ADVANCES IN DRUG DEVELOPMENT

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Tackling the Cancer Drug Shortage

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H&O How bad is the chemotherapy drug shortage right now?

EF The shortage is difficult to quantify. We do not know exactly how many patients' therapy has been disrupted, or the difference between the amount of chemotherapy produced vs the amount needed. In 2023, however, at the height of the shortage, a survey of American Society of Health-System Pharmacists members found that 57% of respondents reported rationing, canceling, or delaying cancer treatment because of shortages.[1]

H&O Which chemotherapy agents are in short supply?

EF We experienced shortages in 2023 and earlier this year of carboplatin and cisplatin, both of which are very broadly used—approximately 500,000 people a year take one of these drugs. Supplies of these drugs have now greatly improved. However, other chemotherapy agents are currently in short supply, including several that are used in pediatric patients. Some of these shortages have been ongoing for years, including Bacillus Calmette-Guérin treatment, dacarbazine, doxorubicin, and paclitaxel. There are currently 277 active drug shortages as of September 30 of this year, including 25 active chemotherapy product shortages. Nearly all of them have been of generic sterile injectable drugs, which are challenging to produce and require that strict manufacturing practices be followed.

H&O What are the effects of chemotherapy shortages?

EF Chemotherapy shortages present numerous dilemmas. If not enough of a particular chemotherapy agent is available to go around, how do we handle this? Do we delay treatment, reduce doses, or choose an alternative drug? Do we prioritize one group of people over another? We do not have satisfactory answers to these questions.[2]

In addition, chemotherapy shortages are very disruptive to patients and providers. Most chemotherapy infusions are given in the outpatient setting, and appointments are scheduled in advance. If the infusion center is running short of a particular agent and does not know when the next delivery will arrive, patients must be rescheduled.

Finally, chemotherapy shortages have a major effect on clinical trials. In August of 2023, at the height of the shortage of carboplatin and cisplatin, more than 1500 clinical trials that were either ongoing or recruiting patients included one of these agents. This does not mean that all 1500 clinical trial were disrupted, but it illustrates the ripple effect of the shortages. So many trials use carboplatin or cisplatin as baseline therapy that shortages of these drugs affect the development of newer drugs. The US Food and Drug Administration (FDA) did not remove cisplatin from the list of drugs in short supply until mid-2024.

H&O What are the reasons for the chemotherapy drug shortage?

MW The carboplatin and cisplatin shortages in 2023 resulted from the suspension of production in a manufacturing facility owned by Intas Pharmaceuticals, a company based in India. The facility closed for several months because of manufacturing quality problems. Facilities that manufacture cancer drugs have been shut down because of manufacturing problems before. For example, back in 2011, a manufacturing facility in Irvine, California, had to shut down because of manufacturing quality problems, and the number of cancer drugs in shortage immediately increased from 4 to 24. And there are other examples, not just with chemotherapy drugs but also with many other types of generic sterile injectable drugs.

The question is, why do we keep on having manufacturing quality problems? To understand that question, we need to look at market dynamics.

The FDA considers generic drugs to be therapeutically equivalent to branded drugs. No additional information is available for buyers to know which companies are doing a better job regarding the reliability of their production processes. With limited information, hospitals and other buyers will naturally want to order the least expensive version that they can find. This situation leads to a race to the bottom on the basis of price. The problem is that even when the products themselves are interchangeable, the reliability of the supply often differs. Increased competition results in reduced profit margins for the manufacturers of generics, who must look for ways to cut costs. These include less willingness to invest in factory upgrades or staff training.

Another difference between branded drugs and generics is that branded drugs generally are produced on dedicated manufacturing lines. The manufacturer of a branded drug will sometimes produce the same product on a given line for years. In contrast, factories that produce generic drugs often swap out the products that a particular manufacturing line produces; some lines will produce as many as 50 products over the course of a year. Each time the line changes to a new product, the manufacturing equipment must be cleaned thoroughly. If the cleaning is not sufficiently thorough, the new product can become contaminated. When that happens, disruptions follow.

An analogy I use to explain why the FDA cannot ensure manufacturing quality is to compare it to a police force trying to enforce speed limits. Drivers tend to slow down as soon as they see a camera or police car, and they speed up again as soon as they are no longer in danger of getting a speeding ticket. Much in the same way, manufacturing plants are on their best behavior during FDA inspections but may revert to shortcuts the rest of the time. When it comes to speeding, drivers are more concerned about getting a ticket if they know that the amount will be high. The threat of a $1000 ticket is likely to convince people not to speed. But what if drivers know that any speeding ticket will cost only $10, or that they will simply get off with a warning? What would be the financial incentive to slow down? In times of potential drug shortages, Congress tells the FDA to avoid shutting down manufacturing facilities whenever possible and instead give the company a warning. As a result, the FDA is between a rock and a hard place.

> We need to change how hospitals go about buying drugs.
> —Marta E. Wosińska, PhD

Some people have blamed the shortages on foreign manufacturing facilities, but this is not a foreign-vs-domestic issue. Historically, most of the shortages of generic sterile injectable drugs have started with production disruptions in US manufacturing facilities.

H&O What policies would reduce the risk of these shortages in the future?

MW We need to change how hospitals go about buying drugs.[3] This can be done by having the Centers for Medicare & Medicaid Services (CMS) influence the buying decisions that hospitals make, so that they put more weight on the reliability of the supply when purchasing drugs.

The Senate Finance Committee has drafted bipartisan legislation in which the power of the Medicare and Medicaid programs is used to prevent or reduce shortages of generic injectable drugs across the United States.[4] The Committee put out a legislative proposal in May of 2024 that is designed to take effect in 2027. Much of what the proposal does is based on the model of the not-for-profit drug company Civica Rx: committed-volume long-term contracts not only with manufacturers but also with participating hospitals. In addition, the model includes a 6-month buffer inventory of every contracted drug. The proposal tries to expand this model by paying hospitals to enter into such long-term contracts for selected generic sterile injectable drugs.

What I like about the Senate Finance Committee proposal is that it not only addresses how to incentivize hospitals to sign long-term contracts but also includes a

complementary policy to prevent the goals of the proposal from being undermined. In particular, the proposal exempts multisource generic drugs from Medicaid inflation rebates.

The way the system works now, manufacturers need to pay Medicaid inflation rebates if the average price of a particular drug increases more than the consumer price index (CPI). These rebates do not acknowledge that some price increases are entirely legitimate. For example, a manufacturer may experience a cost increase that is greater than the CPI increase. Mandatory discounts are not a problem for branded products with high profit margins; they are a problem for generic drugs, however, because they have very low margins to start with. Such rebates can be quite consequential to the profitability of generics because the prices paid by Medicaid are the basis for the 340B program. Cancer drugs are used in the outpatient setting, which has a high 340B presence, so they are particularly vulnerable to this dynamic.

The Senate Finance Committee proposal to eliminate Medicaid inflation rebates is important because it enables passthrough to manufacturers for improving the reliability of their supply. After all, the whole idea behind paying hospitals more for buying from reliable manufacturers is to get hospitals to be willing to pay more to those manufacturers. We cannot then have policies in place that ask manufacturers to send the reliability premium back to Medicaid and 340B hospitals. That would undercut the incentive for them to invest in reliability.

H&O What additional ideas should be adopted?

MW The Drug Enforcement Administration (DEA) controls how much the manufacturers of controlled substances can produce. For the Senate Finance Committee proposal to work, the DEA quota system would have to align so that the DEA rewards more reliable manufacturers with a greater quota.

EF To that point, the Senate Finance Committee proposal also needs a way to ensure that companies are maintaining quality standards and at the same time providing drugs more reliably. Right now, the reliability of supply is not explicitly addressed in the Senate proposal. Just signing a long-term contract is not enough to ensure that manufacturers are going to do the right thing and improve their quality.

At the end of the day, hospitals are going to need to pay more for these products if they want to have a sustained supply. I would argue that we are already paying a lot for shortages because of all the costs that come with managing them. Unfortunately, we are paying for shortages without the benefit of having a guaranteed supply of high-quality drugs.

H&O How are patients dealing with the shortages?

EF Having cancer is already hard, and being worried about whether your treatment is going to be available just makes the situation worse. Patients get scared when they read news reports about a shortage and then automatically assume their treatment will not be available. That is usually not the case, even if treatment is delayed by 1 or 2 days or the patient receives a lower dose. We have not seen many cases of patients being unable to receive therapy entirely because of a drug shortage. We have several workarounds that we can use. Still, patients are understandably very concerned. Adding to the anxiety is that when they ask their providers about the shortages, the providers do not always have the answers. For example, the wholesaler may have just told the provider that it does not know when the next delivery is going to come. These are tough conversations for providers to have with patients.

> There is a lot of variability among hospitals in how they are affected by shortages.
> —Erin R. Fox, PharmD, MHA

H&O What lessons can be learned from the shortages?

MW When shortages happen, much discussion ensues about how to resolve them. It is critical that after the current wave of shortages is resolved, we do not lose our momentum and keep on working to prevent future shortages. The market is broken, which means it is not a matter of if but of when we will have these kinds of shortages again. Providers need to continue pushing for long-term legislative reforms. If not, we will be right back where we were in 2023.

H&O Is there anything you would like to add?

EF I would like to add that there is a lot of variability among hospitals in how they are affected by shortages. Some hospitals can invest a tremendous amount of money to ensure that they have extra medication on hand or can subscribe to programs that try to predict shortages. Health systems want to have predictive information

so that they can stock up ahead of these shortages. Data show that during the cisplatin and carboplatin shortages, manufacturers such as Pfizer and Fresenius Kabi increased the amount they were producing to compensate for the problem with the Intas plant.[5] This fact was not publicized, however, so some hospitals hoarded these inexpensive medications while others went without. Patients can get a very uneven experience depending on the facility. Bigger is not always better, and a small facility that is connected to a larger hospital might be better off than a large hospital. During a shortage, manufacturers and wholesalers are not required to allocate products to health systems according to past use or current patient needs.

MW I want to reiterate the need to continue pushing for long-term solutions that can help prevent shortages. The market is broken and needs resetting. Providers should not rest just because the wave of cancer drug shortages has waned; they need to push Congress to pass reforms that will generate systemic changes. In the meantime, they should push their own hospitals and clinics to pay a premium for greater supply assurance. There are a lot of innovative solutions that can provide greater supply stability at higher prices. I think it is fair to ask providers to pay more for a lifesaving drug than for a cup of Starbucks coffee, right?

Disclosures

Dr Wosińska has received funding from the National Science Foundation, the Commonwealth Fund, and Arnold Ventures for her work on drug shortages. She also serves as an expert witness on pharmaceutical antitrust cases on unrelated topics. For Dr Fox: the University of Utah (U of U) Health funds the U of U Drug Information Service (UUDIS) as a part of the Department of Pharmacy. U of U Health is a member of Vizient, a group purchasing organization. The UUDIS has a contract to provide Vizient with drug shortage information. The total value of the contract represents less than 5% of the total budget for UUDIS. No funds from Vizient are provided to Dr Fox, the associate chief pharmacy officer of shared services (includes UUDIS). Dr Fox is frequently quoted in the media in regard to drug shortages or drug pricing issues, but she does not speak on behalf of U of U Health or any other organization. Dr Fox is also a member of the advisory board for Civica Rx. This is a volunteer and unpaid position.

References

1. ASHP. ASHP meets with White House on cancer drug shortages [press release]. https://news.ashp.org/News/ashp-news/2023/07/28/ashp-meets-with-white-house-on-cancer-drug-shortages. Posted July 28, 2023. Accessed August 13, 2024.
2. Metzger ML, Billett A, Link MP. The impact of drug shortages on children with cancer--the example of mechlorethamine. *N Engl J Med.* 2012;367(26):2461-2463.
3. Wosińska ME, Frank RG. Federal policies to address persistent generic drug shortages. https://www.brookings.edu/articles/federal-policies-to-address-persistent-generic-drug-shortages/. Posted June 21, 2023. Accessed May 14, 2024.
4. United States Senate Committee on Finance. Wyden and Crapo release draft legislation to combat prescription drug shortages [press release]. https://www.finance.senate.gov/chairmans-news/wyden-and-crapo-release-draft-legislation-to-combat-prescription-drug-shortages. Posted May 3, 2024. Accessed May 14, 2024.
5. Vizient. Vizient: lack of information across supply chain exacerbating oncology drug shortage [press release]. https://newsroom.vizientinc.com/en-US/releases/releases-vizient-lack-of-information-across-supply-chain-exacerbating-oncology-drug-shortage. Posted August 23, 2023. Accessed August 13, 2024.