are required to notify FDA of supply disruptions, delays, or discontinuations. Early notification by manufacturers is essential for FDA to take action to prevent or mitigate shortages.

However, based on current laws, FDA *cannot* require a manufacturer to report an increase in demand that may lead to a drug shortage. Appropriately, we *cannot* require a company to manufacture a drug. We *cannot* require a company to make greater quantities of the drug—specifically, to step-up production. We *cannot* require a distributor to report on the quantities that are distributed and specific purchasers who may be given priority.

In addition, FDA *cannot* require that essential drugs, such as cancer therapeutics, have diversified supply chains such that there is not overreliance on a

single facility or country for an active pharmaceutical ingredient (API) or key starting materials.

However, even when there is more than one manufacturer for a drug, most facilities are operating near capacity and are unable to rapidly fill the void if a manufacturer ceases production due to a manufacturing quality issue.

What are the root causes—specifically, the underlying problems—that directly or indirectly causes drug shortages?

RP: FDA doesn't have the authority to order manufacturers what or how much to produce. It is the action of the generic companies that ultimately resolve shortages. Increasingly, companies are exiting the marketplace—either voluntarily or through bankruptcy¹—and have informed the FDA that manufacturing costs, especially of older oncology drugs, exceed the sale price.

We have seen the net profits of leading generic companies plunge into the negative or barely positive range. Generic medicines are commodity products, because by design they are interchangeable and, therefore, compete on price. This has led to significant price erosion—greater than 50% since 2016.²

Patients receiving generic drugs are benefiting from an industry providing over 90% of the prescriptions while only accounting for 18% of the U.S. total prescription drug expenditures. Unlike other commodities, no incentives exist for generic drug manufacturers to produce excess drug quantities over market demand.

What does this mean for the generic drug market? Although manufacturers meet regulatory requirements for Current Good Manufacturing Practice (CGMP), when prices and profits decline

over time, manufacturers may make decisions that weaken the resiliency of the supply chain. Frequently these steps sacrifice investment in quality manufacturing or result in over-dependence on a single source. Obviously, these forces are likely to lead to an increase in quality-related drug shortages.

For example, the current cisplatin shortage followed an inspection and subsequent identification of quality issues at a single company's manufacturing facility. The company shut down the production line, leading to the current shortage. As a result of the cisplatin shortage, a ripple effect was observed leading to an increased demand for carboplatin and the manufacturing challenges in meeting an increased carboplatin demand.

To restore supply of cisplatin, FDA has continued to offer assistance to all five manufacturers on anything they can do to increase supply. In addition, we are exploring temporary importation to help meet patients' needs during the shortage. FDA has also requested that manufacturers submit data to support additional expiration dating for lots already in distribution that are approaching their labeled expiration.

We will post any supplies available through temporary importation and any expiration date extensions on the FDA drug shortage website.³ FDA is taking similar actions for carboplatin.

Could I ask you to describe FDA's strategy for addressing these shortages?

RP: Early notification is the key to prevention. Some drug shortages can endure for a prolonged time—ranging from months to years—frequently, depending on the shortage's cause. For example, plant remediations of manufacturing processes may require extensive retooling.

Although the number of *prevented* shortages continues to grow, the number of *actual* new drug shortages have remained relatively flat since 2013. I would like to emphasize that the earlier this work begins, the greater the likelihood that a shortage can be prevented or the most severe impacts on patients can be mitigated.

Our key approaches to the prevention and mitigation of drug shortages include the following:

- Prioritization of medically necessary products,
- Ensuring the availability of drugs while maintaining quality by communicating across the ecosystem to help find new sources, and
- Working with companies to address problems by expediting submissions that can increase supply.
- Much of this work depends upon FDA's ability to communicate with companies that normally compete rather than cooperate, not through direct authority to require changes in production and distribution.

Additionally, we may exercise regulatory discretion—for example, allowing generation of additional stability data as a submission for a new manufacturing line is being evaluated. We may temporarily exercise regulatory flexibility and discretion regarding importation of drug supply from other countries. These actions are contingent upon inspection and compliance of these manufacturing facilities and other conditions, including stability and sterility studies.

If a shortage cannot be prevented, FDA encourages companies to allocate supplies that would evenly distribute drugs. FDA can encourage, although cannot require, companies to have a “safety stock.”

Importantly, FDA's role is to assure the safety, effectiveness, and quality of drugs provided to the American public. Addressing shortages by working with manufacturers to expand or bring new production online and exercise appropriate regulatory discretion is within our regulatory remit.

However, when a drug is in shortage, it is analogous to the patient already being in the intensive care unit. Addressing the underlying market forces, which is beyond FDA's remit, is the preventive medicine that ultimately is needed to address the problem.

Do drug shortages share any common features?

RP: Yes, a 2019 Report to Congress, “Drug Shortages: Root Causes and Potential Solutions,” concluded that most shortage drugs are older sterile injectable generic drugs, most drug shortages are attributed to quality issues causing disruption to the drug's supply, and that quality issues stem from underlying economic issues. I addressed these issues above.

Multiple external working groups have highlighted some of my above comments. There may be a downward pressure on prices—even below profitable levels—due to concentration of power in purchasing organizations. Approximately 90% of wholesale drug distribution is concentrated in three companies. Generic drug companies compete with each other to obtain contracts with the three main wholesalers, and these wholesalers, therefore, have leverage in determining prices for generics.⁴

As prices fall near or even below profitable levels, manufacturers may sacrifice investments in manufacturing that prevent quality-related disruptions to continue production. Because quality manufacturing is neither transparent

nor rewarded, companies might underinvest in quality manufacturing practices even for profitable products.

You have addressed the root causes of the problem, which I presume may take years to fix—if this can be done at all. Are there potential short-term remedies?

RP: To reiterate the above, extensive discussions regarding drug shortages involving multiple stakeholders, including patient and professional groups, such as Friends of Cancer Research and the American Society of Clinical Oncology, have occurred over many years.

Many have acknowledged that the long-term solutions are an industry-wide policy providing economic incentives to foster technology upgrades to compete with off-shoring of manufacturing processes and create a robust “re-shoring” or “near-shoring” manufacturing of critical drugs. This desired stability may require long-term contracts at fixed pricing to ensure constant, uninterrupted availability of quality products to U.S. patients.

In the interim, we need to assure American patients a stable, safe drug supply of critical drugs used in oncology, especially in those indications where they are used in potentially curative or life-extending situations.

This is particularly true when it comes to the treatment of cancers in the most vulnerable populations—children with cancers who may be facing life-threatening diseases that may have curative potential. Many drugs used to treat these diseases have been in shortage or at risk of shortage.

Discussions in the oncology community have focused on the proposal that the government contract with manufacturers to produce a “buffer stockpile”

of “essential” oncology drugs. The drugs would include those administered in the front-line setting, in potentially curative settings, and in clinical situations where substitutions with other drugs are not feasible or practical.

For example, this proposal for stockpiling may involve drugs used in pediatric oncology and the reserve may be a six-month supply that would be rotated periodically into the commercial market. This rotation of stock would avoid drug expiration and waste.

Since these same drugs may also be used in adults, sufficient quantities would need to be available to avoid competition for limited supplies that may foster ethical dilemmas regarding drug rationing. In addition, economic incentives have been discussed aimed at fostering robust U.S. domestic manufacturing to avoid supply chain problems due to any geopolitical, natural, or pandemic disruptions.

What are the current oncology-related drug shortages? Can you provide specific reasons?

RP: As of May 2023, there are 17 oncology-related drug shortages. They included the following: amifostine injection, azacitidine injection, capecitabine tablets, carboplatin injection, cisplatin injection, cytarabine injection, dacarbazine injection, dexamethasone injection, fludarabine injection, fluorouracil injection, hydrocortisone injection, leucovorin injection, lutetium Lu 177 vipivotide tetraxetan injection, methotrexate injection, palifermin injection, and streptozocin injection.

I have already provided many common reasons above for drug shortages; however, there are some specific reasons that deserve comment. For fludarabine injection, all three manufacturers experienced supply issues that caused

shortages and experienced markedly increased demand over historical levels due to fludarabine use in patients receiving CAR T-cell therapies.

One of the three approved manufacturers was granted regulatory discretion to release product made with an unapproved raw material that was evaluated by FDA and deemed to have no risk for patients.

In addition, FDA worked with a Canadian company to temporarily import supply to meet patient needs. This Canadian facility was evaluated by FDA to ensure no risk to patients. “Dear Health Care Professional” letters are posted on our website addressing the above two actions to ensure continued fludarabine supply.

Can you think of anything we forgot to mention, anything I forgot to ask?

RP: FDA will continue to use all its authorities to work with the industry to resolve these shortages while assuring access to quality medications. Ultimately, FDA cannot solve this problem alone. A shortage is the end result of a failure in the market. While the focus is often on the high price of drugs, there are actually two markets.

The generics industry and the innovator drug industry operate on different business models—generic drugs are low margin and depend on competition for efficiency as a business model, while innovator drugs involve the cost and risk of development with higher prices and margins due to patent protection.

In terms of volume, generics comprise the overwhelming majority of drugs prescribed but less than 20% of the total prescription drug costs. The sustainability of the market for essential medicines is critical to patients and will

require actions and investments that assure a resilient and economically viable market.

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GUEST EDITORIAL

Drug shortages threaten lives—cancer patients cannot wait



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The shortage of certain cancer drugs is a serious and life-threatening issue for cancer patients across the United States. This, however, is not a new issue. Drug shortages are a cyclical event, and we need a durable solution to ensure that cancer patients have access to the drugs and the treatment they need to survive.

Chemotherapy drugs are increasingly in short supply, and have returned to the list of top-five drug classes affected by shortage, according to the [American Society of Health System Pharmacists](#). And, more unfortunately, chemotherapy drugs often do not have alternatives. This forces doctors and patients to determine new next steps in terms of their treatment, which may include delays.

The American Cancer Society (ACS) and American Cancer Society Cancer Action Network (ACS CAN) have heard from patients and practitioners who are directly experiencing the impact of these shortages.

One example is an oncology nurse in Los Angeles who expects her health system will run out of four cancer drugs by the end of this week (Pluvicto, for advanced prostate cancer; BCG, a drug for bladder cancer; and methotrexate and cisplatin, two common chemotherapy drugs).

In another example, a mother called the ACS National Cancer Information Center (NCIC) hotline on behalf of her daughter, who is halfway through her treatment with carboplatin and has

been told the remaining doses she needs are not available.

What drugs are in shortage?

There are currently over [130 products](#) listed as “[Currently in Shortage](#)” by the FDA—including 14 [oncology](#) drugs as of 05/31/23 (carboplatin injection used to treat triple negative breast, ovarian, head, and neck cancers; fludarabine phosphate Injection used for treating B-cell chronic lymphatic leukemia; dacarbazine Injection for treatment of skin cancer; as well as amifostine injection; azacitidine for Injection; capecitabine tablets; cisplatin Injection; cytarabine injection; dexamethasone sodium

phosphate Injection; hydrocortisone sodium succinate injection; leucovorin calcium lyophilized powder for Injection; lutetium Lu 177 vipivotide tetraxetan (Pluvicto) injection; methotrexate injection; and streptozocin (Zanosar) sterile powder).

This list also contains shortages of basic IV materials like saline bags, dextrose drips, contrast agents for imaging, and sterile water used in a variety of medical settings.

In addition to having an impact on all cancer patients, these drug shortages also have an implication on health disparities, particularly existing disparities in breast cancer mortality for Black women. As an example, carboplatin is the first line therapy for triple negative breast cancer, a breast cancer experienced at higher rates by Black women.

What is causing the shortage?

While individual causes of discrete shortages are complex, the overarching theme is that almost all of these products are low-cost generic sterile injectables with low profit margins.

This means manufacturers have little incentive to invest in process upgrades, expanded capacity, or redundancy in production facilities.

One cause of the shortage is consolidation of manufacturing. Another cause is expanded demand for some of these drugs. The population of the United States is growing and aging, and some of these drugs experience modest year-over-year growth in use without associated addition of manufacturing capacity.

Industry economics are an additional factor to examine in these shortages. Companies make business decisions

to discontinue manufacturing certain drugs, particularly generic drugs, based on profitability or other business considerations without always ensuring the continued manufacture of the drug elsewhere.

In many cases, there are only one or two manufacturers of the products in shortage meaning disruption in one site or company results in national shortages.

USP's *Medicine Supply Map* is a tool that includes over 250 million aggregated datapoints to evaluate indicators of drug shortage risk, which includes geographic concentration, manufacturing complexity, price, and quality. The map shows that modest price points for drugs like carboplatin (\$23 per unit) and cisplatin (\$15 per unit) amplifies their susceptibility to supply chain disruptions.¹

Manufacturers and supply chain participants are more hesitant to invest in redundancy for older, lower-priced generic drugs. ACS and ACS CAN partner with USP and are working to connect the group with the U.S. Department of Health and Human Services and the FDA to work on concrete solutions.

Manufacturing difficulties such as quality control issues and lack of availability of raw materials also contribute to the shortage. Both the current problem and the long-term issues that are perpetuating the cycle of periodic drug shortages are creating secondary problems that interfere with patient access to drugs.

How is the drug shortage mitigated?

The FDA issued a strategic plan to address shortages in 2013.² As it stands currently, manufacturers who expect or are experiencing shortages must notify FDA.

FDA's mitigation tools are largely confined to working directly with the manufacturer on whatever is causing the shortage, as well as working with other manufacturers of the same product to urge them to ramp up production.

The FDA's ability to mitigate shortages is limited by the tools at its disposal based on its statutory authority. The general tools described by the plan include:

- Determining whether other manufacturers are willing and able to increase production
- Expediting inspections and reviews of submissions
- Exercising temporary enforcement discretion for new sources of medically necessary drugs
- Working with the manufacturer to ensure adequate investigation into the root cause of the shortage
- Reviewing possible risk mitigation measures for remaining inventory

Notably, companies that fail to provide the six-month notification face no real retribution other than having the FDA non-compliance letters to the company made public.

ACS and ACS CAN's involvement

The House Energy & Commerce Oversight Committee held a [hearing](#) on May 11 entitled *Examining the Root Causes of Drug Shortages: Challenges in Pharmaceutical Drug Supply Chains*.

ACS CAN submitted a Statement for the Record highlighting the impact of oncology drug shortages on cancer patients and encouraged Congress and pharmaceutical manufacturers to do more to both anticipate potential shortages



A mother called the ACS National Cancer Information Center (NCIC) hotline on behalf of her daughter, who is halfway through her treatment with carboplatin and has been told the remaining doses she needs are not available.



and help to ensure that patient cancer treatments are not disrupted.

Previously in March 2023, the US Senate Committee On Homeland Security & Governmental Affairs held a hearing on drug shortages and published a report entitled *Short Supply the Health and National Security Risks of Drug Shortages*.

Both ACS and ACS CAN continue to monitor and actively engage in the medical product shortage issue. ACS is in regular conversations with health systems nationwide to keep tabs on ongoing shortages and the direct impact on patients and their care.

ACS also runs the NCIC hotline and speaks to patients and their families 24 hours per day, 7 days per week, and 365 days per year. When calls related to shortages come in, ACS and ACS CAN work together to reach out to manufacturers to better understand the extent of the shortages.

ACS CAN has been engaged and advocating around this critical issue for cancer patients for more than a decade, having submitted a letter in 2013 in response to the strategic plan on drug shortages.³

Additionally, ACS CAN has and continues to participate in the Alliance for Childhood Cancer Drug Shortage Working Group. The group is looking specifically at shortages in therapeutics for childhood cancer.

Next steps in eliminating cancer drug shortage

Because the root cause of the shortage is multifactorial, creating a durable solution to this problem for cancer patients will require discussion among all key stakeholders.

ACS CAN is urging Congress to look at longer-term solutions that change the fundamental underpinnings of the shortages. In the meantime, ACS CAN also urges the pharmaceutical industry to work with medical practitioners to help identify alternatives where possible to ensure that cancer patients' treatments are not delayed.

The system is broken and needs fixing, and there is no short-term fix option. Cancer patients deserve systemic change at the policy and manufacturing levels, which requires both discussion and action.

Even if policy changes were made immediately, it would still take months to years to see the results.

ACS believes there should be a task force appointed to find a solution for cancer patients and their families, and with so many thought leaders at the ASCO Annual Meeting, in Chicago it will be an opportunity to have more extensive discussion, including with the Biden administration.

In conclusion, we must collectively help cancer patients now to do everything we can to increase access to these critical drugs and importantly, develop a more sustainable approach to mitigate these issues in the future.

References

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