Senate Committee on Homeland Security and Governmental Affairs

Hearing on: “Drug Shortage Health and National Security Risks: Underlying Causes and Needed Reforms”

Statement for the Record

Submitted by Erin R. Fox, PharmD, BCPS, FASHP

Associate Chief Pharmacy Officer, Shared Services

University of Utah Health

Professor (adjunct), University of Utah College of Pharmacy

Thank you, Chairman Peters, Ranking Member Paul, and distinguished Members of the Committee, for holding this hearing and for the invitation to participate in this important discussion this morning. My name is Erin Fox, and I am the Associate Chief Pharmacy Officer for shared Services at University of Utah Health. I am not speaking on behalf of the University. I am here today to provide my perspective on drug shortages.

Background

My team and I at the University of Utah Drug Information Service have tracked national drug shortages since January 2001. We receive voluntary reports from healthcare providers across the United States (US) and we confirm directly with the manufacturer if there is or is not a shortfall of the particular presentation they sell. We post our findings to a public website that is hosted by the American Society of Health-System Pharmacists (www.ashp.org).[1] Specifically, we note which products are available as well as which products are not. We also try to list reasons for the shortage, the expected duration of the shortage, and evidence-based alternatives and safety recommendations. This information is different than the information on FDA's drug shortage website because FDA cannot provide recommendations for alternatives, even though FDA does consider substitutes when making their own market-wide shortage determinations. Our goal in providing these data is to help clinicians mitigate the effects of drug shortages on their patients and to assist clinicians with planning by providing estimated resupply dates and management suggestions.

Drug shortages are frequent. When we began tracking shortages in 2001, we identified 120 new shortages. In 2011, we saw a peak of new shortages at 267, and in 2022, we saw a total of 160 new shortages.[1] However, just because a shortage begins in one calendar year does not mean that it resolves the same calendar year or even the next year. Many shortages last for years. Since 2018, we have been tracking over 200 active and ongoing shortages. For many months in that timeframe, there were over 250 active and ongoing shortages, and at the end of 2022, we were monitoring 295 active and ongoing shortages.[1]

The most common type of drug in short supply is a generic injectable drug used in hospitals and clinics. Some current examples include local anesthetics such as lidocaine with epinephrine, steroids such as dexamethasone, and older chemotherapy agents such as cytarabine or dacarbazine. Because of shortages, patients and hospitals routinely cannot access the most basic and essential prescription medications.[2]

Causes

The cause of a specific shortage is rarely known to the public. Manufacturers are not required to publicly provide specific reasons for shortages, and we typically do not identify a reason for at least half of the shortages we track. My team asks manufacturers directly for causes and uses available FDA data and press reports to infer causes, but frequently we are unable to understand what triggered the shortage. Was it a manufacturing quality problem? A demand increase? Business decision to prioritize other products? Problems accessing ingredients? Answers to these questions can give us clues about how long a shortage will last. A

manufacturing problem takes much longer to resolve than a shipping delay. For 2022 shortages, my team could identify the reason for only 44% of them.[1]

Because drug manufacturers are not required to provide a public explanation for shortages, the best data are those summarized by FDA, which does have access to manufacturers' immediate reasons for shortages. FDA's Drug Shortages Task Force published a report in 2019 identifying supply disruptions as the key reason for shortages and economic forces as the root cause of those disruptions.[3]

First, the Task Force found that there are few incentives for manufacturers to produce difficult to make generic injectable drugs that have low profit margins. The low prices for some of these products are due to a "race to the bottom"—the result of pressure from hospitals that are paid for most hospital stays with capitated payments and group purchasing organizations (GPOs) that contract on behalf of hospitals.[4] Manufacturers cannot be expected to produce products at a loss.

Second, even if a new supplier would like to enter the market, there are significant regulatory hurdles to receive FDA approval for a product.[3] Even more challenging is building new manufacturing operations, partly due to regulatory hurdles and anecdotally, partly due to the lack of readily available capital for funding such investments for low margin generics in the US.

Third, there is no recognition for manufacturers that choose to invest in quality. FDA sees clear quality differences between products and manufacturing sites, but this information is confidential.[5] Sixty-two percent of shortages between 2013 and 2017 were due to manufacturing or quality problems based on the most current aggregate data from FDA that outlines reasons.[6]

Lack of Transparency

Purchasing medications is different from other products as there is no requirement for the manufacturer to publicly disclose which company made the product and where the product was made.[7] Currently, price is the only differentiating factor for pharmacy buyers.

Buyers can also have skewed views about a product's potential availability or the true number of manufacturers. For example, a purchaser using DailyMed[8] may see listings for 5 to 6 products. However, contract manufacturing means that one company can make a medication for multiple other companies who then put their label on the product. The true manufacturers are not known as there is no requirement to disclose this information. Market share information is also not publicly available. This means that when a shortage occurs for just one supplier, buyers can have a false sense of security about a product's availability. The situation may look like just one supplier is out of a product, but 4 to 5 others are available. However, if contract manufacturers are making the product for several companies, there may only be 2 manufacturers. Further, they cannot see that one of those products has a much larger market share than others. The public information about shortages is insufficient to buyers. This lack of information prevents making timely decisions and plans to mitigate patient impact during a shortage.

Buyers also have no information about quality when making purchasing decisions. FDA provides notices of quality issues, but most forms are highly redacted. It's impossible for a buyer to know which products are made in a particular facility. Even if we could map products to facilities, it would be difficult for purchasers or GPOs to act on that information and avoid purchases from companies with poor compliance reports. Unlike in European inspection reports, FDA's inspection reports list observations, without an indication as to how serious of a problem that observation is or what FDA recommends to remedy that observation.

Our ability to act on FDA's compliance records is also complicated by the fact that FDA is unable to hold the line on Good Manufacturing Practices (GMPs).[9] FDA exercises regulatory flexibility to mitigate the impact of shortages, in some cases allowing injections to remain on the market despite containing particles.[10] Healthcare professionals are instructed to use a filter in these cases. This regulatory flexibility has unintended consequences. Quoting from a 2013 paper[9] by Janet Woodcock and Marta Wosinska *"The FDA's need to use regulatory flexibility on behalf of patients to avert and mitigate shortages could have unintended long-term consequences when coupled with the market's lack of reward for quality. Economic models predict that, in the face of the seeming intertemporal inconsistency created by dual FDA objectives, quality investments would be lower than if the FDA could use preemptive enforcement without regard for disruptions in medically necessary products. This dynamic may further reinforce the economic incentives to minimize quality investments given the nature of competition (based on price, not quality)."*

What would be helpful to us is a rating system that would consolidate all the relevant compliance information in a way that is easy to interpret. FDA been working to develop such quality metrics system, but they do not intend to make the scores publicly available.[10]

Shortages Affect Patients

Shortages adversely impact patients, healthcare professionals, and health systems. An entire generation of clinicians has never practiced during a time without shortages. A survey from 2018 noted that 95% of medicine, anesthesiology, and emergency medicine residents have had to manage shortages, often on a daily basis, with little or no training on how to manage these situations.[12]

The true number of patients harmed by shortages is difficult to quantify as there is no national reporting system. But some examples have been documented. For example, in 2011, at least 15 patients died due to drug shortages, most as a result of medication errors where substitute drugs were dosed incorrectly or an emergency product was not available.[13] Patients also suffer when alternative drugs have worse outcomes than the drug of choice, such as patients with sepsis who had a higher mortality rate during a shortage of norepinephrine.[14] Shortages of chemotherapy have led to delayed treatments, delayed clinical trials for new therapies, reduced doses, and poor outcomes.[15]

Shortages Affect Hospital Operations

Hospitals have invested in technology such as barcode scanning, electronic health records, and automated dispensing cabinets to improve patient safety, but these systems require stable supplies of drugs. Switching products is time-consuming and challenging, especially when faced with ongoing labor shortages. For example, after Hurricane Maria devastated Puerto Rico, disrupting the operations of a key saline manufacturer, creating a critical shortage of saline, our health system went to great lengths to conserve supplies of saline bags and administer some drugs in syringes.[16] Switching just 2 drugs to be administered in syringes instead of saline bags required review and changes to 700 patient treatment plans in a single day. Because of these challenges, most health systems have one or more full-time employees devoted exclusively to shortage management.

Recommendations

Patients and hospitals need access to routine supplies of medications. I was part of the National Academies of Sciences, Engineering, and Medicine's (NASEM) consensus committee on building resilience into the nation's medical product supply chains.[17] Our committee's report provides comprehensive recommendations to build resilience and security into the supply chain, and improve the drug shortage problem. I urge you to review it.

I would like to put forward to the Committee two recommendations that build on the NASEM report.

First, in line with the NASEM report, the most important step towards resolving the problem addressing shortages is requiring additional transparency to allow for rating systems for pharmaceuticals. Ratings systems with checks from accreditation agencies would set the stage, perhaps for payers to shift hospitals to preferentially purchase products from manufacturers with higher quality and less chance of shortages.

Health systems will need to use a rating system and pay more for products from manufacturers that meet all quality standards and are able to offer more reliable supplies. Health systems are already paying more for shortages with employees and time spent making drug switches. Hospitals would be wise to consider paying more for reliable supply agreements than to spend money on staff dealing with shortages, particularly in the current setting of significant healthcare labor shortages. Payers can also incentivize hospitals to do the same to prevent poor patient outcomes and associated higher health spending.

Second, to the extent that the Federal Government intends to strengthen specific supply chains through tax credits, loans or subsidies, the government would be wise to reassess[18] which drug supply chains are most vulnerable because FDA's current list of critical medications[19] may not be a good starting point. In particular, that list was developed in response to a 2020 Executive Order[20] focusing on "outbreaks of emerging infectious diseases and chemical, biological, radiological, and nuclear (CBRN) threats." A 2021 Executive Order[21] directed vulnerability assessments for supply chains to include "extreme weather events, terrorist attacks, geopolitical and economic competition, and other conditions" but using the existing FDA list.

FDA's list of essential medicines should not be the starting point for identifying critical medicines that may need their supply chains strengthened because it is not comprehensive for essential medical care and in many cases the selections do not make sense from a clinical perspective or resource allocation perspective. It is also critical that the government supplement any updates to the list with supply-side analytics to identify vulnerabilities. For example, filgrastim is included on the list, however former FDA Commissioner Scott Gottlieb has provided significant details about how Amgen has hardened their filgrastim manufacturing to avoid any potential shortfalls no matter the threat.[22] While filgrastim is an essential medication, it's supply chain does not need strengthening. The government should seek to have a comprehensive view, not only focusing on finished dosage forms (FDF) and active pharmaceutical ingredients (API) but also on excipients and key starting materials. FDA has information on FDF and API, but not key starting materials and excipients. Without such data, we cannot know the true extent of vulnerability and target strengthening measures. From a clinical perspective, essential products like chemotherapy used in curative regimens (bleomycin, vinblastine, cisplatin) are not included on FDA's list, and all have had significant shortages in the past.

Adjusting the essential medicines list and expanding the government's analytical capabilities is important because we need both to assess the risk to supply chains, be it single source of raw material or manufacturing site, or products solely produced in countries we have tenuous relationships with. Understanding which products are most at risk would allow targeted, more effective actions to prevent or mitigate shortages with limited resources. I am concerned that without addressing the scope of the FDA list and the scope of our analytical capabilities, the government may be overlooking some critical supply chains and their vulnerabilities and opportunities to strengthen supply chains.

Thank you once again for holding this hearing and for the opportunity to share my perspective on how shortages impact patient care, healthcare professionals, and health systems. I look forward to learning more and participating in ongoing discussions on this critically important issue. I welcome any questions you may have.

References

1. ASHP (2023) Drug shortages, www.ashp.org
2. Packer-Tursman, J. UPI, U.S. drug shortages put people with life-threatening illness at risk. https://www.upi.com/Health_News/2022/09/16/drug-shortages-lorazepam-cancer/6681663190912/
3. U.S. FDA, Drug Shortages: Root Causes and Potential Solutions (2019). https://www.fda.gov/media/131130/download
4. Hernandez I, Hershey TB, Donohue JM. Drug Shortages in the United States: Are Some Prices Too Low? JAMA. 2020 Mar 3; 323(9): 819–820.

5. CDER, Office of Pharmaceutical Quality. 2022 Annual Report. https://www.fda.gov/media/165352/download

6. U.S. FDA (2019), To Reduce Drug Shortages, We Need Manufacturers to Sell Quality, Not Just Medicines. https://www.fda.gov/news-events/fda-voices/help-reduce-drug-shortages-we-need-manufacturers-sell-quality-not-just-medicine

7. Park M, Conti RM, Wosinska ME, et al. Building Resilience Into US Drug Supply Chains. Health Affairs. 2023 Jan 31. https://www.healthaffairs.org/content/forefront/building-resilience-into-us-prescription-drug-supply-chains

8. DailyMed (2023). https://dailymed.nlm.nih.gov/dailymed/

9. Woodcock J, Wosinska ME. Economic and technological drivers of generic sterile injectable drug shortages. Clin Pharmacol Ther. 2013 Feb; 93(2):170-6.

10. Jazz Pharmaceuticals. Dear Healthcare Provider (2020). Notice of *New* Special Handling Instructions Use a 0.2-micron, low protein binding, in-line filter for IV administration of ERWINAZE® (asparaginase Erwinia chrysanthemi) from BATCH 196K. https://www.fda.gov/media/138335/download

11. CDER Quality Management Maturity (2022) https://www.fda.gov/drugs/pharmaceutical-quality-resources/cder-quality-management-maturity

12. Mazer-Amirshahi M, Fox ER. Teaching Trainees to Prescribe During the Public Health Crisis of Critical Medication Shortages. J Grad Med Educ. 2020 Feb; 12(1): 44–45.

13. Institute for Safe Medication Practices. (2012) A Shortage of Everything Except Errors: Harm Associated With Drug Shortages. https://www.ismp.org/resources/shortage-everything-except-errors-harm-associated-drug-shortages

14. Vail E, Gershengorn HB, Hua M, et al. Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock. JAMA. 2017;317(14):1433-1442.

15. Fox ER, Sweet BV, Jensen V. Drug Shortages: A Complex Health Crisis. Mayo Clin Proc. 2014;89(3):361-373.

16. Mazer-Amirshahi M, Fox ER. Saline Shortages – Many Causes, No Simple Solution. N Engl J Med 2018; 378:1472-1474.

17. Consensus Committee. National Academies of Sciences, Engineering, Medicine. (2022) Building Resilience Into the Nation's Medical Product Supply Chains. https://nap.nationalacademies.org/catalog/26420/building-resilience-into-the-nations-medical-product-supply-chains

18. Wosinska ME, Frank RG. (2022) To Prevent Public Health Crises We need to Update the Essential Medical Product List. https://www.brookings.edu/blog/usc-brookings-schaeffer-on-health-policy/2022/06/24/to-prevent-public-health-crises-we-need-to-update-the-essential-medical-product-list/

19. Executive Order 13944 List of Essential Medicines Medical Countermeasures and Critical Inputs. https://www.fda.gov/about-fda/reports/executive-order-13944-list-essential-medicines-medical-countermeasures-and-critical-inputs

20. Executive Order on Ensuring Essential Medicines, Medical Countermeasures, and Critical Inputs Are Made in the United States. (2020) https://trumpwhitehouse.archives.gov/presidential-actions/executive-order-ensuring-essential-medicines-medical-countermeasures-critical-inputs-made-united-states/

21. Executive Order on America's Supply Chains. (2021). https://www.whitehouse.gov/briefing-room/presidential-actions/2021/02/24/executive-order-on-americas-supply-chains/

22. Gottlieb S. (2021) Uncontrolled Spread: Why COVID-19 Crushed Us and How We Can Defeat the Next Pandemic. Harper Collins, NY, NY.