Drug Shortages:

Root Causes and Potential Solutions

2019

Executive Summary

FDA U.S. FOOD & DRUG ADMINISTRATION

ACKNOWLEDGMENTS

This report is based on work of a Federal task force chaired by the U.S. Food and Drug Administration (FDA). FDA is grateful for the valuable contributions of all participating and consulting agencies and for their assistance in developing this report. The full version of this report is available on the FDA website at http://www.fda.gov/media/131130/download.

FDA thanks the following agencies for their participation in the Drug Shortages Task Force:

- *Centers for Medicare and Medicaid Services, Department of Health and Human Services*
- *Department of Defense*
- *Department of Veterans Affairs*
- *Federal Trade Commission*
- *Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services*

FDA thanks the following agencies for consultations in preparing this report:

- *Defense Advanced Research Projects Agency*
- *U.S. Department of the Treasury*
- *Drug Enforcement Administration, U.S. Department of Justice*

The following FDA centers and offices were instrumental in developing and producing this report:

- *Office of the Commissioner*
- *Center for Drug Evaluation and Research*
  - *Office of the Center Director*
  - *Office of Compliance*
  - *Office of Executive Programs*
  - *Office of Generic Drugs*
  - *Office of Pharmaceutical Quality*
  - *Office of Regulatory Policy*
  - *Office of Strategic Programs*
- *Center for Biologics Evaluation and Research*
- *Center for Devices and Radiological Health*
- *Center for Veterinary Medicine*
- *Office of Regulatory Affairs*

A Report by the Drug Shortages Task Force

2019 Executive Summary

Drug Shortages:

Root Causes and Potential Solutions

The full version of this report is available on the FDA website at http://www.fda.gov/media/131130/download

Drug Shortages Pervade Many Aspects of Patient Care

Shortages can worsen patients' health outcomes by causing delays in treatment or changes in treatment regimens, such as substituting less effective therapies, when a drug of choice is not available. Even when alternatives to the preferred drug are available, a patient's care may be compromised. According to a recent study, 56 percent of hospitals reported they had changed patient care or delayed therapy in light of drug shortages; 36.6 percent said they had rescheduled non-urgent or emergent procedures.

Childhood Cancer

Drug shortages can have a drastic impact on the most vulnerable patients. An estimated 90 percent of the 3,000 children afflicted with T-cell acute lymphoblastic leukemia (ALL) are curable (5-year event-free survival). However, many of the drugs used to treat children with ALL (the most common childhood cancer) are older drugs, potentially making them more vulnerable to shortage. From 2009-2019, 9 of the 11 drugs used to treat ALL were in and out of shortage. Despite recent evidence that adding nelarabine to children's treatment regimens improves survival rates and is thus becoming the new standard of care, nelarabine has been in shortage recently, causing much anguish and grief for patients, parents, and clinicians.

"I am caring for a 12-year-old girl with newly diagnosed T-cell acute lymphoblastic leukemia. As soon as the diagnosis was confirmed, I reached out to pharmacy colleagues who confirmed that our hospital had no nelarabine. Nelarabine was recently proven to improve survival in children like my patient with T-cell ALL. Through their herculean efforts, enough nelarabine was secured for at least the first cycle of treatment. It remains to be seen whether we will be able to obtain enough drug for subsequent cycles."

— Yoram Unguru, MD, MS, MA, The Children's Hospital at Sinai, Johns Hopkins Berman Institute of Bioethics

Septic Shock

A shortage of norepinephrine in 2011 led to some patients with septic shock being treated with alternative drugs. When patients with septic shock were admitted to hospitals experiencing the shortage, they were more likely to die than at hospitals not experiencing the shortage.

Palliative Care

Bleomycin is used for palliative treatment of a number of forms of cancer including Hodgkin and non-Hodgkin lymphoma. In 2016, a severe shortage of bleomycin led to use of alternative treatment regimens. Although just as effective, the alternatives require inpatient stay, increasing stress for patients and families, potentially exposing patients to pathogens in the hospital environment, and substantially increasing costs.

Anesthesia and Sedation

Drug omissions due to shortages negatively impact patient care and the patient experience. Lidocaine is used to diminish the burning sensation often associated with propofol, a common anesthetic. The American Association of Nurse Anesthetists reports that a lidocaine shortage has resulted in patients who receive propofol feeling a burn on induction, leading to agitation at precisely the time a patient should be relaxed and without stress as they undergo sedation or anesthesia.

Drug Shortages: Root Causes and Potential Solutions

2019 Executive Summary

In June 2018, a bipartisan group of 31 U.S. Senators and 104 members of the House of Representatives wrote to Scott Gottlieb, MD, then Commissioner of Food and Drugs, to ask for assistance in addressing the Nation's drug shortage crisis. Their letters urged the Food and Drug Administration (FDA or "the Agency") to convene a task force to study the problem, prepare a report on the root causes of drug shortages, and make recommendations for enduring solutions. The full version of this report is available on the FDA website at http://www.fda.gov/media/131130/download.

In response to this request from Congress, the FDA convened an inter-agency Drug Shortages Task Force ("Task Force") of senior officials drawn from its own ranks and several partner Federal agencies.[1] The Agency invited public participation through a public meeting on November 27, 2018 with a docket to receive comments, and invited stakeholders to a series of listening sessions. The Task Force commissioned a team of FDA economists and other scientists to analyze drugs that went into shortage between calendar years 2013-2017 with a view to understanding the underlying forces that were driving them. The analysts relied on the statutory definition of drug shortage, as a period of time when the demand or projected demand for the drug within the U.S. exceeds the supply.[2] The Agency is now issuing this report containing the Task Force's analysis of root causes and recommendations for addressing them. Although the focus of the report is on human drugs,[3] many of the same concerns apply to veterinary medicines used to treat service, companion, and food-producing animals.[4]

---

1. The Drug Shortages Task Force brings together officials not only from the U.S. Food and Drug Administration, but also from several partner agencies including the Centers for Medicare and Medicaid Services, the Department of Defense, the Department of Veterans Affairs, the Federal Trade Commission, and the Office of the Assistant Secretary for Preparedness and Response within the Department of Health and Human Services (HHS). In addition, the Task Force consulted with officials from the Defense Advanced Research Projects Agency, the U.S. Department of the Treasury, and the Drug Enforcement Administration within the U.S. Department of Justice. This Task Force is not to be confused with a previously established drug shortage task force, which was formed in 2012 to implement some provisions of FDASIA and has focused its activities on preventing and mitigating actual drug shortages.
2. The Federal Food, Drug, and 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)(2) (21 U.S.C. 356c(h)(2)). The statutory definition of "drug shortage" is not limited to medically necessary drugs.
3. Section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)(1)) provides that the term "drug" means: "(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C)."
4. Under certain conditions, the Animal Medicinal Drug Use Clarification Act of 1994 allows for the use of approved human drugs in animals. Because veterinarians, especially those in the companion animal field, often use human drugs in their patients, shortages of human drugs can affect veterinary medicine.

As the Congressional letters noted, drug shortages, including those that arise during emergencies, have been a persistent problem despite public and private sector efforts to prevent and mitigate them. Analysis presented by FDA at the November 2018 public meeting showed that the number of ongoing drug shortages has recently been increasing after declining from a peak in 2011, and drug shortages have been lasting longer, in some cases more than 8 years. FDA analyzed 163 drugs that went into shortage in the 5-year period between 2013 and 2017. Of the 163 drugs[5] in the sample, 63 percent (103) were drugs administered by injection ("sterile injectables") and 67 percent (109) were drugs that have a generic version on the market.[6] They were also older drugs, with a median time since first approval of almost 35 years. After many years off patent, the injectables typically were sold at relatively low prices. In the year prior to going into shortage, the median per unit price was $8.73 for all the shortage drugs, $11.05 for injectables, and $2.27 for orally administered drugs.[7, 8]

Information from health care providers, patients, and research studies suggests that the clinical and financial effects of shortages are substantial.

Information from health care providers, patients, and research studies suggests that the clinical and financial effects of shortages are substantial. However, comprehensive data about these effects are lacking and FDA believes that some recent attempts to quantify the impacts have underestimated them. Purchasers need more information on the clinical and financial impacts of shortages on patients and health care delivery to make informed buying decisions, which could play a role in preventing and mitigating drug shortages. Having high-quality quantitative data would help determine which strategies, or combinations thereof, would prove most useful in addressing the problem.

5. For purposes of this analysis, FDA defined a drug as a unique combination of active ingredient(s), route of administration, and dosage form — potentially grouping together multiple strengths, types of packaging, and manufacturers. These 163 drugs corresponded to 130 shortages as defined by FDA.
6. About half (47 percent) of the 163 drugs studied that went into shortage between 2013 and 2017 were both generics and sterile injectables.
7. FDA analysis of IQVIA data. The prices are the average 12-month price prior to the shortage start date with a 3-month leave-out period. The prices are inflation-adjusted to August 2018 based on the Producer Price Index for Pharmaceuticals. Per unit means per injection for injectables, and per pill or capsule for orally administered drugs. IQVIA, formerly Quintiles and IMS Health, Inc., is an American multinational company serving the combined industries of health information technology and clinical research.
8. These percentiles were calculated by comparing the earlier prices of shortage drugs to the prices of all other drugs with the same dosage form sold during that period. The aggregate numbers are then the mean of these percentiles within each group (injectables, orally administered, all drugs).

ECONOMIC FORCES ARE THE ROOT CAUSES OF DRUG SHORTAGES

Drug shortages persist because they do not appear to resolve according to the "textbook" pattern of market response. In this more typical pattern, prices rise after a supply disruption and provide an incentive for existing and new suppliers to increase production until there is enough supply of a product to meet demand. In this respect, the market for prescription drugs and especially generic drugs differs from other markets. A prime question that the Task Force sought to answer is, why does the drug market differ?

After reviewing the FDA analysis, published research studies, and stakeholder input, the Task Force identified three major root causes:

- ***Root Cause 1: Lack of Incentives to Produce Less Profitable Drugs.*** When market conditions limit manufacturers' profitability, they reduce a firm's motivation to maintain a presence in, or enter the market for older prescription drugs, and to invest in manufacturing quality and redundant capacity. Manufacturers of older generic drugs, in particular, face intense price competition, uncertain revenue streams, and high investment requirements, all of which limit potential returns. Current contracting practices contribute to a "race to the bottom" in pricing.

- ***Root Cause 2: Market Does Not Recognize and Reward Manufacturers for Mature Quality Management Systems.*** All manufacturers must meet regulatory requirements for adherence to Current Good Manufacturing Practices (CGMPs), which set a minimum threshold that companies must achieve in order to be allowed to supply the U.S. marketplace. Mature quality management, however, starts with a foundational quality management system that conforms to CGMPs and builds in a performance and patient focus that utilizes technology, statistical process control, and planning activities to ensure a reliable supply of the drugs manufactured at the facility.

  Currently, purchasers have only limited information that can be used to assess the state of quality management of any specific facility and have little information linking the drug products they buy with the facilities where they were manufactured. The lack of information does not enable the market to reward drug manufacturers with price premiums for mature quality management, back-up manufacturing capabilities, or risk-management plans, nor does it penalize manufacturers that fail to invest in modernization of manufacturing equipment and facilities to ensure a reliable supply. Thus, manufacturers are more likely to keep costs down by minimizing investments in manufacturing quality, which eventually leads to quality problems, triggering supply disruptions and shortages.

- ***Root Cause 3: Logistical and Regulatory Challenges Make It Difficult for the Market to Recover After a Disruption.*** Over the past two decades, the drug supply chain has become longer, more complex and fragmented as companies have located more production overseas (U.S. Department of Commerce 2011 and Van Den Bos 2009) and increased the use of contract manufacturers (Kuehn 2018). Although typical markets would respond to a shortage by increasing production, logistical and regulatory challenges, especially the complexity of the supply chain, can limit the ability of drug manufacturers to increase production. When companies wish to increase production, either by modifying an existing facility or building a new one, they may have to obtain approvals from many different national regulatory bodies, and/or find a new source of active pharmaceutical ingredients (APIs). If a new manufacturer wants to enter the U.S. market and start selling a drug that addresses a shortage, the manufacturer must first develop and file an application with FDA and await its approval.

RECOMMENDATIONS FOR ENDURING SOLUTIONS

Although a complex array of factors contributes to the occurrence and prolongation of drug shortages, the root causes themselves are foundational. They reflect market behavior driven by a search for cost savings in the face of a seemingly inexorable rise in health care spending. Quantifying the extent and effects of drug shortages and addressing the problem over the long term will require the active participation of private sector players – purchasers, intermediaries, and manufacturers – as well as the public sector. To address the root causes of shortages, the Task Force offers three recommendations:

RECOMMENDATION 1: CREATE A SHARED UNDERSTANDING OF THE IMPACT OF DRUG SHORTAGES AND THE CONTRACTING PRACTICES THAT MAY CONTRIBUTE TO THEM

Despite providers' widespread recognition that drug shortages profoundly affect health care delivery in the United States, there has been little private or public sector effort to collect and analyze comprehensive information to characterize shortages, quantify their effects, or closely observe the contracting practices that may be driving them. Some of the areas most needing attention are the following:

- ***Quantification of the harms of drug shortages, particularly those that lead to worsened health outcomes for patients and increased costs for health care providers***
  Previous efforts to assess the costs of drug shortages have generally been limited in scope and depth, but nevertheless suggest that the total national impact of shortages may be very large ("Identifying the Root Causes of Drug Shortages" 2018, slide 40). Given that FDA has recognized and posted on its website more than one hundred shortages at a single point in time,[9] it will require additional research to assess the full impact of shortages on patient outcomes and, more generally, on health care delivery and health care system costs. Previous estimates, at hundreds of millions of dollars annually (Kacik 2019; Kaakeh et al. 2011; "Drug Shortages Cost U.S. Care Providers" 2011), may have drastically underestimated the harms of drug shortages.

- ***Better characterization of shortages***
  Currently, neither private nor public sector stakeholders quantitatively characterize shortages in terms of their frequency, persistence, or intensity; nor do they quantify the impact of shortages on available treatments in specific therapeutic categories.[10] Having this information available to the public would help improve the understanding across all stakeholders of the impact shortages have on the Nation's health care, and support public and private strategies to prevent and mitigate shortages.

- ***Greater transparency in private sector contracting practices***
  Generic drug manufacturers have cited contracting practices as a source of business uncertainty and "race to the bottom" pricing dynamics. FDA heard from stakeholders that some contracts currently include "low-price clauses" that allow group purchasing organizations (GPOs) to unilaterally walk away from a contract if a competing manufacturer is willing to supply the same product or bundle of products for a lower price. FDA also reviewed evidence that "failure-to-supply clauses" in contracts are

---

9. CDER's drug shortage list is accessible at https: www.accessdata.fda.gov/scripts/drugshortages/default.cfm; CBER's drug shortage list is accessible at https: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages

10. FDA publishes data on current shortages on its website and makes annual reports to Congress on the number of new shortages and the number of continued shortages by year, however. See https://www.fda.gov/media/130561/download

sometimes relatively weak (Haninger et al. 2011). More systematic study of current contracting practices is needed and could support development of model contracts designed to promote reliable access to safe, effective, and affordable drugs.

RECOMMENDATION 2: CREATE A RATING SYSTEM TO INCENTIVIZE DRUG MANUFACTURERS TO INVEST IN ACHIEVING QUALITY MANAGEMENT SYSTEM MATURITY

The second root cause of drug shortages, as discussed above, is that the market does not recognize and reward mature quality management systems. This recommendation aims to rectify this failure by suggesting the development of a system to measure and rate the quality management maturity of individual manufacturing facilities based on specific objective indicators. The rating would evaluate the robustness of a manufacturing facility's quality system and reward facilities that achieve a high degree of quality system maturity.

Historically, many pharmaceutical manufacturing firms have focused their efforts on compliance with CGMPs, which include standards for material systems, equipment and facilities, production, laboratory, packaging and labeling, and a quality system. These standards, however, are foundational and set a minimum threshold that companies must achieve in order to be allowed to supply the U.S. marketplace. They do not include more advanced levels of quality management, which aim to robustly detect vulnerabilities and address them in order to prevent the occurrence of problems, nor do they establish a culture that rewards process and system improvements. As companies move from a focus on compliance with CGMPs to institutionalizing continual process and system improvement efforts, they begin to advance in quality management maturity.

A rating system could be used to inform purchasers, GPOs, and even consumers about the state of, and commitment to, the quality management maturity of the facility making the drugs they are buying. Pharmaceutical companies could, at their discretion, disclose the rating of the facilities where their drugs are manufactured. GPOs and purchasers could require disclosure of the rating in their contracts with manufacturers. This effort would introduce transparency into the market, and provide firms committed to quality management maturity with a competitive advantage, potentially enabling them to obtain sustainable prices as well as grow market share.

RECOMMENDATION 3: PROMOTE SUSTAINABLE PRIVATE SECTOR CONTRACTS

The combination of more complete information about contracting practices and greater transparency of the quality management maturity of specific manufacturing sites would enable payers, purchasers, and GPOs to consider new contracting approaches aimed at ensuring a reliable supply of medically important drugs. The objectives of these contracts should address the first two root causes discussed above by:

- ***Providing financial incentives***
  Contracts should ensure that manufacturers earn sustainable risk-adjusted returns on their investment in launching or continuing to market prescription drugs, especially older generic drugs that remain important elements of the medical armamentarium.

- ***Rewarding manufacturers for mature quality management***
  Similarly, contracts should recognize and reward manufacturing quality maturity. This could be done through several different mechanisms, such as paying higher prices for drugs manufactured at top-rated facilities, requiring a certain quality maturity rating as a condition of contracting, or guaranteeing purchase of a set volume of products from sites achieving a certain quality maturity rating.

FDA INITIATIVES TO PREVENT AND MITIGATE DRUG SHORTAGES

In addition to the recommendations above, there are several legislative proposals and planned FDA initiatives that focus primarily on enabling the Agency to help prevent supply disruptions from leading to shortages and mitigating shortages when they occur.

- ***Improved data sharing***
  A legislative proposal in the President's FY 2020 budget would expand the information required to be provided to the FDA about interruptions in manufacturing under section 506C(a) of the Federal Food, Drug, and Cosmetic Act (FD C Act) and would authorize FDA to impose penalties for failing to provide timely and adequate notification.

- ***Improved data sharing guidance***
  By the end of calendar 2019, FDA plans to publish a new draft guidance for industry that will further discuss the requirement in section 506C(a) of the FD&C Act for manufacturers to notify FDA of a permanent discontinuance in the manufacture of certain products or an interruption in the manufacture of certain products that is likely to lead to a meaningful disruption in supply of that product in the U.S. The guidance will also request that manufacturers provide additional details about the situation to ensure FDA has the specific information it needs to help prevent or mitigate shortages.

- ***Risk management plan requirement***
  A legislative proposal in the President's FY 2020 budget would authorize the Agency to require application holders of certain drugs to conduct periodic risk assessments to identify vulnerabilities in their manufacturing supply chain and develop plans to mitigate the risks of the identified vulnerabilities.

- ***Risk management plan guidance***
  By the end of calendar 2019, FDA plans to publish a new draft guidance for industry, "Risk Management Plans to Mitigate Potential for Drug Shortages." This guidance would outline a new recommendation for pharmaceutical stakeholders to develop, implement, and maintain a risk management plan for the purpose of preventing and mitigating drug shortages.

- ***Lengthened expiration dates***
  A legislative proposal in the President's FY 2020 budget would authorize FDA to require, when likely to prevent or mitigate a shortage, that an applicant evaluate, submit studies to FDA, and label a product with the longest possible expiration date (shelf life) that FDA agrees is scientifically justified. Shortages can be exacerbated if drugs must be discarded because they exceed a labeled shelf life based on unnecessarily short expiration dates.

- ***ICH Guideline Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management***
  This internationally harmonized guideline is currently being finalized. This guideline outlines ways to enhance understanding of product and process development and establish an effective pharmaceutical quality system. Incentives for adopting these guidelines include opportunities for less stringent regulatory oversight of certain post-approval manufacturing changes. Global implementation of this guideline, once finalized, could facilitate the efforts of manufacturers who wish to modernize processes and equipment, but have found the regulatory landscape to pose a financial burden.

CONCLUSION

The Task Force believes that there is no simple solution for addressing drug shortages. The root causes of shortages involve economic factors that are driven by both private and public sector decision making. The types of enduring solutions proposed here will require multi-stakeholder efforts and rethinking of business practices throughout the health care system. A fuller characterization of the true costs of shortages and more comprehensive and reliable information about their effects on patients and the health care system would be an important component, as they would better enable purchasers to factor the costs of shortages into their buying decisions. Recognizing and rewarding quality manufacturing would provide companies an incentive to achieve greater reliability in production, thus reducing the risk of supply disruptions and shortages. Finally, changes in how drugs are paid for, including potential changes in contracting, could enable generic manufacturers to charge sustainable prices for their products. Given the potential scale of impacts from drug shortages, and the fact that these impacts have continually been underestimated, it is likely that drug shortages will continue to persist absent major changes to this marketplace.

CITATIONS

Haninger, K, et al., 2011, Economic Analysis of the Causes of Drug Shortages, ASPE Office of Science and Data Policy
Accessed September 27, 2019
https://aspe.hhs.gov/report/economic-analysis-causes-drug-shortages

Kaakeh, R, et al., 2011, Impact of Drug Shortages on U.S. Health Systems, American Journal of Health-System Pharmacy (AJHP): 68 (19): 1811-1819
Accessed September 27, 2019
https://www.ncbi.nlm.nih.gov/pubmed/21930639

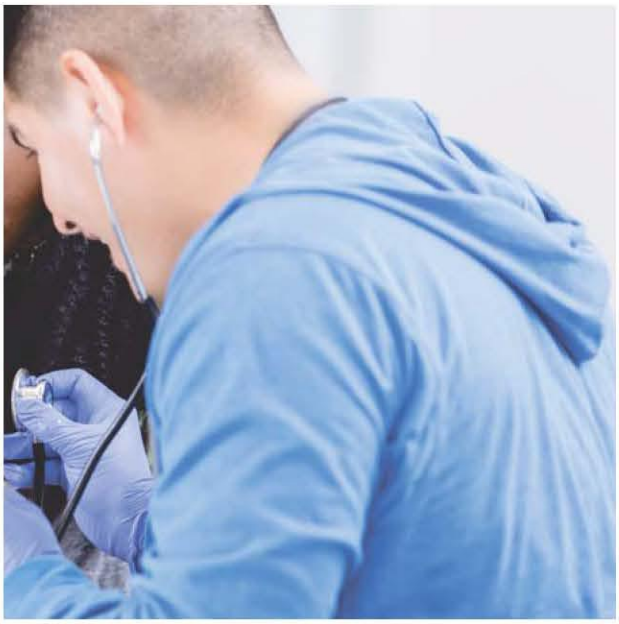
Kacik, A, 2019, Drug shortages drain at least $359M from health systems, Modern Healthcare, June 26
Accessed September 27, 2019
https://www.Modernhealthcare.Com/Finance/Drug-Shortages-Drain-Least-359m-Health-Systems

Kuehn, S, 2018, Pharmaceutical Manufacturing: Current Trends and What's Next, CEP Magazine
Accessed August 1, 2019
https://www.aiche.org/resources/publications/cep/2018/december/pharmaceutical-manufacturing-current-trends-and-whats-next

U.S. Department of Commerce, Bureau of Industry and Security, Office of Technology Evaluation, 2011, Reliance on Foreign Sourcing in the Healthcare and Public Health (Hph) Sector: Pharmaceuticals, Medical Devices, and Surgical Equipment
https://www.hida.org/App_Themes/Member/docs/GA/Industry-Issues/Emergency-Pandemic/Dept-Commerce-Study_Healthcare-Foreign-Sourcing.pdf

Van Den Bos, J, 2009, Globalization of the Pharmaceutical Supply Chain: What are the Risks?
Health Watch, Issue 61, May 2009

U.S. FOOD & DRUG ADMINISTRATION



Drug shortages can harm patients and impose burdens on healthcare providers.