

Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions

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Discussion Guide

Introduction

Drug shortages¹ continue to persist in the United States despite the efforts of federal agencies, health care providers, group purchasing organizations (GPOs) and distributors, and the pharmaceutical industry. In 2017, the U.S. Food & Drug Administration (FDA) reported 39 new drug and biologic shortages, as well as 41 ongoing shortages as of the end of the year.² Although the number of new shortages has declined from peaks during 2011-2013, many important products remain in shortage, including injectable saline and sodium bicarbonate.³ In general, the FDA's Drug Shortages Staff (DSS) focuses on shortages of medically necessary products that have a significant effect on public health.

Drug shortages impose numerous negative consequences on public health. Studies have estimated that responding to drug shortages costs hospitals \$216 million each year in labor costs⁴ and another \$200 million each year to substitute drugs in shortage with alternatives.⁵ However, these results likely understate the total economic and labor costs that health care providers incur to revise and review their medication dispensing procedures, update their informatic systems, and procure, prepare, and dispense alternative medications.⁶ Ultimately, neither estimate captures the significant patient harm and public health impacts that can accompany these financial burdens.^{7,8,9}

Drug shortages can harm patients in many ways. Patients may experience treatment delays, receive alternative treatments that are not as effective or well-tolerated, or may never receive treatment.^{10,11} These outcomes can prolong patient suffering, contribute to disease progression, and result in other adverse health outcomes that reduce patient well-being and increase morbidity.¹²

Empirical evidence highlights the various risks drug shortages pose to patients. In 2017, the Institute for Safe Medication Practices (ISMP)¹³ surveyed nearly 300 pharmacy directors, managers, and purchasing agents. ISMP's survey found that most respondents (71%) reported they were unable to provide patients with the recommended drug or treatment for their condition due to shortages, and nearly half (47%) thought that this resulted in patients receiving a less effective drug. Three-quarters (75%) of respondents stated that patient treatments had been delayed because of drug shortages. Some reported other types of adverse outcomes related to drug shortages, such as increased pain or discomfort during a procedure due to the unavailability of a required analgesic or sedation drugs.

The survey results also indicated that over half (55%) of all respondents reported that more than 20 drugs were involved in shortages during the 6 months prior to the survey. Shortages affected all treatment categories but were particularly notable in some critical areas. Over two-thirds of respondents reported that shortages impacted emergency care (87%), anesthesia care (85%), pain management (81%), infectious disease treatment (71%), and cardiovascular care (68%). More than half of the respondents experienced shortages that affected parenteral nutrition (55%), while one third involved obstetrics/gynecology (33%), and hematology/oncology (33%) services.

In response to persistent drug shortages and upon request from members of Congress, Dr. Scott Gottlieb, Commissioner of Food and Drugs, established the Inter-Agency Drug Shortages Task Force (Task Force) in July 2018 to identify the root causes of drug shortages and to propose enduring solutions. As part of this work, the FDA has opened a docket for public comments, held a series of listening sessions, and is convening this public meeting with the Robert J. Margolis, MD, Center for Health Policy at Duke University. Input from this meeting, as well as from the public docket and listening sessions with stakeholders, will be considered during the drafting of a report that the Task Force plans to submit to Congress.

Drug Shortages -- Potential Root Causes and Contributing Factors

To develop enduring solutions that mitigate and prevent drug shortages, it is important to understand their root causes, what drives these root causes, and what can be done to address them. Previous initiatives have tended to focus on the events that directly lead to shortages. According to FDA historic drug shortage data, nearly two-thirds of drug shortages were caused by a problem maintaining product quality.¹⁴ Other causes include challenges in sourcing raw materials, business decisions to discontinue products, and increased demand stemming from changes in the marketplace.^{15,16}

Less is known about the systemic, or root causes that drive or sustain shortages. Academic articles along with industry and government reports have discussed the systemic conditions and potential root causes of drug shortages. The Task Force continues to consider these as well as perspectives from other stakeholders throughout the drug supply chain. The Task Force is interested in hearing all perspectives regarding the contributing factors and possible root causes of drug shortages, as well as potential approaches to prevent and mitigate shortages.

Potential Root Causes

Currently, little consensus exists regarding the most significant root causes of drug shortages. Several previously-hypothesized root causes are summarized below.

1. Buyers of pharmaceutical products typically do not have information to assess reliability of supply.

In listening sessions with FDA, health care providers and administrators reported that they value a reliable supply of safe and effective drugs.¹⁷ However, FDA approval of a drug product pertains to safety and effectiveness and not the reliability of supply. Because products are not differentiated with respect to supply reliability, buyers often don't have information to assess supply reliability, making it difficult to determine how much more they might be willing to pay for improved reliability.^{18,19,20, 21}

2. Low profit margins, particularly among generic drugs, make products less attractive to produce.

Several factors apply downward pressure on profit margins. First, the generic drug market is highly competitive, and new companies entering the market may drive generic prices to levels that are too low for manufacturers to be able to sustainably produce the drug. Such depressed prices potentially drive established competitors out of the market. Second, increasing market power among purchasing organizations can lead to reduced prices for certain drugs, decreasing profit margins and making certain products less attractive to produce. In recent years, consolidation among purchasing organizations such as wholesalers, GPOs, and pharmacy benefit managers (PBMs) has required manufacturers to compete for fewer available contracts.^{22,23,24} Third, research indicates that changing reimbursement rates may

play a role in drug shortages. For instance, one study suggests that 2006 changes in Medicare Part B's drug reimbursement rates²⁵ reduced the returns on certain sterile injectable products, an outcome that some researchers suggest could have further increased the risk of these drugs going into shortage.²⁶

With lower prices in place for these drugs, manufacturers may face pressure to either exit these markets or cut back on investments in quality and supply reliability, including investments in additional manufacturing capacity. Commodity pricing can also limit the incentive for manufacturers to invest in upgrading their equipment and maintaining supply capability. Over time, decisions to forego investments and upgrades can contribute to manufacturing deficiencies that lead to shortages.

Besides making it difficult to invest in capital infrastructure and maintain production, slim profit margins also present ongoing quality challenges. Some have posited that changes to FDA's approach around Current Good Manufacturing Practices have imposed additional costs on manufacturers that then triggered market exit.²⁷ Others believe, however, that FDA has occasionally been too flexible with respect to the sale of potentially lower quality products during drug shortages, discouraging proactive steps to maintain product quality.²⁸

3. When a shortage does occur, manufacturers face barriers to market entry that impede their ability to address the shortage. Complexity and lack of agility in the production process coupled with market uncertainty associated with long lead times for production make market entry challenging. In addition, preparing applications, paying fees associated with the Generic Drug User Fee Amendments (GDUFA) program, and waiting on approval^{29,30} involve costs to drug sponsors that may pose particular barriers in markets where potential profits and revenues are already low. However, FDA has made major improvements under the GDUFA program to shorten review times and help increase first-review cycle approvals for ANDAs and supplements.^{31,32} The increased funding under GDUFA II has allowed FDA to build a more robust generic drug review program with improved transparency and support for generic drug sponsors. The result is a more efficient and predictable review process that has yielded fewer average review cycles and more first cycle approvals. Thus, industry can take products to market faster and make more proactive and accurate business plans.

Contributing Factors

In addition to the root causes described above, there are numerous factors that if addressed proactively could reduce the likelihood that a supply or demand disruption precipitates a drug shortage. Generally, addressing these factors involves decisions about how much inventory to hold, as well as how much to invest in the ability to maintain or rapidly increase production.

Certain characteristics of manufacturing and supply have the potential to reduce supply chain resiliency. For example, just-in-time manufacturing may lead to less inventory on hand to mitigate unexpected shortages. Participants in FDA's listening sessions noted that agreements among intermediaries (e.g., GPOs, PBMs, distributors) and health care providers may require providers to purchase a certain percentage of their volume from drug purchasers, limiting their flexibility to seek alternate suppliers and potentially encouraging stockpiling of hard-to-get medicines. Furthermore, the increasing globalization of sourcing and production limits the flexibility of manufacturers to make quick changes to their supply chain if challenges arise.³³

Multi-Stakeholder Proposals to Eliminate Drug Shortages

Although individual agencies within the federal government and private organizations have worked to address drug shortages, persistent shortages of important products highlight the need for further stakeholder collaboration and new ideas to address root causes. The following approaches that have already been undertaken may serve as guiding principles for developing new and enduring solutions.

Other Efforts Intended to Address Drug Shortages

As drug shortages continue to cause negative health and economic consequences, public- and private-sector organizations have developed strategies to prevent and mitigate them. At the same time, academics have focused attention on supply-chain economics to identify causes and propose possible solutions.

Most of FDA's efforts to date have addressed the immediate causes of drug shortages, without focusing expressly on identifying and remedying root causes. For example, in 2013 FDA issued a [Strategic Plan for Preventing and Mitigating Drug Shortages](#) to strengthen FDA's policies and procedures regarding responses to shortages.³⁴ With the enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, manufacturers of most drugs that are life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition are required to notify FDA of a permanent discontinuance or an interruption in manufacturing that is likely to lead to a meaningful disruption in supply in the United States.³⁵ In addition, FDA has used expedited reviews and inspections, as well as regulatory flexibility, to help ensure access to medically necessary products during drug shortages.³⁶

FDA has also taken steps within its regulatory authority to address the root causes and contributing factors for drug shortages. For example, FDA is developing a quality metrics program for pharmaceutical manufacturers. Information generated could be used by FDA to identify drugs at greater risk of shortage and proactively reduce that risk before a disruption occurs.³⁷ Another FDA initiative encourages manufacturers to adopt advanced manufacturing technologies that increase production reliability and capacity (e.g., continuous manufacturing).³⁸ To support this effort, FDA has established an Emerging Technology Program to foster dialogue between FDA and manufacturers as they work to develop and implement these approaches.

Beyond the work of FDA, non-government stakeholders have established task forces³⁹ and developed reports and tools to evaluate and respond to the root causes and factors contributing to drug shortages. In 2014, the International Society for Pharmaceutical Engineering (ISPE) released its Drug Shortages Prevention Plan,⁴⁰ and in 2015 they followed with a Drug Shortage Assessment and Prevention Tool intended to be used by manufacturers to document and ameliorate their supply chain vulnerabilities.⁴¹ In 2017, the Pew Charitable Trust, in collaboration with ISPE, released a report that examined the structure of the supply chain and potential economic challenges that may contribute to drug shortages.⁴² In September 2018, the National Academies of Sciences, Engineering, and Medicine (NASEM) held a public meeting to explore ways to better anticipate and respond to shortages driven by natural disasters.⁴³

Through a partnership with the University of Utah Drug Information Service, the American Society of Health-System Pharmacists (ASHP) offers a publicly accessible database of current and resolved drug shortages. Medications are added to the ASHP database when the shortage is verified with the manufacturer and it affects the way a pharmacy prepares or dispenses a product, or when the use of an alternative product is required. The [ASHP Drug Shortage Resource Center](#) also contains information to help clinicians understand and navigate shortages, including ASHP guidelines on managing drug product shortages.

Many non-governmental stakeholders have also taken steps to identify and in some cases implement innovative solutions to respond to drug shortages. Some GPOs have invested in creating private drug labels and contracting with API suppliers and manufacturers themselves, directly supporting the production of critical medicines.⁴⁴ Recently, more than 120 health organizations have extended this strategy and created a not-for-profit generic drug company that will manufacture, or sub-contract manufacturing of, critical hospital-administered drugs.⁴⁵ Furthermore, academic researchers have developed and modeled proposals to reduce the incidence of drug shortages. For example, one study argues for implementing supply-chain contracts that pair higher prices with stronger failure-to-supply clauses.⁴⁶

While U.S. stakeholders continue to grapple with persistent shortages, it may also be useful to explore how other nations are working to address shortage challenges. In France, for example, more than 500 drugs experienced supply interruptions in 2017, a 30% increase from 2016. A French Senate task force identified numerous vulnerabilities in the supply chain and recently developed recommendations to address shortages in France and across Europe.⁴⁷

Developing Enduring Solutions

Despite the efforts of many stakeholders, persistent drug shortages continue to cause public health burdens in the United States. Developing new and enduring solutions to drug shortages will require stakeholders to address the systemic root causes and contributing factors that lead to shortages. At their core, these solutions would need to impact the economic environment and incentives that supply-chain actors and institutions face around product quality, supply chain resiliency, and reimbursement for pharmaceuticals. Any approaches need to achieve the desired outcome without imposing undue burdens on the health care system or society. In addition, they need to be developed carefully to avoid unintended consequences.

Potential areas of action might include, but would not be limited to, contracting, tax incentives, increased transparency of manufacturing quality, reimbursement or regulatory changes, as well as any other solutions as appropriate.⁴⁸ The Task Force will evaluate proposed solutions for feasibility and potential effectiveness and cost-effectiveness as it develops its report to Congress. This meeting will provide an opportunity to begin fostering a dialogue between the Task Force and other affected stakeholders, to begin tackling this vital public health challenge, and to avert downstream adverse health and economic consequences.

¹ The Food, Drug & Cosmetic Act (FD&C Act) defines a drug shortage as a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug. FD&C Act s. 506C(h)(1) (21 U.S.C. 356c(h)(1)).

² U.S. Food and Drug Administration. Report on Drug Shortages for Calendar Year 2017. <https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM610662.pdf>. Accessed October, 2018.

³ U.S. Food and Drug Administration. Current and Resolved Drug Shortages and Discontinuations Reported to FDA. FDA Drug Shortages. <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>. Accessed October 16, 2018.

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⁵ Drug shortages cost U.S. care providers at least \$200 million annually, pose patient safety risks, research suggests [news release]. Charlotte, NC: Premier healthcare alliance; March 28, 2011. <https://bit.ly/2zqYhg9>. Accessed September 24, 2018.

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⁸ McBride A, Holle LM, Westendorf C, et al. National survey on the effect of oncology drug shortages on cancer care. *Am J Health Syst Pharm*. 2013;70(7):609-17.

⁹ Vail E, Gershengorn HB, Hua M, Walkey AJ, Rubinfeld G, Wunsch H. Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock. *JAMA*. 2017;317(14):1433-1442.

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¹² Ventola CL. The drug shortage crisis in the United States: causes, impact, and management strategies. *P T*. 2011;36(11):740-57.

¹³ Drug Shortages Continue to Compromise Patient Care. Institute for Safe Medication Practices website. <https://www.ismp.org/resources/drug-shortages-continue-compromise-patient-care>. Published January 11, 2018. Accessed on October 18, 2018.

¹⁴ U.S. Food and Drug Administration. Drug Shortages Infographic. <https://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm441579.htm>. Accessed October 16, 2018.

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¹⁶ Pauwels K, Simoens S, Casteels M, Huys I. Insights into European drug shortages: a survey of hospital pharmacists. *PLoS ONE*. 2015;10(3):e0119322.

¹⁷ In September and October 2018, FDA held a series of stakeholder listening sessions to bring together small groups of nationally recognized experts on the drug supply chain and leaders of organizations representing broad segments of the health care system.

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¹⁹ Fox ER, Tyler LS. Call to action: finding solutions for the drug shortage crisis in the United States. *Clin Pharmacol Ther*. 2013;93(2):145-7.

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²¹ Kweder SL, Dill S. Drug shortages: the cycle of quantity and quality. *Clin Pharmacol Ther*. 2013;93(3):245-51.

²² Fein, AJ. The Outlook for Pharmacy Benefit Management: Evolution or Disruption? Talk presented at: PBMI 2018 National Drug Benefit Conference; March 5, 2018; Palm Springs, CA. http://drugchannelsinstitute.com/files/PBMI-PBM_Outlook-Drug_Channels-Fein-Mar2018-Handouts.pdf. Accessed October 16, 2018.

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