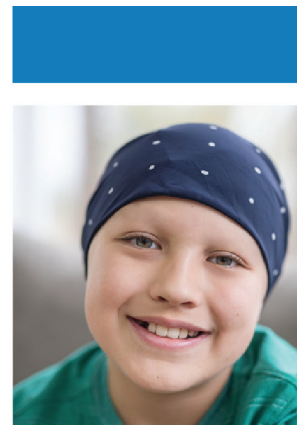


Drug Shortages:

Root Causes and Potential Solutions

2019



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Drug Shortages: Root Causes and Potential Solutions

A Report by the Drug Shortages Task Force

2019



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- 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

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- 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
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- Center for Devices and Radiological Health
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Contents

Acknowledgments.....	1
Executive Summary	4
Economic Forces Are the Root Causes of Drug Shortages	5
Recommendations for Enduring Solutions	7
Recommendation 1: Create a Shared Understanding of the Impact of Drug Shortages and the Contracting Practices That May Contribute to Them	7
Recommendation 2: Create a Rating System to Incentivize Drug Manufacturers to Invest in Achieving Quality Management System Maturity	8
Recommendation 3: Promote Sustainable Private Sector Contracts	8
FDA Initiatives to Prevent and Mitigate Drug Shortages	9
Conclusion	10
Drug Shortages: Root Causes and Potential Solutions	11
Introduction.....	11
Impact on Patients and Health Care Providers	15
Effects on health care delivery systems	19
Financial burdens	21
Root Causes of Drug Shortages	22
Evidence for Root Causes.....	33
Recommendations for Enduring Solutions	47
FDA Initiatives to Prevent and Mitigate Drug Shortages.....	52
Conclusion	54

Appendix A: Bibliography.....	55
Appendix B: Quality Management Maturity	66
Appendix C: U.S. Food and Drug Administration	73
Proposed Legislation and Planned and Current FDA Initiatives	73
Stakeholder Proposals to FDA.....	77
Appendix D: Agencies and Offices Participating in the Drug Shortages Task Force	84
Centers for Medicare and Medicaid Services	85
Defense Advanced Research Projects Agency and HHS Office of the Assistant Secretary for Preparedness and Response	90
Department of Defense	92
Department of Veterans Affairs.....	94
Drug Enforcement Administration	96
Federal Trade Commission.....	98
HHS Office of the Assistant Secretary for Preparedness and Response	102
U.S. Department of the Treasury	104
Appendix E: A Framework for Enduring Solutions to Drug Shortages	106
Appendix F: Technical Summary of FDA’s Analysis	107
Background.....	107
Dataset Development	109
Key Findings.....	110

Drug Shortages: Root Causes and Potential Solutions

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.

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 the Food and Drug Administration Safety and Innovation Act (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 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 drugs⁵ that went into shortage in the 5-year period between 2013 and 2017. Of the 163 drugs 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. 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.

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?

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. This means that a shortage can consist of more than one drug. For example, a shortage might comprise both the tablet and capsule versions. As a result, 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).

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.

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://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>.

- **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 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 management 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 system 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 remedying 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.

Drug Shortages: Root Causes and Potential Solutions

Introduction

This report responds to a written request from Congress. 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.

In response to the Congressional request, the FDA convened an interagency Drug Shortages Task Force (“Task Force”) of senior officials drawn from its own ranks and several partner Federal agencies.^{1,2} 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 its supply.³ The Agency is now issuing this report containing the Task Force’s analysis of root causes and recommendations for addressing them. Although the

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² The Commissioner’s 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 the Food and Drug Administration Safety and Innovation Act (FDASIA) and has focused its activities on preventing and mitigating actual drug shortages.

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focus of the report is on human drugs⁴, many of the same concerns apply to veterinary medicines used to treat service, companion, and food-producing animals.⁵

As the Congressional letters noted, drug shortages have been a persistent problem, despite public and private sector efforts to prevent and mitigate them. Analysis presented by the 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 eight years (“Identifying the Root Causes of Drug Shortages” 2018, slides 32-37). FDA analyzed 163 CDER-regulated drugs⁶ that went into shortage in the 5-year period between 2013 and 2017. Of the 163 drugs 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.⁷ 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.^{8,9} **(See Figure 1)** When compared with all marketed drugs with the same dosage form during the same period, including both generics and brands, the prices of the shortage drugs were at the 36th percentile of prices, while the prices of injectables that were in shortage were at the 33rd percentile and oral products in shortage were at the 46th percentile. **(See Figure 2)**

⁴ 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).”

⁵ 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.

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⁷ About half (47 percent) of the 163 drugs studied that went into shortage between 2013 and 2017 were both generics and sterile injectables.

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⁹ 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).

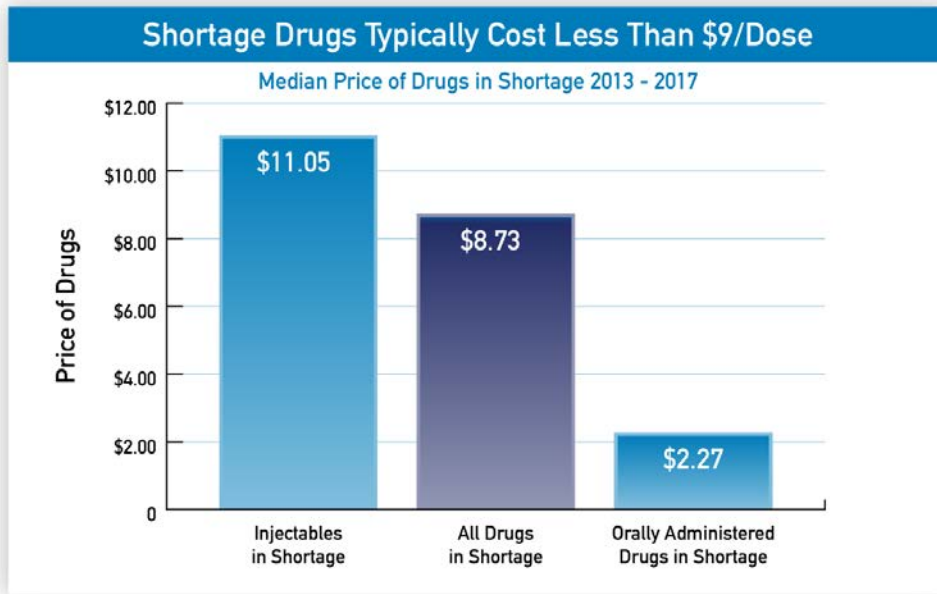


Figure 1. Median price of drugs in shortage from 2013 – 2017 was less than \$9 per dose.

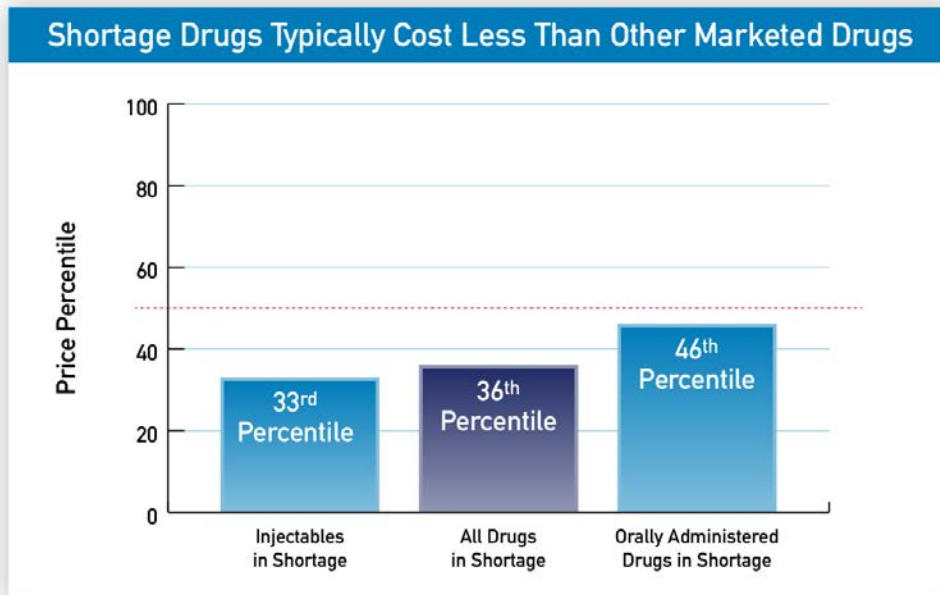



Figure 2. When compared with all marketed drugs with the same dosage form during the same period, including both generics and brands, the prices of the shortage drugs were only at the 36th percentile of all drug prices, while the prices of injectables that were in shortage were at the 33rd percentile and oral products in shortage were at the 46th percentile.

The rest of this report examines some of the impacts of drug shortages on patients and the U.S. health care delivery system; identifies the root causes responsible for drug shortages; presents evidence based on the FDA economic analysis, published research studies, and stakeholder perspectives; and presents solutions that are likely to be most effective against the root causes over the long term.



Drug shortages can harm patients
and impose burdens on health
care providers

Impact on Patients and Health Care Providers

Drug shortages can have a devastating effect on patients who may experience treatment delays, receive alternative treatments that are not as effective or well-tolerated, or may have to forgo treatment (McLaughlin et al. 2013; Pauwels 2014). 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 (Ventola 2011).

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 report based on a survey of U.S. community hospitals, 56 percent of hospitals reported they had changed patient care or delayed therapy during FY 2015 – 2017 because of drug shortages; 36.6 percent said they had rescheduled non-urgent or emergent procedures (“Recent Trends in Hospital Drug Spending” 2019).

Empirical evidence highlights the various risks drug shortages pose to patients. In 2017, the Institute for Safe Medication Practices (ISMP) (“Drug Shortages Continue to Compromise Patient Care” 2018) surveyed nearly 300 pharmacy directors, managers, and purchasing agents. ISMP's survey found that most respondents (71 percent) reported that in the 6 months prior to the survey, they were sometimes unable to provide patients with the recommended drug or treatment for their condition due to shortages, and nearly half (47 percent) thought that this resulted in patients receiving a less effective drug. Three-quarters (75 percent) 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 procedures due to the unavailability of appropriate analgesic or sedation drugs.

The survey results also indicated that over half (55 percent) 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 affected emergency care (87 percent), anesthesia care (85 percent), pain management (81 percent), infectious disease treatment (71 percent), and cardiovascular care (68 percent). More than half of the respondents experienced shortages that affected parenteral nutrition (55 percent), while one third involved obstetrics/gynecology (33 percent), and hematology/oncology (33 percent) services.



Of pharmacy directors, managers, and purchasing agents responding to a national survey about drug shortages:

- 71% were unable to provide patients with a recommended drug or treatment
- 47% said this resulted in patients receiving a less effective drug
- 75% reported that patient treatments were delayed

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 newly diagnosed with 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. 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.”

— Dr. Yoram Unguru, MD, MS, 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.



Effects on health care delivery systems

Increased time spent managing and coping with drug shortages takes resources – such as staff time – that could otherwise be used to treat patients.

- Staffing needs may increase when employees must spend time managing shortages, including prioritizing procedures due to limited drug availability and rationing drugs for the highest priority cases.
- Pharmacists may need to conduct costly and time-consuming searches to find the drug in question or its alternatives.
- Emergency response teams must reconfigure procedures and retrain responders when drugs that are routinely used in emergencies are not available and substitutions are required.
- Hospitals, clinics, and other care settings may need to modify IT systems to accommodate changes in available drugs and ensure that dosing and dispensing of the substitutions are accurate. They may also need to find other suppliers, renegotiate contracts, delay infrastructure investments, and undertake other time-consuming and costly processes.
- Despite the scope and scale of these effects, most hospitals and other health systems have not comprehensively quantified the costs of managing drug shortages and the total cost to the nation's health care delivery system is not known.

Despite the scope and scale of shortages' impact on health care delivery, most hospitals and other health systems have not comprehensively quantified the costs of managing drug shortages. The total cost to the Nation's health care system remains unknown.



Drug Shortages Impact Life-Saving Nutritional Therapies

“Parenteral nutrition provides life-saving therapy for patients with gastrointestinal dysfunction or complete intestinal failure. Some patients require life-long, life-sustaining therapy to provide adequate nutrition; others in the acute-care setting only. Patients receiving this therapy cover the entire lifespan from neonates to the elderly.

Parenteral nutrition is composed of a complex mixture of sterile injectables and may include as many as 40 ingredients. Since 2010, every component of parenteral nutrition has been in short supply at least once, including multiple vitamins, which have been in short supply for eight years. For many of the products, there is only one source. As a result, patients may receive ever-changing formulations and specific nutrients may be eliminated completely when there is no alternative. Changes to complex parenteral mixtures can lead to adverse patient outcomes such as from a nutrient deficiency. Tragically, neonates have died due to zinc deficiency.

An additional consequence of these shortages is that younger clinicians including physicians, nurse practitioners, pharmacists, and dietitians are not always versed in appropriate doses of particular nutrients. They have been working under shortage conditions their entire career. I have polled young clinicians and they've never had the opportunity or the privilege of prescribing this therapy in a world where they had every component in full supply. That's quite concerning as we look at the education and training of those who may be prescribing parenteral therapy.”

— Statement from Beverly Holcombe, PharmD, BCNSP, FASHP, FASPEN, American Society for Parenteral and Enteral Nutrition at public meeting about drug shortages, November 2018



Every day in emergency departments across the country, providers are discussing what medicines might or might not be available for care.

- Having to constantly find alternatives to drugs delays treatment.
- New processes and protocols must be created each time another medication shortage is announced.
- Emergency department staff and first responders working in the field must be trained and re-trained on which drugs to use in particular cases.
- Overall, shortages cause inconvenience and risk for patients, frustration for emergency care providers, and higher costs for care.

Financial burdens

When drugs are in shortage, their prices may increase, placing financial burdens on patients, providers, and payers (Dave et al. 2018; Hernandez et al. 2019).¹⁰ Additionally, drugs used as substitutes may be more expensive or may not optimize clinical therapy when compared to the original drug of choice. Shortages of critical medications and subsequent rising drug prices are affecting patient care and straining hospital budgets and operations, according to a 2019 report released by the American Hospital Association, the Federation of American Hospitals, and the American Society of Health-System Pharmacists. According to this report, almost 80 percent of hospitals said drug shortages resulted in increased spending on drugs to a moderate or large extent (“Recent Trends in Hospital Drug Spending” 2019).

Studies have estimated that responding to drug shortages costs hospitals \$359 million each year in labor costs (Kacik 2019) and another \$200 million each year to substitute drugs in shortage with alternatives (“Drug Shortages Cost U.S. Care Providers” 2011). However, these reports likely understate the total impact of drug shortages as they were unable to quantify the amount

¹⁰ FDA analysis found sustained price increases for only 18% of drugs that went into shortage in 2013- 2017, as will be explained below.

hospitals spent on additional staffing, overtime wages, other staff benefits and overhead, updating technology, and the loss of revenue caused by postponing medical procedures. Ultimately, neither estimate captures the potential patient harm and significant public health impacts that can accompany these financial burdens (Metzger et al. 2012; McBride et al. 2013; Vail et al. 2017).

Root Causes of Drug Shortages

Basic economic theory holds that in instances where demand exceeds supply, prices typically rise, thereby providing an incentive for existing and new suppliers to increase production until there is a sufficient supply of a product to meet demand. Drug shortages, however, persist after supply disruptions despite some price increases. In this respect, the market for prescription drugs and especially generic drugs, which account for most drug shortages, appears quite unusual. The Task Force sought to determine why the drug market is so different from many other markets.

To understand this difference and identify the underlying drivers of drug shortages, the Task Force relied on findings from a team of FDA economists and other scientists who analyzed a sample of drugs that went into shortage during calendar years 2013-2017.¹¹ The Task Force also looked at other published research studies and considered stakeholder comments made at a public meeting and submitted to FDA in a related docket. Finally, the Task Force considered information provided to FDA in individual listening sessions with stakeholders and in meetings with organizations representing stakeholders throughout the supply chain.

Evidence from FDA's analysis, supported by the published literature and stakeholders' testimony, points to economic factors as the major drivers of drug shortages. Drug manufacturers make business decisions across the life cycle of a drug: e.g., whether to launch a new product; to maintain an existing product; or to invest in improvements in manufacturing facilities or remediating a facility where problems have occurred. If a manufacturer anticipates that a drug will be unprofitable or have uncertain profitability, its management may decide not to launch the drug, even when holding an approved biologics license application (BLA), new drug application (NDA), or abbreviated new drug application (ANDA). If the firm is already marketing the drug and its profitability erodes, management may discontinue production or make minimal investments in manufacturing, leading to supply disruptions. These disruptions may result in

¹¹ The 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 506C(h)(2) (21 U.S.C. 356c(h)(2)). The statutory definition of "drug shortage" is not limited to medically necessary drugs. FDA presented some of its analysis of drugs in shortage at a public meeting in November 2018. See https://healthpolicy.duke.edu/sites/default/files/atoms/files/duke-fda_drug_shortages_presentation_slides_0.pdf, especially beginning at slide 30.

shortages. Without sustained profitability, the cycle of minimal investment in manufacturing, disruption, and shortage will continue.

After reviewing the FDA analysis, 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.
 - **Unfavorable pricing dynamics.** Over the past few decades, sectors of the health care system – including hospital systems, group purchasing organizations (GPOs),¹² wholesalers, and the pharmaceutical industry – have consolidated to achieve efficiencies and increase negotiating power with suppliers and customers. For example, GPOs have consolidated their market power, so that by 2018 the four largest GPOs accounted for about 90 percent of the market for medical supplies in the United States (Bruhn et al. 2018). As a result, GPOs have been able to negotiate low prices, especially for multi-source generics.

Furthermore, prevalent contracting practices often constrain the ability of manufacturers to raise their prices, while leaving them open to price challenges from competitors who may try to undercut them to gain market share. When a manufacturer is confronted with a price challenge, the management usually has a choice of either meeting the challenge by lowering its price, even to an unsustainable level, or losing market share. As a result, prescription drug manufacturers may face "a race to the bottom" and in some cases end by selling the drug at or below its cost to manufacture.

- **Price sensitivity among health care providers.** Consistent with standard business practices, purchasers look for the lowest possible price, especially when unable to measure reliability or effective quality management of product manufacturing. Additionally, reimbursements under bundled payments and managed care contracts may increase price sensitivity. Thus, providers are motivated to reduce their costs wherever it is feasible to do so.

¹² A Group Purchasing Organization is an entity that enables health care providers – including hospitals, nursing homes, surgery centers and clinics, and home health agencies – to realize savings by aggregating their purchasing volume and using that as leverage to negotiate discounts with manufacturers, distributors, and other vendors.

- **Disconnect regarding the impact of purchasing decisions on shortages.** High-volume drug buyers, including group purchasing organizations and large hospital or pharmacy chains, may not have adequate incentives to purchase drug products from potentially more reliable (and possibly costlier) suppliers. A drug buyer typically bears only a small portion of the costs of a shortage while other parties (health care providers, third party payers, and patients) bear larger portions. As described above, these costs extend to many aspects of health care.

Information from stakeholders suggests that such drug buyers may select the supplier of a low-priced drug, even if a competing and otherwise identical drug product is available from a more reliable supplier for only a modest premium. Stakeholders suggest that these decisions may result from high-volume buyers lacking information about the impact of shortages. In addition, parties bearing most of the costs of shortages may not have contractual or other relationships with high-volume buyers that could allow them to communicate the importance and value of reliable supplies of drugs of requisite quality. This disconnect between high-volume buyers and those most affected by shortages may contribute to the lack of incentives for manufacturers of drug products to invest in systems that would improve reliability and manufacturing quality.

- **High investment requirements.** Manufacturers must often make expensive capital investments in manufacturing facilities and processes to enter or remain in the market. For example, expanding or modernizing a manufacturing facility capable of producing multiple products can take one or more years and can cost more than \$100 million (Ferierra et al. 2016). Manufacturers of sterile injectable products must also invest in highly specialized equipment to produce their products, adding additional costs.¹³ They typically evaluate the risk-adjusted return on this investment in making business decisions.
- **Business uncertainty.** Because of the intensely competitive nature of the prescription drug market, especially for generics, manufacturers may find it difficult to forecast a product's revenues, volumes, and profit margins. In addition, they may face uncertainty in managing an increasingly global supply chain. With many manufacturing sites located overseas, changes in exchange rates, labor costs, or regulatory requirements in other countries could suddenly increase costs and reduce the profitability of a firm's product portfolio.
- **Manufacturing capacity constraints.** Most generic manufacturers cannot afford to support redundant capacity and must make decisions about how to make the best use of their available capacity. Management may have little incentive to

¹³ <https://www.particlesciences.com/blog/aseptic-manufacturing-and-sterile-fill-finish-for-complex-drug-products/>

continue marketing a less profitable drug, particularly if the firm has opportunities to market more profitable drugs that can be manufactured on the same equipment.¹⁴

- **Root Cause 2: Market Does Not Recognize and Reward Manufacturers for Mature Quality Management Systems.** The prescription drug market, especially for generic drugs but also for brand drugs, often does not provide incentives for manufacturers to invest in current manufacturing technologies and improvements in quality management. As noted above, drugs in shortage are typically older drugs, with a median time since first approval of almost 35 years. Following first approval, continual technical improvement and updating is needed because facilities age, routine operations require updates to maintain a state of control, technology evolves, suppliers change, and scientific expectations may also change. A failure to implement such updates and improvements can lead to quality problems that result in drug shortages.

Historically, many pharmaceutical manufacturing firms have focused their efforts on compliance with Current Good Manufacturing Practices (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 to prevent the occurrence of problems, as well as establishing a culture that rewards process and system improvements. As companies move from focusing on compliance with CGMPs to institutionalizing continual process and system improvement efforts, they begin to advance in quality management maturity.

- Several factors contribute to the market’s failure to recognize and reward quality management maturity.
 - **Challenges in assessing quality management maturity.** A quality management system is a collection of business processes focused on consistently meeting expectations, expressed as the organizational goals and aspirations, policies, processes, documented information and resources needed to implement and maintain quality. Quality management maturity is a measure of the consistency and reliability of business processes related to an organization’s goals (see Appendix B).

¹⁴ In FDA’s conversations with stakeholders, some manufacturers stated that they would continue to produce an unprofitable prescription drug if it is in shortage or at risk of going into shortage, or if it fills a needed space in a broader portfolio of products. Hence, the profitability of the individual drug is not the only criterion that the pharmaceutical industry uses in making business decisions to continue production.

FDA inspects manufacturing facilities and takes regulatory action, if needed, to enforce CGMP regulations. The Agency's investigators look for deficiencies in meeting CGMPs, but these assessments of CGMP compliance do not measure how far the facility is above the CGMP requirements in its quality management systems. Simple adherence to CGMP standards does not indicate that a firm is investing in improvements or planning or deploying statistical process control techniques that could better enable it to prevent supply disruptions.

Even when a firm does invest in such improvements, it may be difficult to identify measures of quality that could be used to predict operating outcomes, such as shutdowns of manufacturing lines resulting in supply disruptions.¹⁵ And even if these measures were readily available, FDA might not have access to the needed data regarding the performance of the manufacturing facility.

This is why it is critical that industry progress towards quality management maturity. Some pharmaceutical firms have been slow to implement robust, mature quality systems and the accompanying quantitative measures of quality that have been the foundation of success in other industries, such as automotive and aerospace (Fuhr et al. 2014). These industries exercise quality oversight by vigilantly monitoring ongoing process performance and product quality data, and promptly correcting operations when needed. Numerous organizations and quality experts have worked to develop conceptual models and standards for advancing the maturity of industrial quality management systems, as discussed in Appendix B. These models could be used more broadly in the pharmaceutical industry to improve supply reliability and shift from doing only what is necessary to meet CGMP requirements to proactively focusing on achieving quality management maturity.

- **Lack of transparency across the supply chain.** In general, product-specific information regarding supply chains is tightly guarded by firms as trade secret or commercial confidential information (Department of Homeland Security 2018). Purchasers of drugs, and intermediaries such as GPOs, generally have little or no information linking the drug products they buy, or contract for, with the specific sites where they were manufactured. In addition, they have only limited information that could be used to assess the quality management maturity of specific sites. This lack of transparency, coupled with difficulty assessing quality

¹⁵ Despite these challenges, FDA supports the development and use of quality metrics. FDA has recently published two *Federal Register Notices* to collect information from industry stakeholders on quality management programs now in use by industry. For more information, see Appendix C. In November 2016 FDA published a draft guidance for industry entitled "[Submission of Quality Metrics Data.](#)" proposing to initiate a voluntary industry reporting program of selected quality metrics. Data from the quality metrics reporting program would be used to focus FDA's resources on the areas of highest risk to public health: e.g., by identifying establishments and products that may pose significant risks to consumers, or that have the potential for supply disruptions.

management maturity, makes it challenging for health care providers and GPOs to distinguish manufacturers based on whether they can consistently and reliably provide adequate supplies of a drug. Instead, they tend to differentiate between competing drug products, particularly generics, based solely on price. Similar transparency issues apply to active pharmaceutical ingredient (API) manufacturers, leading drug manufacturers to prioritize API procurement based on price, rather than quality.

- **Lack of market reinforcement of effective quality management maturity.** Because of the limited information available about the effectiveness of a drug firm's quality management maturity and health care providers' drive to cost reduction, the market does not compensate drug manufacturers with price premiums for mature quality management, which could include proactive steps such as establishing risk management plans and identifying back-up manufacturing capabilities. Conversely, the market does not penalize manufacturers that fail to invest in modernization of manufacturing equipment and facilities to assure a reliable supply. Although manufacturers' contracts with GPOs may include "failure to supply" clauses intended to create an incentive to provide a reliable supply, these are generally weak (Haninger et al. 2011). Thus, manufacturers who invest minimally in facilities or risk management and experience supply disruptions may face little more than transient loss of some revenue and reputation.
- **Root Cause 3: Logistical and Regulatory Challenges Make It Difficult for the Market to Recover After a Disruption.** Logistical and regulatory challenges can limit the ability of drug manufacturers to increase production after a supply disruption has occurred. 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 increased the use of contract manufacturers (Kuehn 2018). 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 APIs. Supply recovery is particularly a problem for drugs that already have few suppliers. For example, generic drug markets tend to have very few application holders actively supplying the market (Berndt et al. 2017; Conti and Berndt 2019),¹⁶ so when one firm ceases production, e.g., to remediate a manufacturing problem, its competitors would need to increase output substantially to meet demand.

This root cause is closely connected with unfavorable price dynamics mentioned above, because the financial investment, time, and management attention required to build new

¹⁶ Conti and Berndt 2019 found that forty percent of generic drug markets were supplied by only one manufacturer, and the median number of manufacturers per drug market was two.

or increase established production capacity may reduce the incentive for manufacturers to launch or increase production of a shortage product.

- **Logistical challenges.** Firms face capital, technological and sourcing challenges that make it difficult to expand production capacity. As mentioned above, expanding or modernizing a plant can take one or more years and cost more than \$100 million (Ferierra et al. 2016). Sterile injectables also require additional specialized equipment to produce and may be even more expensive.¹⁷ Since drug manufacturing facilities typically operate above 80 percent capacity (U.S. Census, 2019), pharmaceutical firms often cannot increase production substantially without incurring additional costs associated with purchasing new equipment or new property and a critical mass of qualified personnel. In turn, this makes it very difficult for firms to increase production when a shortage occurs.

Manufacturers also face difficulties in changing their API source; e.g., when they need to increase production or respond to a disruption from their API supplier. One major challenge is identifying an API source that is of high quality and complies with global regulatory requirements.¹⁸ Although FDA lists approved API suppliers and recently inspected API manufacturing facilities, there is no complete, centralized source of information on API suppliers, so firms often incur time and expense seeking such suppliers. In addition, changing API suppliers generally requires additional FDA approvals (Mallu et al. 2015).

According to FDA data on regulated manufacturing facilities for approved application products, in 2018, 88 percent of the manufacturing sites making APIs and 63 percent of sites making finished dosage forms (FDFs) were located overseas (FDA Internal Memorandum 2019; Van Den Bos 2009).¹⁹ (See **Figure 3 and Table 1**) Although these moves may have resulted in cost savings, they have also made it more difficult for firms to coordinate across the entire supply chain and enforce quality management in manufacturing sites.

¹⁷ <https://www.particlesciences.com/blog/aseptic-manufacturing-and-sterile-fill-finish-for-complex-drug-products/>

¹⁸ API facilities are included in the [FDA Inspections Classification Database](#), which includes final classifications for surveillance inspections of all API facilities in the human pharmaceutical program. This database includes results of FDA inspections and where FDA has made use of an inspection conducted by a capable inspectorate under the Mutual Recognition Agreement (MRA). API facilities not currently supplying the U.S. market would not be included in this database. Furthermore, the Database does not list the products being made at the facilities.

¹⁹ These numbers apply to manufacturers named in approved applications. Medical gas, compounding, pending application and non-application (OTC) facilities are excluded.

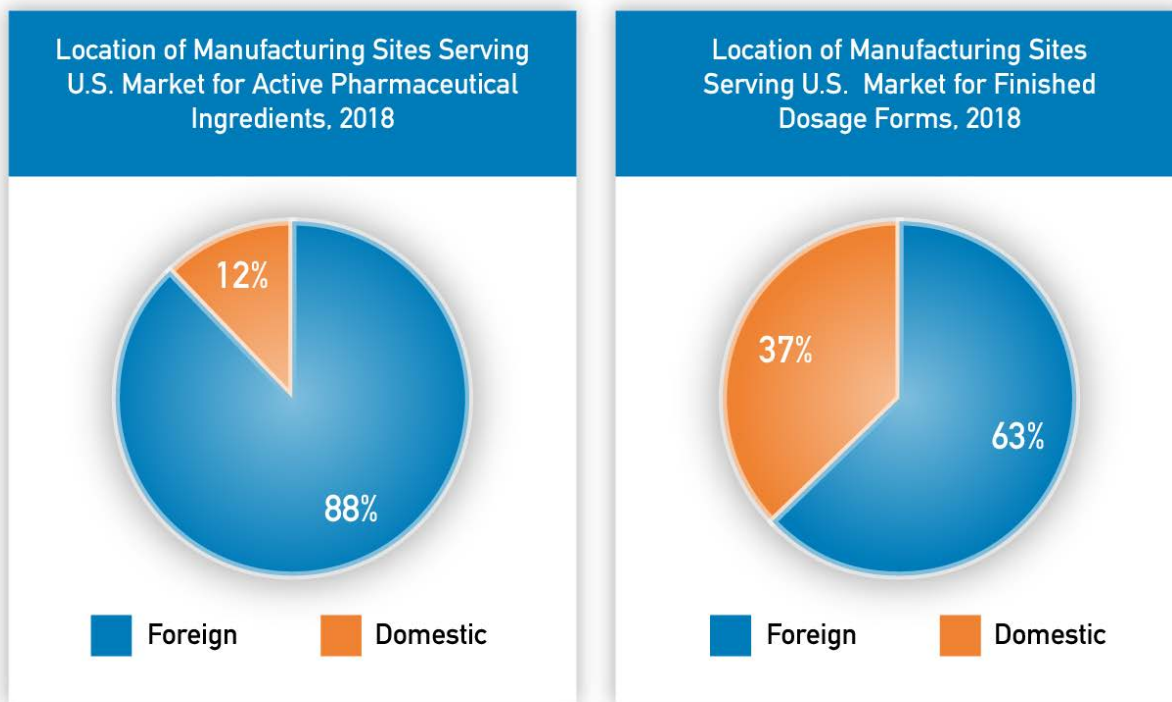


Figure 3. In 2018, the majority of manufacturing sites making active pharmaceutical ingredients and finished dosage forms for the U.S. market were located abroad.²⁰

²⁰ These numbers apply to manufacturers named in approved applications. Medical gas, compounding, pending application and non-application (OTC) facilities are excluded.

Regional Distribution of Facilities Manufacturing Finished Dosage Forms and Active Pharmaceutical Ingredients in 2018.		
Region	FDF MANUFACTURE	API MANUFACTURE
Canada	4%	0%
China	8%	14%
EU	18%	31%
India	24%	31%
Latin America	0%	2%
Rest of World	10%	11%
USA	37%	12%
Total	100%	100%

Table 1. For finished dosage forms (FDFs), the predominant overseas contributors were located in EU countries and India. For active pharmaceutical ingredients (APIs), the predominant overseas manufacturers were located in European Union countries, India, and China.²¹ (Percentages in table have been rounded.)

- **Regulatory requirements.** In general, after a drug has been approved by FDA and is on the market, a manufacturer wishing to expand capacity through alternative suppliers (e.g., for API) or alternative manufacturing sites (e.g., for the finished product) must submit a regulatory filing to have the new supplier or manufacturing facility approved by FDA.²²

Many drug manufacturers supplying the U.S. market are in fact global operations that also supply other regions. Making post-approval changes to update manufacturing operations generally requires that they seek approval not only from FDA but the regulators in the other markets. According to industry observers, many post-approval changes to regulatory filings require prior approval by the

²¹ These numbers apply to manufacturers named in approved applications. Medical gas, compounding, pending application and non-application (OTC) facilities are excluded.

²² See generally 21 CFR 314.70.

regulatory authority of every country individually, and this can be over 100 countries for globally marketed products. The global approvals for changes can often take years because of varying requirements and timelines across different regulatory authorities, and this creates disincentives for timely improvements to manufacturing operations that could reduce the risk of drug shortages.

For example, when the International Society for Pharmaceutical Engineering (ISPE) developed a model timeline for upgrading aseptic processing equipment or facilities, it found that it would take approximately seven years from the initial planning phase to secure approval from all global health authorities (ISPE 2014). ISPE noted that because health authority reviews are not performed in parallel, manufacturers normally must maintain dual operations until they receive all approvals. The risks and technical complexities associated with these dual operations, including the increased complexity of material management and related supply chain modifications, may increase the chance for a drug shortage and help explain why some manufacturers are reluctant to upgrade their aseptic equipment and facilities.

Finally, manufacturers wishing to address a drug shortage by bringing to market the drug product in shortage, can find the effort both time-consuming and costly. For example, some studies have estimated that, for small-molecule generic drugs, it can cost \$1 million to \$5 million and take between 3 to 5 years to prepare an application for FDA approval.²³ If an original ANDA²⁴ could help mitigate or resolve a drug shortage and prevent future shortages, FDA may give it priority status for review (FDA MAPP 5240.3). The performance goals of the Generic Drug User Fee Amendments of 2017 call for 90 percent of priority ANDAs to be reviewed and acted on within 8 months or 10 months, depending on their type (GDUFA II Commitment Letter 2018).

Based on available data, however, the Task Force believes that the cost and speed of gaining an ANDA approval are unlikely to be major factors in causing or extending shortages. FDA analysis shows that as of June 2019, for all generic drugs with approved applications, 39 percent were observed to be marketed, and the remaining 61 percent were approved but not marketed.²⁵ (See **Figure 4**) The

²³ <https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf>. The Agency notes that the cost and timeframe cited in this study may not accurately reflect the cost to develop and file a generic version of an older, off-patent injectable drug, which is the primary profile of the majority of drug shortage products in FDA's analysis.

²⁴ An abbreviated new drug application (ANDA) contains data that are submitted to FDA for the review and potential approval of a generic drug product. (Source: [FDA](#))

²⁵ As of June 2019, 1,671 products had an active generic application and at least one approved brand or generic application listed in the active section of FDA's [Orange Book: Approved Drug Products with Therapeutic](#)

gap between total approved applications and those that are marketed is even more extreme for the drugs that were in shortage between 2013 and 2017, as will be discussed below in the FDA Analysis section. Rather than the speed of ANDA approval, pharmaceutical firms' disinclination to market drugs for which they are already holding an approved ANDA may contribute substantially to shortages.

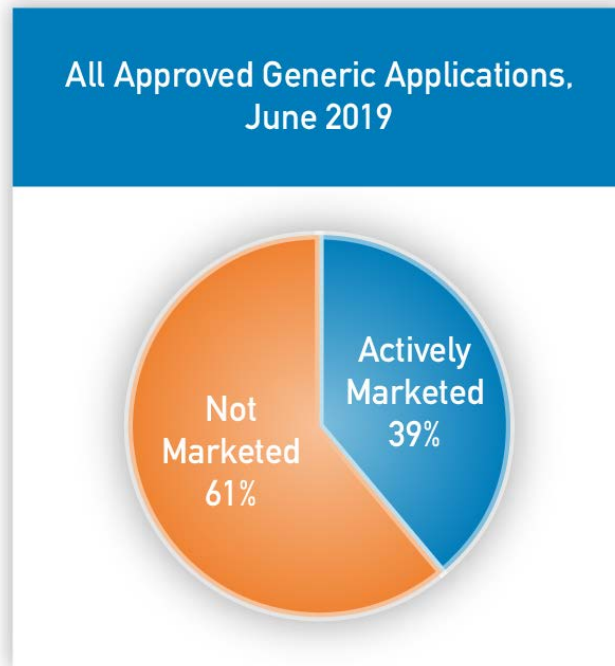


Figure 4. As of June 2019, for all generic drugs with approved applications, 39 percent were observed to be marketed, and the remaining 61 percent were approved but not marketed.

The economic forces driving drug shortages arise primarily from private sector behavior, including business decisions made by pharmaceutical firms, GPOs and other intermediaries in the supply chain, as well as drug purchasers such as hospitals and other health care providers. However, these business decisions may be affected by FDA regulation and by reimbursement

Equivalence Evaluations. In this context, FDA defines a product as approved applications with unique combinations of active ingredients, dosage form, and route of administration, ignoring strength and package size. For these products there were 17,848 total approved applications, or about an average of 10.7 with a median of 7 approved applications. These data exclude products for which all applications are listed in the discontinued section of the Orange Book, as they have effectively left the market and are no longer available. Marketed applications had (1) an active NDC listed in FDA's NDC Directory for June 2019, and (2) positive sales in the IQVIA National Sales Perspective database from June 2018 through June 2019. Based on these criteria, we identified 6,982 applications as marketed. Thus, for each product there is an average of 4.2 marketed applications and a median of 3 marketed applications.

policies including those established by Federal programs, such as Medicare and Medicaid, and by private payers.

Evidence for Root Causes

As discussed above, to identify the root causes, the Task Force relied on evidence from FDA’s analysis of drug shortages and published research studies. It also considered stakeholder contributions made at a public meeting with a related docket, at listening sessions with stakeholders, and in FDA meetings with organizations representing stakeholders throughout the supply chain.

FDA Analysis

Drug shortages often follow the lifecycle pattern shown in **Figure 5** below. Root causes, which may be accompanied by other contributing factors, lead to an event or situation that triggers a supply disruption: that is, a temporary market imbalance in which the demand for a product exceeds its supply. Root causes may exacerbate a supply disruption as well as initiate one: e.g., the lack of a financial incentive to market or increase production of a less profitable drug may constrain an increase in supply. Not all supply disruptions lead to shortages, since actions can be taken in between that prevent the onset of a shortage, but nearly all shortages are preceded by supply disruptions.

If a supply disruption persists, it becomes a drug shortage, an extended period in which existing and new suppliers are unable to increase production enough to meet U.S. demand. Eventually, suppliers increase production and/or demand for the product falls until the drug is available to everyone who wants it and the shortage is resolved.

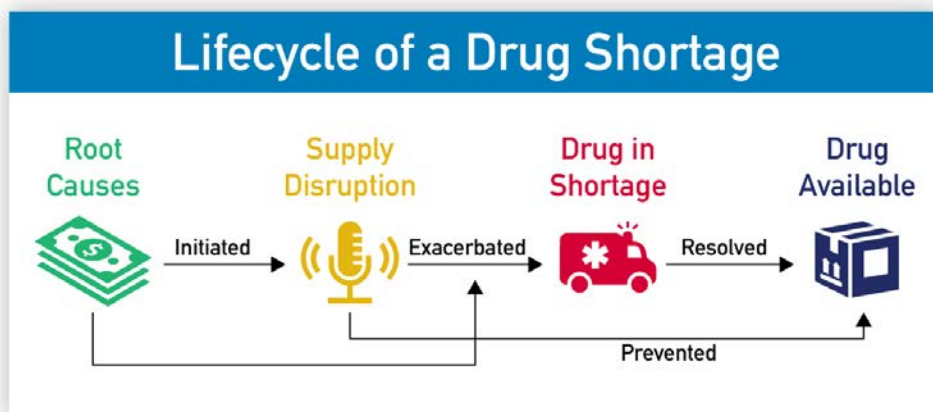


Figure 5. Root causes lead to a supply disruption. When exacerbated, this disruption becomes a shortage that may be resolved when production increases or demand decreases.

As mentioned earlier, to capture information about market forces that may have been active both during the period leading up to a drug shortage and the period after the shortage had occurred, a team of FDA economists examined a sample of 163 drugs in the Agency’s database that first

went into shortage between calendar years 2013 and 2017.²⁶ They combined this list of drugs with sales data from the IQVIA National Sales Perspective (NSP) database (see Appendix F for more information about the analysis). They found that of the 163 drugs in shortage, 62 percent went into shortage after supply disruptions occurred that were associated with manufacturing or product quality problems. Another 18 percent went into shortage for unknown reasons, and much smaller percentages were associated with unanticipated increases in demand (12 percent), natural disasters (5 percent), or product discontinuations (3 percent). (See Figure 6)

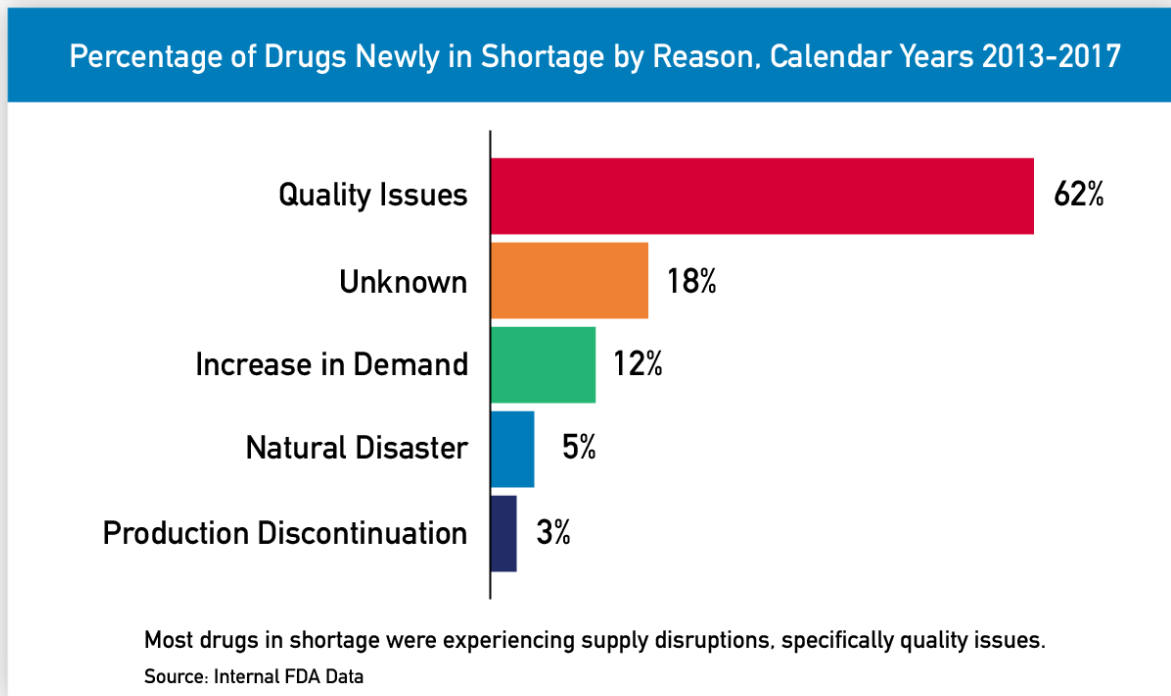


Figure 6. Of 163 drugs that went into shortage between 2013 and 2017, 62 percent went into shortage after supply disruptions occurred that were associated with manufacturing or product quality problems.

²⁶ 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. This means that a shortage can consist of more than one drug. For example, a shortage might include both oral liquid and solid oral versions. As a result, these 163 drugs in shortage occurred in 130 shortages defined by FDA. FDA's Center for Biologics Evaluation and Research also maintains a list of products in shortage. As of the end of September 2019, most of those products were vaccines, with the notable exception of a) immune globulin and b) an anticoagulant (sodium citrate), and c) several products for use to counter insect stings.

In this analysis, the economists relied on classifications of the reasons for shortages made by Center for Drug Evaluation and Research (CDER) Drug Shortage Staff (DSS). When FDA adds a drug to the shortage list that it is required to maintain pursuant to the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) ([Pub. L. 112-144](#)), it identifies one of the following reasons for the shortage: 1) Requirements related to complying with good manufacturing practices, 2) Regulatory delay, 3) Shortages of an active ingredient, 4) Shortage of an inactive ingredient component, 5) Discontinuation of the manufacture of the drug, 6) Delay in shipping of the drug, 7) Demand increase for the drug, or 8) Other reason.²⁷

When a shortage occurs, FDA usually requests additional information from the manufacturer(s) so the Agency can best target its shortage mitigation efforts based on the specific situation. This additional information requested from the manufacturer(s) can include the specific causes of the shortage including product-specific quality issues (which can include particulates and sterility issues), facility quality issues (manufacturing line or plant issues, for example), raw material issues (related to quality or delays, for example), increased overall demand, loss of manufacturing sites, and permanent discontinuations. FDA conducts periodic analyses of the data containing these specific causes and these data have consistently shown that the majority of shortages are related to quality problems. These quality problems can be either related to specific quality defects in individual drugs or quality problems at the manufacturer such as production lines breaking down or experiencing contamination or even entire facilities experiencing quality problems such as lack of sterility assurance for intravenous (IV) or ophthalmic drugs, and other facility-wide problems.

Events that Happen Prior to Occurrence of a Shortage

FDA found characteristics that were common among drugs that later went into shortage. Some of these characteristics were related to the markets for these drugs, and were manifested in trends in revenue, price and contribution to the manufacturer's total revenue. Other characteristics were associated with the facilities where these drugs were produced.

FDA's analysis identified these characteristics by comparing the 163 shortage drugs with a group of similar drugs that did not go into shortage during the same period from 2013-2017 (see Appendix F for more information about the analysis).²⁸ FDA found statistically significant differences between the shortage drugs and those in the comparison group, leading to the conclusion that about half of the shortage drugs (86 drugs or 53 percent) may have had inadequate financial incentives to market the product or invest in ensuring manufacturing capability and capacity prior to the shortage. From January 2010 to the time they went into shortage, these 86 drugs were characterized by declining revenues and prices:

²⁷ See section 506E(b) of the FD&C Act; 21 CFR 310.306(b); 314.81(c)(3)(iii)(d); *see also* 600.82(d)(1)(iii).

²⁸ Of these 163 drugs, only 144 drugs had adequate data for this analysis. Please see the technical appendix for more information. The comparison drugs were matched with drugs in shortage based on the route of administration, time since first approval or marketing, price, and quantity sold.

- **Steeply declining revenues**
Prior to the shortage, the revenues of the 86 shortage drugs in this group declined at an average annual rate of 12.9 percent versus a 3.3 percent decline in the comparison group ($p < 0.001$).
- **Declining prices**
Prior to the shortage, the prices of these 86 drugs declined an average of 2.5 percent annually, compared to a 2.9 percent increase in price among the comparison drugs ($p < 0.01$).
- **Very limited contribution to the firm's total revenues**
Stakeholders indicated that quality issues could also arise among products or in facilities where there are inadequate financial incentives to invest in manufacturing quality and redundant capacity.
 - On average, these 86 drugs accounted for just 0.16 percent of their company's total revenues, compared with 0.34 percent for similar drugs that did not go into shortage, in the 4 months just prior to the shortage ($p < 0.01$).
 - In the 4 months prior to the shortage, the facilities that manufactured these drugs accounted for just 2.6 percent of their company's total revenues, compared with 5.8 percent for similar drugs that did not go into shortage ($p < 0.001$).²⁹

The remaining 77 drugs that went into shortage, when compared with similar drugs that did not go into shortage, did not exhibit the same patterns of statistically significant declines in revenues and prices before the shortage occurred. The analysts found a statistically significant difference between these drugs and the comparison group, for the facilities that manufactured these drugs. In the four months prior to going into shortage, the facilities that are registered to manufacture these drugs accounted for just 3.7 percent of their company's total revenues, compared with 5.9 percent for similar drugs that did not go into shortage ($p < .05$).³⁰ FDA lacks information about

²⁹ The facility level analysis is based on a smaller sample of 104 shortage drugs that could be matched to manufacturing facilities that were registered with the FDA to produce the drug.

³⁰ FDA's available data sources did not enable the Agency to observe the quantities and revenues of a drug made at each manufacturing facility that is registered to produce it (this applies to approximately 26% of the shortage drugs and 33% of the comparator drugs in their respective samples). Therefore, the Agency assumes in this analysis that if a drug is registered at multiple manufacturing facilities, production levels are divided evenly among these facilities. FDA chose this assumption because it did not appear to clearly favor one set of facilities over another.

As a robustness check, FDA restricted the analysis to the remaining 74% of shortage drugs and 66% of comparator drugs where the available data allowed the Agency to precisely estimate the quantities and revenues of all drug products made at their respective facilities. Specifically, these are products where the manufacturer had approval to manufacture at a single facility and other products approved for manufacture at that facility were not approved to be manufactured at other facilities owned by that company. This alternative analysis indicated that in both groups, the facilities that manufactured the shortage drugs still accounted for a smaller amount of their company's total

how this difference could have affected business decisions that may have led to supply disruption and shortage. It is possible that the firm's management did not prioritize investment in a relatively small facility, leading to quality problems and a supply disruption. Or, management may have decided to use the available capacity to manufacture more profitable products.

FDA analysis shows that the majority of drugs that went into shortage had these characteristics:

- Steeply declining revenues
- Declining prices
- Very limited contributions to a company's total revenues

Events that Happen After Occurrence of a Shortage

According to the textbook model of how product shortages resolve, after a supply disruption prices should increase sharply as product becomes scarce and remain high for an extended period. Existing suppliers and/or market entrants should then increase production to fill the gap between supply and demand, and supply should eventually be restored to close to the level prior to the shortage. However, in the case of the 163 drugs in FDA's database that went into shortage (See Figure 7):

- Only 29 (18 percent) had a sustained price increase of 50 percent or more that began during the shortage and lasted for 6 months.³¹ Of these 29, only 7 saw the entry of a new manufacturer or increased production from an existing supplier. Only 9 of the 29 had production restored to the level prior to the shortage.³²
- Only 54 (33 percent) of the shortage drugs either experienced significant production increases (up to 50 percent or more) by companies that were already in the market, or had

revenues. However, the finding for the drugs in shortage that exhibited increasing revenues and prices was no longer statistically significant at the 5 percent level. Sources: IQVIA. National Sales Perspective. January 2010 to August 2018. Extracted: October 2018; Internal FDA Data

³¹ These results are robust to using alternative price increase thresholds (alternative price thresholds ranged between 5 and 50 percent increases) and an alternative time horizon of 3 months. There are two reasons why the results could also potentially overestimate the total number of sustained price increases occurring after shortage. First, roughly half of shortage drugs exhibited increasing price trends prior to going in shortage, and it is possible that their prices could have continued to increase even if they had not gone into shortage. Second, the analyses may also include gradual price increases that accumulated over a longer time period.

³² This conclusion, that sustained drug prices are relatively uncommon, is not that different from prior published work because we focus on relatively large price increases given our earlier observation that the average shortage is quite intense, volumes sold fall by 70 percent of volumes prior to the shortage. In addition, some of the difference may stem from our use of price measures that aggregate among all drug products including within each of the 163 drugs in shortage.

new suppliers enter the market. In the latter case, the median time to market entry was 13 months.

- Only 60 (37 percent) of the shortage drugs had the quantity of the drug restored to at least 80 percent of its amount just prior to the shortage during the 4th to 9th month following the shortage.

Taken together, these findings lead to the hypothesis that drugs that go into shortage are products that companies may not have a strong financial incentive to market or to produce using mature manufacturing quality management.

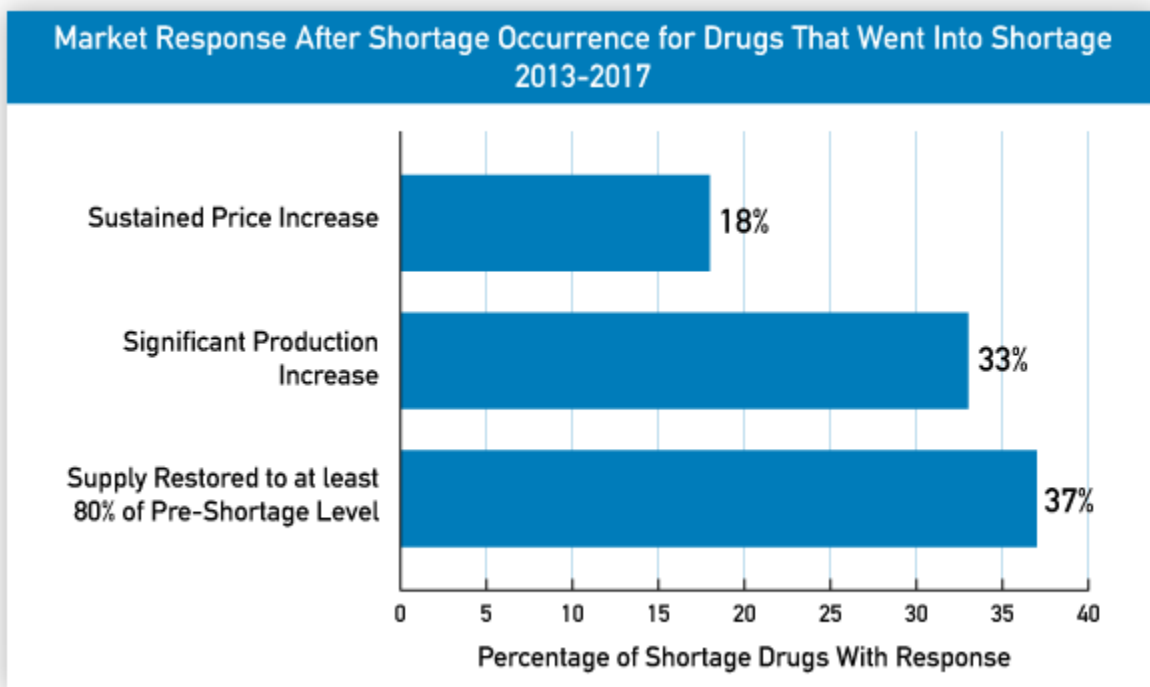


Figure 7. Few drugs in shortage experienced market response milestones that could help the shortages self-correct.

As discussed in the Root Causes section above, drug manufacturers face barriers to market entry, including the time and financial investment required to obtain approval from FDA to market their products and comply with regulatory requirements. However, regulatory requirements are only one of many factors contributing to the lack of market participants. Multiple generic companies are often approved to market drugs that are in shortage but make business decisions not to market them. In fact, for the shortage drugs studied, most had multiple applications approved by FDA, but only a small number of these were for drugs that were marketed. FDA

analysis shows that, just prior to the shortage, there were on average three companies per drug in shortage (“Orange Book” 2019) that were not marketing their approvals (see **Figure 8**).³³



Figure 8. For the shortage drugs studied, there were, on average, three companies that were approved to market the shortage drug but were not doing so.

Published Research

Academics, Federal agencies, and private organizations have conducted studies to shed light on the factors potentially associated with drug shortages. The Task Force conducted a literature review to identify research contributions to the understanding of market, logistical, and regulatory factors affecting drug shortages. Preference was given to publications that were cited multiple times in peer-reviewed journals and to government publications or those from established private-sector organizations. A complete bibliography is provided in Appendix A; the material below highlights some notable contributions.

Ventola offered an assessment of causes, impact and management strategies just prior to a peak in drug shortages. They called attention to the role of manufacturers’ business decisions, “including insufficient profits, the introduction of generic products, market share, anticipated clinical demand, patent expiration, drug-approval status, regulatory compliance requirements, expense to correct manufacturing problems, or mergers.” Ventola also noted that, “Many of the drugs in short supply also tend to be generic medications, which aren’t very profitable, so

³³ This analysis studied 152 of the 163 shortage drugs that we could match to FDA’s Orange Book database.

companies don't plan for backup capacity. Economic pressure on manufacturers can also lead them to maintain lower inventories of low-profit drugs or take them off the market.” (Ventola 2011)

Soon after the 2011 peak in shortages, the HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE) issued a 2012 report finding that a rapid expansion in the scope and volume of products produced by the industry in a short period of time, without a corresponding expansion in manufacturing capacity, led to a high rate of capacity utilization in the industry. This may have made it difficult to maintain manufacturing quality (Haninger et al. 2011).

Woodcock and Wosinska identified the fundamental driver of drug shortages as the market's inability to observe and reward quality manufacturing (Woodcock and Wosinska 2012). This lack of reward for quality can reinforce price competition and encourage manufacturers to keep costs down by minimizing quality investments. They conclude that these dynamics may have produced a market situation in which quality problems have become sufficiently common and severe to result in drug shortages.

Berndt *et al.* (Berndt et al. 2017; Conti and Berndt 2019) examined longitudinal trends in generic drug markets from 2004-2016 and found that quarterly sales revenues for generic drugs were surprisingly small. The median for a unique, generic molecule, dosage-form product was just over \$300,000 in the third quarter of 2016. Among non-oral drugs, there were fewer market entrants than exits. The markets for generic drugs are highly concentrated and becoming more so. Forty percent of drug markets were supplied by only one manufacturer, and the median number of manufacturers per drug market was two. These findings appear consistent with FDA's analysis, which suggests that some drugs have gone into shortage because manufacturers do not have strong financial incentives to begin or continue to market them. It is not surprising that such small and highly concentrated markets – where one or two manufacturers are common – often have variable or unstable prices and quantities sold.

In 2004 - 2016, markets for generic drugs were highly concentrated.

- Forty percent of these markets were supplied by only one manufacturer.
- The median number of drug manufacturers per drug market was two.

Frank et al. (2019) reported finding declines in the total consumer price index for generic prescription drugs sold at retail pharmacies of about 80 percent between 2007 and 2016. They noted that this decline provides context for interpreting some price spikes for selected old, off-patent drugs that have been widely reported in the media.

Dave et al. performed a retrospective study of a large cohort of generic drugs that were marketed in the United States during 2008-2014 to determine the association between drug shortages and changes in generic drug prices.³⁴ They found that low-priced generic drugs were at higher risk for drug shortages compared with medium- and high-priced generic drugs, and that periods of drug shortages were associated with modest increases in drug prices. However, the authors noted that their findings might not be generalizable to drugs that became generics after 2008 or those commonly used in an inpatient setting. (Dave et al. 2018)

Yurukoglu et al. examined whether reduced reimbursement under Medicare Part B contributed to shortages of sterile injectable drugs (Yurukoglu et al. 2017). They found that, after the policy change under the Medicare Modernization Act, shortages rose more for drugs with (1) higher shares of patients insured by Medicare, (2) greater decreases in provider reimbursement, and (3) greater decreases in manufacturers' prices. They hypothesized that lower reimbursement put downward pressure on manufacturers' prices, which reduced incentives to invest in capacity, reliability, and new launches.

A 2017 report (Pew Charitable Trusts and ISPE 2017) on market factors potentially contributing to shortages of sterile injectable drugs identified several reasons that a manufacturer might decide to withdraw from a market, thus reducing the number of a drug's suppliers: quality issues, the introduction of replacement drugs into the market, and business decisions to realign a portfolio to focus on products with either greater margins or a high risk of shortage. The companies also cited the need to upgrade to new equipment, achieve better supply chain design, establish purchaser-manufacturer incentives that would help companies mitigate the risks of making investments, and obtain more accurate information about the expected demand for a product, particularly low-volume, low-margin products. Without such information, companies would be reluctant to invest in setting up additional manufacturing capabilities to protect against future shortages.

Stakeholder Perspectives

FDA gathered information on the root causes of drug shortages and recommendations for solutions from a diverse array of stakeholders and by several means. On November 27, 2018 FDA hosted a [public meeting](#), "Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions," with the Robert J. Margolis, MD, Center for Health Policy, to solicit stakeholders' perspectives on the forces driving shortages and potential interventions. In connection with the public meeting, FDA established a [docket](#) to receive public comments. In addition, FDA held a series of listening sessions in September and October 2018 with members of academia, medical societies, pharmacists' associations, patient advocates, manufacturers,

³⁴ This article relies on a database of outpatient commercial prescriptions, whereas many shortages are for injectable drugs used primarily in hospitals that would not be captured well using prescriptions data.

GPOs, and drug distributors. FDA also met individually with several concerned stakeholders representing hospitals, physicians, intermediaries (GPOs), and the pharmaceutical industry.

Stakeholders provided additional information about the market forces driving shortages, the impact of shortages on patients and the health care system, the regulatory burdens on manufacturers and other stakeholders, and potential solutions. Some of the major themes that emerged from stakeholders were the following:

The Market Does Not Foster a Reliable Supply of Generic Drugs

Manufacturers of generic drugs state that they face a challenging business environment, which limits their ability to invest in manufacturing and reduces their incentives to launch new products or maintain existing ones. They say that they are under intense pricing pressure due to cost reduction efforts by health care providers and the negotiating power of a consolidated GPO sector, which enables GPOs to extract price concessions.

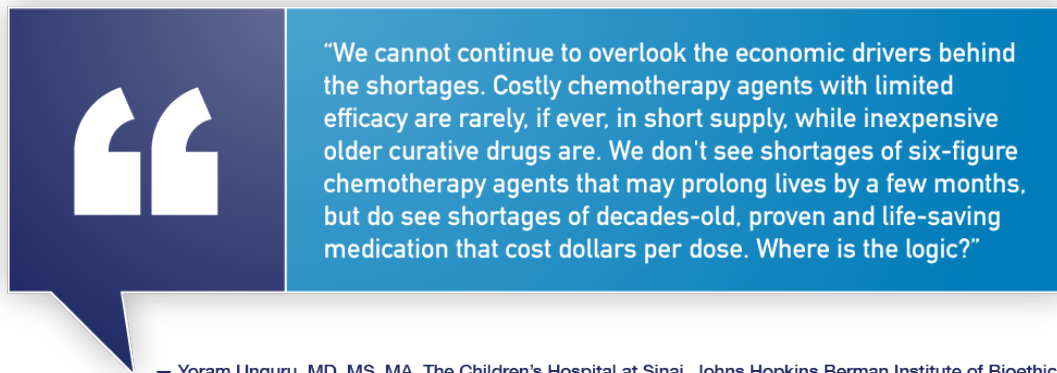
Manufacturers of generic drugs also believe that current contracting practices create a high level of business uncertainty as they generally do not guarantee that a certain volume of products will be purchased at an agreed upon price. Contracts often contain clauses that leave the manufacturer vulnerable to predatory pricing from competitors that are willing to undercut them to obtain market share, even at unsustainable prices. As a result, some generic drugs have low profit margins or are even selling for less than they cost to produce. Their sponsors may not have resources to invest in manufacturing or redundant capacity for these generic drugs.

The pharmaceutical industry also states that it has limited ability to respond to supply disruptions for several reasons, and this limitation increases the probability that disruptions will lead to shortages. For example:

- Manufacturers, GPOs, and distributors have moved toward “just in time” inventory management, so there is little redundancy in the supply chain when a disruption occurs.
- After a supply disruption, manufacturers cannot quickly increase production because of the lead time and investment required to expand production capacity, and to file and gain regulatory approval (if needed) for any related post-approval changes to their manufacturing operations.³⁵
- Firms must also deal with an increasingly complex and global supply chain, which can make it difficult to procure API quickly.

³⁵FDA helps to prevent or mitigate shortages by using regulatory discretion when appropriate, while ensuring the highest standards of safety and efficacy.

However, manufacturers are not heavily penalized for supply disruptions resulting from problems with their manufacturing facilities. Although GPO contracts with companies may include “failure to supply” clauses, these often have limited effectiveness. These clauses usually require the manufacturer to reimburse the GPO for the difference between the negotiated price and the purchase price of a drug. However, such clauses may be limited in duration and ineffective in situations where the required quantity of the drug is not available from another manufacturer. FDA responses to specific proposals from manufacturers and other stakeholders are in Appendix C.



Shortages Affect Every Level of the Health Care System

Stakeholders shared information about the way drug shortages affect every level of the health care system, ultimately compromising the standard of care, producing waste, and increasing costs. For example:

Medical Care

- Physicians stated that when they cannot obtain the preferred drug needed to treat patients, they may have to deny or delay care, or resort to using alternative medications that they believe may be less safe and effective for their patients. Shortages have created particularly difficult challenges for specialties that rely heavily on sterile injectable drugs, such as oncology, anesthesiology, and emergency medicine.
- Long-lasting shortages may have a detrimental effect on medical care, as young doctors and other health care providers who have been trained in an environment where the preferred drugs are unavailable may become unaccustomed to, and eventually unaware of the standard of care.

Hospitals

- Hospitals stated that to cope with drug shortages, they may divert staff from patient care, or hire additional staff to cope with drug shortages, which adds to their costs. They explained that shortages can have a profound impact on hospital operations: e.g., staff must adjust electronic health records, recode IT systems, repackage medications into different size containers, and relabel medications. Hospitals have also had to revise treatment protocols to adjust for drug shortages. These revisions can be extensive.
- Hospitals also shared that when low-cost generic drugs are in shortage, they may have to pay more for brand or other alternative drugs or obtain medications from compounding facilities, which are not subject to the same level of oversight as manufacturers, or gray market sources. In general, they cannot pass the additional costs to payers but must absorb the resulting losses themselves. Although providers believe that the costs drug shortages impose on the health care system and patients are high, hospitals generally do not track the costs systematically and, as a result, management may not recognize the full financial impact of shortages.
- Hospitals, pharmacists, and GPOs raised concerns about the gray market,³⁶ which takes advantage of drug shortages by charging exorbitant prices for hard to find drugs. They believe more investigation and insight into these practices is warranted.

Patients

- Although health care providers expressed concern about the impact of shortages on their patients, stakeholders reported that prescribers rarely inform patients when they are using alternative prescription drugs. As a result, patients may have little awareness of the effect of drug shortages on their care.
- Patients with rare diseases are particularly vulnerable to prescription drug shortages, because there may be only one drug approved to treat their condition and one manufacturer. If a supply disruption or shortage occurs, they have no alternative.

The Supply Chain Lacks Transparency

Stakeholders stated that currently GPOs, health care providers, and patients do not have access to information about where their drugs are manufactured, or the level of quality associated with the manufacturer or the manufacturing site. Thus, the opacity of the supply chain extends from the manufacturing site to the patient. Although health care providers and GPOs stated they want more transparency through the supply chain, the appropriate level is unclear, as stakeholders have different interests and needs. Stakeholders also stated that crucial pieces of information needed to assess a manufacturing site's quality may be unavailable.

³⁶ Gray market refers to distribution channels not authorized by prescription drug manufacturers.

- Health care providers shared that they would like more transparency through the supply chain to be able to identify reliable manufacturers, anticipate shortages before they occur, and plan their strategy for coping with the shortage. However, stakeholders acknowledge that individual responses to mitigate a suspected or impending shortage, such as hoarding, could exacerbate the shortage.
- By contrast, the pharmaceutical industry regards the location of their manufacturing facilities as confidential commercial information and claim that keeping this information private is a matter of supply security, e.g. to prevent theft or diversion attempts.
- Some private sector efforts to characterize manufacturers' quality and reliability are underway. However, these efforts are hindered by lack of information about specific manufacturing facilities. For example, FDA's significant observations of an inspection (FDA Form-483) are not proactively posted for all inspections. However, redacted Warning Letters (WL) are publicly available via proactive posting.³⁷

Regulatory Requirements Can Affect Industry's Responses to Supply Disruptions

Some stakeholders have stated that FDA and other agencies' regulatory requirements may impede industry's ability to mitigate shortages: e.g., by increasing the time and cost of responding to a supply disruption. Appendix C addresses some of the specific suggestions for FDA and other agencies made by industry and other stakeholders. The material below introduces some of those suggestions from stakeholders on their views of FDA policies and regulation as they relate to more efficient pathways to FDA approval of manufacturing changes, faster ANDA approvals, and increased harmonization of regulatory standards across international borders.

- Under FDA regulations, a pharmaceutical firm making "major" manufacturing changes (which can include the remediation of a facility) must submit a prior approval supplement (PAS).³⁸ FDA approval of a PAS can take up to 4, 8, or 10 months depending on whether an inspection is required, and the applicant meets certain requirements.³⁹ By contrast, firms making "moderate" manufacturing changes must generally submit a Changes Being Effected in 30 days (CBE-30) supplement at least 30 days before the drug product is

³⁷ FDA may issue a Warning Letter (WL) close-out letter ("close-out letter") once the Agency has completed an evaluation of corrective actions undertaken by a firm in response to a WL. A close-out letter may issue when, based on FDA's evaluation, the firm has taken corrective action to address the violations contained in the WL. This procedure applies to WLs issued on or after 9/1/2009.

³⁸ See 21 CFR 314.70(b).

³⁹ For example, in the case of a generic drug, per the [GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022](#) (GDUFA II Commitment Letter), FDA has a performance goal of approving a PAS within 4 months if no inspection is required, 8 months if an inspection is required and an applicant meets requirements under I(B)(2)(b) of the GDUFA II Commitment Letter, and 10 months if an inspection is required and an applicant does not meet the requirements under I(B)(2)(b) of the GDUFA II Commitment Letter.

distributed.⁴⁰ Changes that are moderate in nature and qualify for submission as a CBE-30 may be implemented by the sponsor after 30 days have passed and prior to completion of any review by the FDA. Because the CBE-30 process is much faster than gaining approval of the PAS, these industry representatives said it would be preferable to have more manufacturing changes made in response to a supply disruption handled through the CBE-30 pathway.

- The pharmaceutical industry would like FDA to waive the pre-approval inspection for new processes when similar existing processes have been inspected at sites that are deemed lower inspectional risk by FDA.
- Drug manufacturers have stated that they rely on an increasingly global supply chain and having to navigate different regulatory requirements across international borders may hinder their ability to launch new drugs or respond to supply disruptions. They would like to see increased harmonization of FDA’s regulatory standards with those of other countries.⁴¹
- Health care providers would like more complete information about drug shortages and coordination between FDA and other agencies. In particular, they would like to see better coordination between FDA and the Drug Enforcement Administration (DEA) to help prevent and mitigate shortages of drugs containing controlled substances.⁴²
- Health care providers would like FDA to provide more information about drug shortages, including how long they are expected to last.⁴³ This would aid providers in their efforts to plan a response to the shortage.⁴⁴

⁴⁰ See 21 CFR 314.70(c).

⁴¹ As noted earlier in this report, drug companies seeking to update and improve manufacturing operations often must seek permission from multiple global regulatory authorities in multiple regions, creating a significant obstacle to timely improvements that could reduce the risk of drug shortages. To address this, FDA is working closely with other pharmaceutical regulators and industry representatives around the globe, through the International Council on Harmonization, to develop a harmonized regulatory guideline titled: *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*. Q12 provides a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle, to promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain adjustments. For more information, see Appendix C and <https://www.ich.org/page/quality-guidelines>.

⁴² Please see information in Appendix C of this report about the steps DEA and FDA have taken to improve communications and coordination to help prevent and mitigate shortages containing controlled substances.

⁴³ However, it should be noted that under section 506E of the FD&C Act, FDA is generally required to publish its determination regarding the estimated duration of a shortage. FDA provides this information to the best of its ability in all shortage postings.

⁴⁴ Please note that FDA’s Draft Guidance for “Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing of Drug or Biological Products” which is under development and also mentioned further in the report under Current FDA Initiatives discusses the requirement in section 506C of the FD&C Act for applicants and manufacturers to notify FDA of a permanent discontinuance in the manufacture of certain drugs or an interruption in

- Stakeholders noted that the American Society of Health-System Pharmacists (ASHP) has a broader definition of shortage than FDA, which uses the definition from the FD&C Act. The Act defines a drug shortage as a period of time when the demand or projected demand for the drug within the United States exceeds its supply.⁴⁵ ASHP defines a shortage as a supply issue that affects how a pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent. As a result, ASHP’s published list of shortages is much larger than FDA’s. Some providers find the ASHP list more comprehensive and useful for their mitigation efforts.⁴⁶

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. 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. In addition, FDA offers a framework for policymakers considering addressing the issue of drug shortages (see Appendix E).

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 U.S., 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. The resulting lack of information limits the ability to monitor or predict the frequency, duration, and intensity of shortages. It also undermines the motivation of both private and public sector actors to prevent them or mitigate their effects by paying a sustainable price for a more reliable supply of safe and effective drugs, especially older generics, that may be at risk of going into shortage.

the manufacture of certain drugs that is likely to lead to a meaningful disruption in supply of that product in the United States. This guidance is also expected to recommend that manufacturers submit additional information and follow additional procedures to further assist FDA’s efforts to prevent or mitigate a drug shortage. Finally, the guidance is expected to discuss how FDA communicates information about supply disruptions and shortages to the public.

⁴⁵ The statutory/regulatory definition of “drug shortage” does not limit itself to medically necessary drugs (see 506C(h)(2)).

⁴⁶ Please note that FDA and ASHP routinely share information about drug shortages and have co-authored a posting on their respective websites outlining the reasons for the differences between the two shortage websites with regard to the information provided. <https://www.ashp.org/Drug-Shortages/Current-Shortages/FDA-and-ASHP-Shortage-Parameters>.

Better characterization of shortages would help FDA in its work to anticipate, prevent and mitigate shortages. Providing more comprehensive information on shortages' costs to patients and the health care delivery system may help purchasers understand the tradeoffs between paying the lowest possible price for generics and having reliable access to these often life-saving drugs over the longer term. Finally, a more detailed understanding of current contracting practices may suggest options for enabling manufacturers to earn sustainable risk adjusted returns on their products. In this way, the increased information may help address Root Cause 1: Lack of Incentives to Produce Less Profitable Drugs.

Among the areas most needing attention are:

- *Quantification of the harms of drug shortages, particularly those that lead to worsened health outcomes for patients*

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 2018⁴⁷). Given that FDA has recognized and posted on its website more than one hundred shortages at a single point in time,⁴⁷ it is especially important to have 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, private and public sector stakeholders have limited information to quantitatively characterize shortages in terms of their frequency, persistence, intensity, and impact on available treatments in specific therapeutic categories.⁴⁸ Having this information would help improve stakeholders' understanding of the impact shortages have on the Nation's health care.

Several stakeholders maintain information sources that, if combined, could shed more light on the extent of drug shortages and their potential impacts on the health system. For example, wholesalers track order fill rates and inventory changes, and manufacturers oversee proprietary data on production capacity and production volume by facility.

⁴⁷ 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://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages>

⁴⁸ 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>.

Combining this data could enable better measurement of the frequency, persistence and intensity of shortages and of their impacts.

- *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 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 sometimes relatively weak, requiring that an alternative source of the drug is available and typically recovering just 10 percent of the lost value (Haninger et al. 2011). More systematic study of current contracting practices is needed and could support development of a model contract designed to promote reliable access to safe and effective 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. This proposal 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. A rating would evaluate the robustness of a manufacturing facility’s quality system and could be used to inform purchasers and GPOs about the state of, and commitment to, the quality management 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 top-rated producers with a competitive advantage, potentially enabling them to obtain sustainable prices as well as grow market share. For a full discussion of quality management maturity, please see Appendix B.

As discussed above, FDA’s analysis found that quality problems are responsible for 62 percent of the drugs that went into shortage between 2013 and 2017. Having a robust and mature quality management system is essential to ensure consistent and reliable drug manufacturing and quality performance. A system focused primarily on CGMP compliance is a quality management system focused on meeting minimum quality standards rather than on ensuring a stable drug supply for patients.

A stronger, more mature quality management system is one that focuses on performance, especially outcomes that affect the patient including reducing complaints, shortages and quality-related adverse events. Elements of a mature system include vigilant attention to upgrading facilities and equipment, training that promotes superior performance, increased understanding

of the product and manufacturing process, and statistical-based monitoring of manufacturing processes and laboratories. Quality management maturity provides strong oversight that involves early detection of major variability in any of these areas, which enables senior management to take action to avoid quality failures before patient harm, including drug shortage, occurs.

Transparency into quality management maturity and a facility's ability to reliably address quality problems and produce a quality product will provide insight into whether a drug will be likely to go into shortage. However, measuring quality management maturity, in terms of what and how to measure, is an evolving science. Several organizations have been studying various elements of quality management maturity, as discussed in Appendix B (St. Gallen FDA Quality Metrics Research Final Reports Year 1 2017 and Year 2 2018; ISPE "Quality Metrics Pilot Program"; Patel et al. 2015).^{49, 50}

Developing a system to measure and provide transparency regarding a facility's quality management maturity requires engagement from FDA, industry, academia, Congress and other stakeholders. To provide adequate incentives to firms for investing in the quality management necessary to reduce the risk of drug shortages, it is important that purchasers and consumers be able to accurately distinguish whether a manufacturing facility has demonstrated quality management maturity for the products they are buying.

It is important that the quality management maturity threshold for drugs be set high enough to appreciably reduce the risk of drug shortages, but not so high that it either pushes manufacturers out of the market or dramatically increases purchasing costs. Once purchasers have this information, they need to be able to assess how much they would be willing to pay for drugs supplied from sites with a mature quality management system that ensures a consistent supply of safe and effective drugs. The development and adoption of this rating would:

- Communicate the value of quality management maturity so it can be adopted by manufacturers and priced into contracts by purchasers;
- Promote the adoption of better tools to measure manufacturing performance to allow earlier detection of potential problems that could lead to shortage;
- Incentivize improvements to manufacturing infrastructure that enhance reliability of manufacturing and thus supply.

No such rating system currently exists for drug manufacturing facilities. A rating system would need to provide clear, concise, objective information about the maturity status of a manufacturing site's quality management. FDA has experience in the development and application of frameworks similarly focused on quality, and with appropriate resources could

⁴⁹ See also <https://www.pda.org/scientific-and-regulatory-affairs/quality-culture>

⁵⁰ <https://cmmiinstitute.com>

work closely with industry and other stakeholders to determine the appropriate measurements, standards, other metrics and processes, and incentives to identify firms with superior ratings.

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 will enable the development of new contracting approaches aimed at ensuring a reliable supply of medically important drugs. To succeed, this proposal will require the active engagement of both the private and public sectors. Purchasers, payers and GPOs will need to consider ways to shift some financial risk and uncertainty away from producers of drugs, especially older generics. Manufacturers will need to support a rating system for their facilities and be willing to selectively disclose their facilities' ratings to introduce transparency into the drug market. The Agency must serve as an independent and reliable source of information about the quality management maturity of a given manufacturing facility.

FDA heard from stakeholders that current contracting practices create a high degree of financial uncertainty for generic manufacturers, and thus may contribute to business decisions leading to shortages. The Agency does not have expertise in private sector contracting and thus is not in a position to provide specific recommendations on how contracts should be designed. Instead, FDA believes that the private sector should establish contracts that address the first and second root causes of shortages 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 a number of 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 maturity rating. By offering escalating premiums for drugs from more highly rated facilities, where the rating system recognizes different levels of achievement, purchasers could provide the incentives and means for manufacturers to move up the quality management maturity spectrum.

Payers, purchasers, and GPOs have already begun to explore options for designing contracts to achieve these goals, albeit without the quality maturity rating. For example, under one model, purchasers could agree to long-term purchasing contracts that guarantee both a minimum

purchasing volume and a “fair” price for the drug, an approach that was presented at the November 27, 2018 public meeting.⁵¹ In exchange for these commitments, the contractor would work with manufacturers to establish supply chain redundancies, such as multiple manufacturing sites and safety stock, that could buffer against the risk of supply or demand disruptions turning into drug shortages. Another proposal by several in academia is to establish purchasing contracts that pay more for certain drugs in exchange for stronger failure-to-supply penalties (Jia and Zhao 2017).

It is likely that making information available about a given manufacturing facility’s ability to provide a reliable supply of safe and effective drugs, coupled with better financial rewards for more reliable producers, will reduce the incidence of shortages over time. However, currently available data are not sufficient to validate projections of the short- and long-term effects of such market reforms.

FDA Initiatives to Prevent and Mitigate Drug Shortages

In addition to the recommendations described above, there are several legislative proposals and planned FDA initiatives that focus primarily on enabling the Agency to help prevent and mitigate drug shortages. Although the Agency undertook some of these prior to its investigation of root causes, the efforts will complement the Task Force’s first recommendation, by increasing the Agency’s access to more complete information to characterize shortages. Some other initiatives will reduce logistical and regulatory challenges to increasing production after a supply disruption, the third root cause of shortages. They will achieve this by ensuring that manufacturers of products vulnerable to shortage have risk management plans in place and by harmonizing global regulatory requirements for approval of manufacturing changes. Appendix C provides additional information on FDA initiatives, some of which are described briefly below.

- **Improved Data Sharing.** In a legislative proposal in the President’s FY 2020 budget, FDA recommends clarifying the information required to be provided about interruptions in manufacturing under section 506C(a) of the FD&C Act and expanding FDA’s authority to allow the Agency 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 explain 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

⁵¹ Slides 103-104 from November 27, 2018 Public Meeting, “Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions” accessed July 23, 2019 at: https://healthpolicy.duke.edu/sites/default/files/atoms/files/duke-fda_drug_shortages_presentation_slides_0.pdf

situation to ensure FDA has the specific information it needs to help prevent or mitigate shortages.

- **Risk Management Plan Requirement.** FDA has recommended a legislative proposal, included in the President’s FY 2020 budget, that would expand the Agency’s authority to require application holders of certain drugs to conduct risk assessments to identify vulnerabilities in their manufacturing supply chain and develop plans to mitigate the risks associated with the identified vulnerabilities.
- **Risk Management Plan Guidance.** FDA plans to publish a new draft guidance for industry, “Risk Management Plans to Mitigate Potential for Drug Shortages,” by the end of 2019. This guidance outlines 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.** In a legislative proposal in the President’s FY 2020 budget, FDA recommended expanding its authority to require, when in the interest of public health (e.g., to prevent or mitigate a shortage), that an applicant evaluate and label a product with the longest possible scientifically-determined expiration date (shelf-life). 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 intended to be finalized later in 2019. With significant contributions and leadership from FDA experts, this guideline sets out tools and enablers to incentivize enhanced product and process understanding and an effective pharmaceutical quality system through 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.

FDA expects the two risk management initiatives to help prevent shortages by enabling manufacturers to proactively assess their vulnerabilities in risk management plans and take steps to reduce their risks. If a manufacturing disruption does occur, expanding the Agency’s authority to require increased data sharing about the interruption will enhance FDA’s ability to work with firms to quickly increase production. Extension of expiration dates, where scientifically warranted, will also ease capacity constraints in the wake of a supply disruption. The ICH guideline Q12, when finalized, will reduce the regulatory burden on firms making post-approval manufacturing changes, thus allowing them to increase production more quickly. All of these initiatives will likely address the third root cause by easing logistical and regulatory challenges to increasing production following a supply disruption.

Conclusion

From its work on this report, the Task Force believes 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. Likewise, the types of enduring solutions proposed above will require multi-stakeholder efforts and a 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 mature quality manufacturing would provide companies with incentives 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 that enable them to continue production of their products. In the past, the scale of drug shortages and their impacts have continually been underestimated. Absent major changes to the marketplace, it is likely that drug shortages will continue to adversely affect patient care and add costs to the health care system.

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Appendix B: Quality Management Maturity

Vision for Pharmaceutical Quality in the 21st Century

In 2004, FDA published a report on pharmaceutical quality for the 21st century that laid out the following vision: “a maximally efficient, agile, flexible manufacturing sector that reliably produced high-quality drug products without extensive regulatory oversight.” Although we have made progress towards this vision, more remains to be done.

Current Good Manufacturing Practices (CGMPs) establish standards for systems that ensure proper design, monitoring, and control of manufacturing processes and facilities. Manufacturers that are strongly committed to quality go beyond the CGMP standard to implement enhanced quality management systems (QMSs) that focus on performance, facilitate continuous improvement, and center on patients’ needs. CGMPs provide the foundation for quality management systems. The existing regulatory framework, however, does not measure the capacity of a site to ensure ongoing quality supply.

The capacity for robust quality assurance is determined by the maturity of the quality management system. Fully realizing the 21st century pharmaceutical quality vision requires a transparent method of evaluating and communicating quality management maturity. When manufacturers demonstrate rigorous oversight, understanding, and control over their manufacturing processes, FDA can exercise a more flexible regulatory approach, which should advance the goal of “high-quality drug products without extensive regulatory oversight” while also encouraging continual improvement of manufacturing processes.

What is quality management maturity?

A quality management system is a collection of business processes needed to implement and maintain quality of product in the marketplace. These business processes focus on consistently meeting expectations (expressed as organizational goals and aspirations), and complying with regulations, policies, and processes.

Quality management maturity starts with a foundational QMS that conforms to CGMPs and builds in a performance and patient focus that utilizes technology, statistical process control, and planning activities such as risk- management and continuous improvement plans. These planning activities and improved knowledge of product and process contribute to ensuring a robust supply of drug. As further explained below, a company that attains quality management maturity does not merely spot-check products for problems. Instead, in a mature quality management system, manufacturing problems readily become evident, enabling the company to act promptly and continually improve product quality.

A basic quality management system might be focused, for example, on CGMP compliance. As noted above in the discussion of Root Cause 2, adherence to CGMP standards is foundational, but is not sufficient to demonstrate a firm is applying quality management maturity standards that enable it to predictably prevent supply disruptions.

A stronger, more mature quality management system is one that focuses on performance, especially outcomes that affect the customer/patient, including reducing quality issues that lead to complaints, shortages, and quality-related adverse events. Elements of a mature system include vigilant attention to upgrading facilities and equipment; training that promotes all employees' understanding of their contributions to quality; increased understanding of the product and manufacturing process; and ongoing statistical-based monitoring of manufacturing processes and laboratories. Quality management maturity provides strong oversight that involves early detection of major variability in any of these areas, which enables senior management to take action before drug shortages occur.

Advanced quality management maturity builds in elements such as continual improvement, enhanced communication that encourages staff to raise issues, knowledge management to promote product understanding, manufacturing infrastructure investment, supply chain robustness, data analytics, and risk-management practices that exceed the explicit requirements currently in CGMPs.

Because most drug shortages are related to quality issues,¹ quality management maturity can be helpful in driving consistent production of quality product to meet customer demand. It is essential for the American public that each dosage unit from each manufactured batch has the quality needed to ensure their medications are safe and effective.

Mature quality management systems, when coupled with process and product knowledge and the use of effective risk-management practices, can guide the building of quality into the product. This can also aid in managing many types of changes to facilities, equipment, and processes. In some cases, this may be able to obviate the need for FDA approval via formal regulatory submissions. Therefore, manufacturers with a mature quality management system and appropriate process knowledge may be able to implement certain improvements with less stringent regulatory oversight, facilitating an increased pace at which product improvements can be made.

History of Quality Management Maturity

Industry has long recognized the need for the application of appropriate quality management. Multiple models of excellence, including cross-industry and industry-specific, are available, some of which are described below.

In his seminal 1979 book *Quality is Free*,² Philip B. Crosby formulated a Quality Management Maturity Grid (QMMG) to benchmark the maturity of processes and the extent to which these processes are culturally embedded. In 1987, the QMMG became the precursor maturity model

¹ See Appendix F for information on FDA analysis.

² Crosby, Philip (1979). *Quality is Free*. McGraw-Hill. ISBN 0-07-014512-1.

for the [Capability Maturity Model](#).³ That same year, the Baldrige National Quality Program became a model to recognize U.S. organizations for achievements in quality and performance.⁴

In 2002, the Capability Maturity Model Integration (CMMI) was created as a process level improvement training and appraisal program. Many U.S. Government contracts, especially in software development, require it. The CMMI defines maturity levels (1-5) for processes for use in internal or external appraisal of an organization.⁵ CMMI is currently used as the model in FDA's Center for Devices and Radiological Health's (CDRH) program for medical device quality.⁶ While the CMMI provides a useful rubric, some aspects of this approach (e.g., certain terminology) may not be ideally suited for comprehensive quality oversight of human drugs.

Recent literature shows that while many industries have successfully adopted quality maturity principles and tools, the pharmaceutical sector has been slower to capitalize on these learnings.^{7,8} In 2017, Yu and Kopcha⁹ reinforced and extended the FDA vision for pharmaceutical quality by challenging industry to improve manufacturing capability to ensure reliable supply and minimize risk to consumers.

Research on Pharmaceutical Quality Management Maturity

To advance the pharmaceutical industry, trade associations and academics have conducted significant research on quality management maturity, including quality metrics, quality culture, and operational excellence. For example, since 2004 St. Gallen University has benchmarked hundreds of pharmaceutical manufacturers, collecting numerous quality indicators of performance and cultural excellence. Their research demonstrates that quality metrics programs are a good business practice.¹⁰

The Parenteral Drug Association developed a quality culture maturity assessment tool for industry auditors to evaluate the quality culture of a manufacturing facility. The tool includes

³ Software Engineering Institute (1994). *The Capability Maturity Model: Guidelines for Improving the Software Process*. Reading, Massachusetts: Addison Wesley Longman, Inc. p. 11. ISBN 0-201-54664-7.

⁴ One example is described in a National Institute of Science and Technology (NIST) report: [Comparison of Baldrige Award Applicants and Recipients with Peer Hospitals on a National Balanced Scorecard](#). "Hospitals using the Baldrige process are significantly more likely than peers to become 100 Top Hospitals award winners."

⁵ <https://cmminstitute.com/>

⁶ <https://www.fda.gov/medical-devices/quality-and-compliance-medical-devices/case-quality>

⁷ MDIC Case for Quality Program, Maturity Model Research Report, June 2015, <https://mdic.org/resource/maturity-model-report/>

⁸ McKinsey & Company, *Flawless: From Measuring Failure to Building Quality Robustness in Pharma*, 2014, <https://www.mckinsey.com/business-functions/operations/our-insights/mature-quality-systems>

⁹ X. Yu, Lawrence & Kopcha, Michael. (2017). The future of pharmaceutical quality and the path to get there. *International Journal of Pharmaceutics*. 528. 10.1016/j.ijpharm.2017.06.039.

¹⁰ <http://tectem.ch/institute/opex/fda>

over 20 elements, each with a written maturity model that describes weak maturity (1) to strong maturity (5).¹¹

The International Society of Pharmaceutical Engineering (ISPE) has studied multiple aspects of quality management maturity and drug shortages.^{12,13} In 2014, ISPE published their Drug Shortage Assessment and Prevention Tool to provide a structured assessment of potential supply chain vulnerabilities that is consistent with Quality Risk Management principles.¹⁴ The tool enables the identification of specific risks or products that might merit priority attention. It identifies points to consider when assessing the gap between current operations and the desired robust quality system.

In 2017, an ISPE Cultural Excellence Report was published that focuses on a six-dimensional cultural excellence framework. This framework facilitates a holistic assessment of elements required to improve an organization's quality culture. The report includes a Cultural Excellence Assessment Tool designed for an organization to assess the maturity of 21 key behaviors as part of their quality culture program.

In 2013, the first of two ISPE pilots was initiated to define and operationalize standard metrics reporting to the FDA and refine the proposed set of metrics and definitions, data submission process, and evaluation. The second pilot expanded the data set across segments, geography, and time to expand the knowledge and evaluate trends. Findings from the pilots confirmed the importance of quality culture and emphasized the difficulty in finding simple-to-collect metrics.

ISPE's Advancing Pharmaceutical Quality (APQ) program proposes an industry-led approach to advance pharmaceutical quality beyond the submission of data for harmonized, reportable metrics. This program, still in development, includes a maturity model and evaluation for one element (corrective action and preventive action) of a robust quality system. The finished tool will have a detailed maturity model for each quality system element to assess the maturity level and implement performance metrics.

FDA Supporting Initiatives

FDA has been promoting the modernization of quality management through multiple programs. For example, CDRH's Case for Quality helps to identify and promote practices that support consistent quality manufacturing. This will align CDRH's regulatory, enforcement, and compliance approaches with those practices. The Case for Quality consists of three core components: (1) focus on quality, (2) enhanced data transparency, and (3) stakeholder engagement.¹⁵

¹¹ <https://www.pda.org/global-event-calendar/courses/pda-quality-culture-transformation>

¹² <https://ispe.org/initiatives/drug-shortages/publications-tools>

¹³ <https://ispe.org/initiatives/quality-metrics>

¹⁴ <https://www.fda.gov/media/71543/download>

¹⁵ <https://www.fda.gov/medical-devices/quality-and-compliance-medical-devices/case-quality>

Quality Metrics

FDA is working on implementing a reporting program for certain key metrics (performance indicators).¹⁶ On November 25, 2016, FDA issued a [revised draft guidance](#) that discusses how the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) may utilize submitted data and quality metrics to help ensure that their policies and practices continue to support continuous improvement and innovation in the pharmaceutical manufacturing industry. Many of the elements of Quality Metrics will also help in the larger efforts to implement QMM.

Since 2016, FDA has identified the need for additional discussion with industry. Therefore, FDA initiated two programs: (1) a site visit program for manufacturers to demonstrate their level of quality maturity and (2) a feedback program in which companies can discuss their quality measurement approach in-depth.

New Inspection Protocol Project (NIPP)

FDA is modernizing the manufacturing facility inspections program with a new way of assessing, recording, and reporting data from pre-approval and surveillance inspections for drug products. NIPP uses standardized electronic inspection protocols to collect data in a structured manner for more consistent oversight of facilities and faster and more efficient analysis of findings. The protocols also include additional questions related to *quality maturity observed in facilities*.

The first phase of NIPP was aimed at developing a protocol that could be used during aseptic processing surveillance and pre-approval inspections. Facilities using this processing technique to manufacture sterile drug products are a logical starting place. If the quality of drugs intended for sterile injection is compromised, patient safety can be compromised. In recent years, these types of quality challenges have led to shortages of sterile, injectable drugs. With better and more consistent oversight of these manufacturing facilities, problems can be spotted earlier and mitigated to avert dangerous drug shortages.

Emerging Technology Program¹⁷

FDA recognizes that adopting innovative technologies to manufacturing is key to ensuring continuous improvement and modernizing the industry. However, implementing these new approaches can present technical and regulatory challenges. Pharmaceutical companies may have concerns that using such technologies could result in delays in FDA application approval. To address these concerns, CDER's Office of Pharmaceutical Quality created the Emerging Technology Program (ETP) to promote the adoption of innovative approaches to pharmaceutical product design and manufacturing. Through the program, industry representatives can meet with ETT members to discuss, identify, and resolve potential technical and regulatory issues regarding

¹⁶ <https://www.fda.gov/drugs/pharmaceutical-quality-resources/quality-metrics-drug-manufacturing>

¹⁷ <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/emerging-technology-program>

the development and implementation of a novel technology *prior* to filing a regulatory submission.

*Site Engagement Program (SEP)*¹⁸

FDA is establishing a voluntary program that encourages quality practices at selected drug manufacturing sites with the goal of ensuring the availability of quality pharmaceuticals. FDA is conducting a limited introduction of this concept based on the idea that enhanced interaction between the Agency and identified sites will help to prevent or mitigate shortages of certain finished drug products. For these products, supply disruption would result in higher risk to patients. The program also offers identified sites an additional opportunity to gain clarification on FDA's expectations for pharmaceutical quality.

Defining Quality Management Maturity for the Pharmaceutical Industry

Current good manufacturing practice requirements set a minimum standard for methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. A robust commitment to quality goes beyond the explicit minimum requirements and includes an enhanced quality management system that focuses on continual improvement. However, the use of quality management maturity is far from universal in the pharmaceutical industry. FDA's analysis found that for 62 percent of the drugs that went into shortage between 2013 and 2017, the shortages were triggered by quality problems. FDA seeks better data on the prevalence of mature quality systems in the pharmaceutical industry. Our current focus on inspections has primarily been on identifying and addressing CGMP violations and other problems, rather than evaluating the relative maturity of a manufacturer's quality system.

Based on current research, knowledge-sharing with pharmaceutical manufacturers and trade associations, and benchmarking with other industries, FDA has identified certain performance indicators and behaviors that are indicative of a mature quality management system. For example:

- The ability of a quality system to consistently and reliably deliver quality product despite desired and undesired changes helps determine how well a system can perform over time through various conditions including changes in market demand. To ensure high reliability, mature companies measure delivery performance of their suppliers and themselves (on-time and in-full). They also have robust supplier qualification and management programs that include elements like ensuring supply chain redundancy and routinely surveying customer requirements.
- Operational stability (e.g., measured through statistical process control, process capability and performance) helps identify causes of variation and find opportunities for continual improvement.

¹⁸ <https://www.fda.gov/drugs/pharmaceutical-quality-resources/site-engagement-program-sep>

- Effective continual improvement includes robust root cause analysis using standardized tools and corrective action and preventive action programs (e.g., effectiveness, timeliness). The reduction of human error can lead to a system that can prevent problems before they occur.
- A strong quality culture across the organization demonstrates that product quality and its impact on the patient drives corporate strategy and decisions. For example, this might include ensuring that employees understand patient impact, can escalate potential quality issues effectively, and are rewarded based on quality outcomes. Senior management's commitment to quality can play a central role in driving quality culture by supporting staff development programs (e.g., mentoring, training, staff development plans, and in shop-floor operations.)

Appendix C: U.S. Food and Drug Administration

This report responds to a June 2018 request from Congress to identify the root causes of drug shortages and make recommendations for enduring solutions. However, long before receiving this request, FDA had been working to prevent and mitigate drug shortages through multiple initiatives. Some current initiatives focus on risk management plans, improved transparency, quality metrics, shortage forecasting, and cooperative work with other agencies on advanced manufacturing. The purpose of this Appendix is to (1) discuss proposed legislation and some of the Agency's planned and current initiatives; and (2) respond to proposals that stakeholders have made that would involve changes to FDA policy or regulation.

The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) ([Pub. L. 112-144](#)) gave the Agency new authorities to prevent and mitigate drug shortages, and called for the formation of a task force to carry out its provisions. In response, FDA established the [Drug Shortages Task Force](#) (FDASIA Task Force) with representation from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Office of Regulatory Affairs (ORA). The FDASIA Task Force is not to be confused with the new [Task Force](#) established by then Commissioner Scott Gottlieb, MD, in July 2018 to respond to a Congressional request for a report that would identify the root causes of drug shortages and recommend enduring solutions, a request that this report fulfills.

Since 2012 the FDASIA Task Force, including CDER's Drug Shortage Staff, has worked to implement the provisions of the Act. In 2013, the FDASIA Task Force developed a [Strategic Plan](#) for preventing and mitigating drug shortages, and in every year since has issued a [Report to Congress](#) on the number of new drug shortages as well as the shortages successfully prevented. Because the authorities, activities, and achievements of the FDASIA Task Force are well documented, the purpose of this section of the Appendix is to provide an overview of other actions that FDA is taking, in parallel, to prevent and mitigate shortages.

Proposed Legislation and Planned and Current FDA Initiatives

Risk Management

Risk Management Plan Guidance

FDA is developing a new draft guidance for industry, "Risk Management Plans to Mitigate Potential for Drug Shortages." This guidance will outline a new recommendation for pharmaceutical stakeholders to develop, implement, and maintain risk management plans (RMPs) for the purpose of preventing and mitigating drug shortages. RMPs can provide manufacturers a framework to proactively identify, prioritize, and implement strategies that mitigate hazards that could potentially disrupt the drug supply chain (and could ultimately result in drug shortages.) It is a natural extension of the FDASIA requirement for industry to report potential drug shortages because this program provides a framework to prevent or mitigate the drug shortage.

Legislative Proposal to Require Risk Management Plans

FDA has recommended a legislative proposal, which is in the President’s FY 2020 budget, that would authorize the Agency to require application holders of certain drugs to conduct periodic risk assessments to identify the vulnerabilities in their manufacturing supply chain and develop plans to mitigate the risks associated with the identified vulnerabilities. Currently, many applicants lack plans to assess and address vulnerabilities in their manufacturing supply, putting them at risk for drug supply disruptions following disasters (e.g., hurricanes) or other reasons. Without these plans, recovery can be substantially delayed. One goal of this assessment would be to identify those potential shortage vulnerabilities. Based on the results of the assessment, the applicants would be required to develop a risk mitigation plan (e.g., redundant manufacturing capacity) to address those risks. These requirements would be applied using a risk-based approach to drugs that are considered “life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery”¹ where the drug has been on the FDA drug shortage list in the last 5 years or meets 1 or more criteria determined by FDA to increase risk of shortage.

Increased Transparency

Improved Data Sharing: Ensuring Timely and Informative Notification

In a second legislative proposal, FDA recommends expanding the information required to be provided about interruptions in manufacturing under section 506C(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and authorizing the Agency to impose penalties for failing to provide timely and adequate notification. Currently, some firms do not provide timely or sufficient notification related to drug shortages pursuant to section 506C(a) of the FD&C Act. Failing to provide timely, adequate information in the notification can preclude the Agency’s ability to take effective and appropriate action to address the shortage. Currently, the only “penalty” that FDA may pursue for noncompliance with the notification requirement under section 506C is a letter to the firm that is posted on FDA’s website, and this penalty applies for failure to notify at all or in a timely manner.

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 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.

¹ See section 506C(a) of the FD&C Act.

Quality Metrics Program

Quality issues (e.g., substandard manufacturing facilities or processes, or significant quality defects that are identified in the finished product) are the most common immediate cause of manufacturing disruptions. These situations necessitate remediation efforts to fix the issue, which in turn may interrupt production and lead to a shortage of drugs.

FDA has sought input from industry on the establishment of an FDA Quality Metrics Program as another mechanism to promote continual improvement in manufacturing quality. Through this effort, the Agency has learned that it should obtain additional feedback from manufacturers who have already implemented their own quality metrics programs. Based on this input, FDA initiated a Quality Metrics Feedback Program in June 2018 with the announcement of a pilot program in the *Federal Register*.² This pilot, which ran between July 30, 2018 and July 29, 2019, was voluntary and helped the Agency gather information on quality metrics programs that are established and operational in industry. In addition, FDA launched a Quality Metrics Site Visit Program³ to enable CDER and CBER staff to observe directly at a manufacturing facility how quality metrics data are gathered, collected, reported to management, and used to drive continual improvement.

Predictive Modeling for Drug Shortages

In 2014, GAO published a report, [Drug Shortages: Public Health Threat Continues, Despite Efforts to Ensure Product Availability](#), which recommended that “FDA should strengthen its internal controls over its drug shortage data and conduct periodic analyses to routinely and systematically assess drug shortage information, using this information to proactively identify drug shortage risk factors.” The first recommendation was closed after the implementation of the Shortage Tracker, a commercially developed data system, in March 2016. The Agency is currently attempting to construct a predictive model. FDA anticipates that this project will provide insight into the complexities involved and whether such a model is feasible. If successful, this work may assist FDA in improving identification and mitigation of shortage risk factors.

Cooperative Work with the HHS Office of the Assistant Secretary for Preparedness and Response and the Defense Advanced Research Projects Agency

FDA is working with the Assistant Secretary for Preparedness and Response (ASPR) and the Defense Advanced Research Projects Agency (DARPA) through various paths, including Memorandums of Understanding (MOUs) to strengthen U.S. capabilities critical to protect the Nation from 21st century health security threats.⁴ The partnership will ultimately provide

² “Modernizing Pharmaceutical Quality Systems; Studying Quality Metrics and Quality Culture; Quality Metrics Feedback Program,” *Federal Register*, Vol. 83, No. 126, June 29, 2018, p. 30748 – 30751.

³ “Quality Metrics Site Visit Program for Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Staff; Information Available to Industry,” Notice. *Federal Register*, Vol. 83, No. 126, June 29, 2018 p. 30751.

⁴ <https://www.fda.gov/about-fda/domestic-mous/mou-225-17-015>

flexible, transportable manufacturing platforms that enable response to emerging medical needs in the military or civilian populations, flexibly, on demand, and at the point of need. These systems will enable the U.S. Government to ensure supply of chemical and biological countermeasures and other medicines in austere environments, prevent or mitigate drug shortages, radically shorten the drug supply chain, and reduce U.S. dependence on overseas production and extensive distribution networks.

FDA's work with ASPR and DARPA ensures that the essential technical and policy experts are brought together to develop and navigate the core technologies and policies concurrently, ensuring that U.S. capability and policy is compatible with a changing technology and need landscape. For example, the FDA CDER's Emerging Technology Team⁵ is working with DARPA and ASPR to ensure that the closed manufacturing systems under development will fulfill regulatory requirements, while also assessing how the new paradigm may shift regulatory policy.⁶

Lengthening Expiration Dates

In a legislative proposal in the President's FY 2020 budget, FDA recommended expanding its authority to require, when in the interest of public health (e.g., to prevent or mitigate a shortage), that an applicant evaluate and label a product with the longest possible scientifically-determined expiration date (shelf-life). 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 Lifecycle Management

Mature quality management systems were envisioned as a basis for regulatory flexibility in making post-approval manufacturing changes in the ICH guideline Q10 Pharmaceutical Quality System. However, the regulatory flexibility suggested by ICH Q10 has not yet been fully realized. Further, where requirements for post-approval changes differ amongst global regulatory authorities, implementing the improvements called for by a mature quality management system can involve significant time and expense. These issues have been the basis for the development of an internationally harmonized guideline, ICH guideline Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, which is intended to be finalized later this year. With significant contributions and leadership from FDA experts, this guideline sets out tools and enablers to incentivize enhanced product and process understanding and an effective pharmaceutical quality system through 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.

⁵ <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/emerging-technology-program>

⁶ <https://www.phe.gov/ASPRBlog/pages/BlogArticlePage.aspx?PostID=318>

Stakeholder Proposals to FDA Essential Medicines List

Some stakeholders have suggested that FDA develop a list of essential medicines and explore the possibility of increasing financial incentives and/or reporting requirements for these drugs. As part of the Drug Shortage Task Force activities, FDA set out to develop a set of criteria that would readily allow a manufacturer to determine if a drug is considered at risk for shortage. FDA took this approach because a static list of drugs would not be able to take into account changing factors such as additional drug approvals, changing quality conditions in manufacturing facilities, changes in medical practice, and other variables that could change over time. The Agency considered a variety of risk factors and vulnerabilities, including those related to national security interests, attributes of the drug, and manufacturing facilities. FDA also considered how application of these criteria could be integrated into current FDA processes and inform future FDA actions intended to prevent or mitigate shortage.

Regarding drugs for which shortage could impact national security, FDA considered those drugs used in emergency response and those used in response to specific chemical, biological, and radiological/nuclear (CBRN) threats and emerging infectious diseases. FDA identified a number of existing resources that identify drugs that meet these criteria, such as [the Strategic National Stockpile](#) Formulary (a non-public list), the [HHS Chemical Hazards Emergency Medical Management \(CHEMM\)](#) antidotes for chemical threats (2017), and the [Advanced Cardiac Life Support \(ACLS\) Crash Cart Supply and Equipment Checklist](#) (2016), among others.

When considering product-related risk factors, FDA explored how to identify drugs of interest (referred to as “medically necessary,” “essential,” or “important” by various stakeholders). As there are different definitions available from different organizations, FDA proposed to apply the criteria from section 506C of the FD&C Act, which outlines drug shortage notification requirements. Under section 506C(a), the requirement for notification to FDA about a possible or actual shortage applies to drugs that are life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery that are not radio pharmaceutical drug products or other products designated by FDA. FDA also sought product-specific factors associated with drug shortage. The only specific predictive factor FDA identified was prior history on the FDA drug shortage list. In particular, the analysis found that a drug that was on the FDA drug shortage list in the past 3 to 5 years has an approximately 15-20 percent chance of reappearing on that list within 1 year.

FDA also evaluated possible manufacturing facility-related risk factors that might assist in identifying drugs at risk for shortage. Our assessment revealed that a component supply chain with limited capacity (e.g., a single active pharmaceutical ingredient [API] facility or a single finished dosage form facility) was not a sufficiently discerning risk factor, as a large percentage of currently marketed drugs meet this criterion and yet many of those drugs have not experienced shortage. Narrowing this criterion to where such a single facility has experienced significant

quality issues may further enhance the ability to predict the risk of shortage, but the impact of this added criterion requires further assessment.

FDA considered other factors such as market share, volume of the market, and environmental factors (e.g., weather, conflict), but did not find that these factors provided any additional predictive capability. The Agency will continue its efforts to identify factors that help FDA and manufacturers predict and/or mitigate shortage.

Better Coordination Between FDA and the Drug Enforcement Administration (DEA)

In the past 15 years, shortages of prescription drugs containing controlled substances, such as narcotics and stimulants, have increased nationwide, limiting providers' and patients' access to medications needed for treatment. During FDA's solicitation of public input into the drivers and solutions for drug shortages in 2018-2019, some stakeholders expressed a desire for better coordination between the FDA and the DEA, with a view to better mitigation of shortages of drugs typically used for anesthesia and pain management.

In February 2015, the U.S. Government Accountability Office (GAO) reported on a study⁷ examining shortages of drugs containing controlled substances. In the 2015 report, GAO made seven recommendations, including that the DEA and FDA should update their MOU and agree on steps each should take regarding drug shortages. In March 2015, FDA and DEA implemented a recommendation to finalize an information-sharing agreement with FDA regarding drug shortages.

- In March 2015, DEA and FDA updated the MOU to establish procedures regarding the exchange of proprietary and other sensitive information between the two agencies. The MOU calls for the development of separate plans to specify what information is to be shared and with whom it is to be shared.
- After establishing the MOU, DEA and FDA met to determine the specific procedures for sharing information about drug shortages and developed draft work plans. While the drafts circulated between the two agencies for comment, FDA and DEA began to actively share information and by August 2017 had successfully completed numerous exchanges.
- In March 2018, the work plans were cleared through both agencies and signed. FDA believes that it has now completed implementation of this recommendation.

Faster ANDA Approvals

Industry members made suggestions to evaluate existing regulatory frameworks and further expedite application reviews and facility approval processes to accelerate the entry of generics and API suppliers. FDA has decreased the time it takes to review and approve applications over the years and continues to seek ways to improve overall processes, but FDA remains focused on

⁷ "DRUG SHORTAGES: Better Management of the Quota Process for Controlled Substances Needed; Coordination between DEA and FDA Should Be Improved," GAO-15-202. February 2015.

protecting the public health and must perform due diligence in its drug reviews and facility inspection processes.

Better Communication and Coordination During ANDA Review

Industry stated that navigating multiple FDA offices can be confusing and suggested FDA appoint a senior-level drug shortage navigator to coordinate with each manufacturer who submits an ANDA for a drug shortage product. This position should reside within the OGD and responsibilities would include shepherding drug applications through the internal review and approval processes at FDA and maintaining contact with the manufacturer.

The Drug Shortage Staff within CDER, who report to the Office of the Center Director, already provide overall coordination of priority ANDAs and supplemental ANDAs that are expected to prevent or address a drug shortage. CDER's Office of Generic Drugs (OGD) also has project management staff charged with tracking reviews of ANDAs and helping to resolve issues, and a Drug Shortage Coordinator. For shortage-related ANDAs and supplemental ANDAs, the Drug Shortage Staff works closely with the OGD Drug Shortage Coordinator to expedite reviews and inspections for submissions that could help mitigate or resolve a drug shortage and prevent future shortages.

Expand the FMD-135 Program

Industry recommended that FDA enhance the FMD-135 Program through its Office of Regulatory Affairs and the Center for Drug Evaluation and Research, so that it can devote more resources and expedite advice under the FMD-135 program. Providing manufacturers with hands-on advice about new manufacturing processes or facilities could expedite a supply of critically needed drugs to market.

FDA appreciates industry's interest in increasing production capacity to address a drug shortage. The FMD-135 is a narrowly defined program targeted at reviewing plans for construction of new or modifications of facilities prior to commercial production, most useful when a firm wishes to take a manufacturing approach for which the technology or design requirements have not been well clarified by existing guidance. It is therefore necessarily limited in scope, and only one of several resources that FDA provides to industry to help bring new capacity online or remediate manufacturing sites that have had a quality problem.

Drug Efficacy Study Implementation Compliance Policy Initiative

Industry recommended refining the unapproved Drug Efficacy Study Implementation (DESI) drugs compliance policy initiative to permit the use of real-world evidence to demonstrate efficacy and streamline and simplify the filing requirements for DESI drugs.

The 1962 Kefauver-Harris Amendments to the FD&C Act require that new drugs be proven effective, as well as safe, to obtain FDA approval. The amendment also required FDA to evaluate the effectiveness of the approximately 3,400 drug products that the Agency had approved only for safety between 1938 and 1962. DESI is FDA's administrative implementation of this effectiveness evaluation.

FDA has made substantial progress with the DESI program, as nearly all DESI proceedings have been closed. Only a few DESI proceedings that lack FDA’s final determination of effectiveness remain open today.

The use of real-world evidence in the evaluation of drugs that were part of or are currently being reviewed under DESI proceedings neither depends on nor requires any changes to CDER’s Marketed Unapproved Drugs—Compliance Policy Guide (CPG), Section 440.100 (September 19, 2011). Instead, once a DESI proceeding closes, and regardless of the Agency’s final effectiveness determination, each drug firm marketing the drug that was subject to the DESI proceeding is required to obtain an FDA approved application (or approved supplement to a previously approved application) that demonstrates both safety and effectiveness. The drug does not retain its DESI status once the proceeding closes. Rather, older drugs that were previously part of the DESI program would, like any drug subject to section 505 of the FD&C Act, fall into one of two categories: they become approved (for both safety and effectiveness) or they remain unapproved.

With respect to marketed unapproved drugs, prior inclusion in a DESI proceeding is not relevant to consideration of real-world evidence in FDA’s evaluation of an application for drug approval. Such drugs should be treated like all other drugs for which an application has been submitted, and whether real-world evidence is appropriate under that circumstance should be considered in light of the guidance, [Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics, Guidance for Industry](#).

For those drugs currently subject to open DESI proceedings, the consideration of real-world evidence would significantly delay the administrative closure of those still-open proceedings. For the open DESI proceedings, volumes of effectiveness data have already been submitted to the Agency over the past several decades, and this data has been reviewed and evaluated by the Office of New Drugs (OND). It is an FDA priority to administratively close the remaining open DESI proceedings and provide a final effectiveness determination for the drugs in these proceedings. When a DESI proceeding closes, if the drug subject to that proceeding is determined to lack substantial evidence of effectiveness, firms can resubmit applications to be evaluated by OND for safety and efficacy under the appropriate standards applicable to all drugs subject to section 505 of the FD&C Act.

Finally, pursuant to [CDER’s Marketed Unapproved Drugs CPG](#), drugs subject to an ongoing DESI proceeding are permitted to remain on the market during the pendency of that proceeding.

Expanded Use of the Changes Being Effected-30 Program

Industry stakeholders proposed adjusting regulations to enable what are considered to be moderate manufacturing changes to be submitted as **Changes Being Effected-30 (CBE-30)** supplements. Re-entering the market may require a new API source and manufacturing site, which would require a prior approval supplement (PAS). Changes that qualify for submission as a CBE-30 may be implemented by the sponsor 30 days after the submission of the supplement to FDA, and the CBE-30 supplement process is therefore a faster process than filing a PAS.

The CBE-30 program is already intended to be used for “moderate” manufacturing changes, while “major” ones must be approved under a PAS. However, if a facility has a compliance history, the firm may use the “comparability protocol” to reduce the time for approval. FDA published a draft guidance for industry, [Comparability Protocols for Human Drugs and Biologics](#), in April 2016 and expects to finalize it in calendar 2019. However, FDA cannot rely on a comparability protocol for a new facility with no compliance history.

Medical Device Reporting

Some stakeholders have suggested that the Agency require medical device manufacturers to notify FDA in the event of an interruption or discontinuation of certain medical devices and equipment needed to administer drugs, such as containers to dilute drugs for IV infusion. Currently, no law requires medical device manufacturers to notify FDA when they become aware of a circumstance that could lead to a device shortage. Such circumstances may include, for example: discontinuation of a device; interruption of the manufacture of the device (e.g., due to scarcity of a raw material or unavailability of a component part); or loss of or damage to a manufacturing facility. [FDA’s Fiscal Year 2020 Budget Request](#) includes a legislative proposal to address device shortages. This proposal would ensure FDA has timely and accurate information about likely or confirmed national shortages of essential devices to enable FDA to take steps to promote the continued availability of devices of public health importance. Specifically, under this proposal, FDA would be granted authority to: require firms to notify FDA of an anticipated significant interruption in the supply of an essential device; require all manufacturers of devices determined to be essential to periodically provide FDA with information about the manufacturing capacity of the essential device(s) they manufacture; and authorize the temporary importation of devices whose risks presented when patients and health care providers lack access to critically important medical devices outweigh compliance with U.S. regulatory standards.

Enhanced Industry Reporting of Inventories.

Some stakeholders have recommended that FDA require manufacturers of essential critical drugs to report their monthly inventories to the FDA by entering data directly into an FDA database. This information would give FDA transparency to the supply levels with an overall picture of drug supply capacity across manufacturers. FDA is currently exploring additional data sources.

Extend FDASIA Title 10 Requirements.

Stakeholders recommended extending Title 10 requirements to require industry to provide FDA with information on API sources, production locations, duration of expected shortages, and more details on manufacturing quality issues. FDA is pursuing an extension of FDASIA Title 10 requirements through legislative proposals in the President’s FY2020 budget, as discussed above.

Publicly Identify Manufacturing Locations

Some stakeholders recommended making manufacturing locations transparent. However, the pharmaceutical industry generally regards these locations as trade secret or confidential

commercial information and has stated that revealing them to the public would create a security risk.⁸

Early Warning System

Industry recommended that FDA establish an early warning system to alert companies when a contract manufacturing firm is cited for GMP issues that could negatively impact multiple products. However, companies already have access to this information.

FDA's inspection classification data base is updated every 30 days with results from surveillance inspections. Final classifications of inspection results are made within 90 days of the close of inspection. Stakeholders who are interested can check the data base once a month to determine the status of contract manufacturers. FDA also notes that pharmaceutical firms could specify in their contracts with contract manufacturing firms that the latter notify them promptly of any GMP issues found in an FDA inspection.

Monitoring Distribution Patterns for Drugs in Shortage

Industry recommended that FDA require national wholesalers to implement checks and balance systems for shortage drugs, similar to suspicious order monitoring requirements for controlled substances, to identify potential diversions of shortage drugs to the gray market. However, FDA's governing statutes do not set up such systems specifically to address potential diversions of shortage drugs.

Better Communication and Navigation with FDA Processes

Industry suggested that FDA pursue post-483⁹ meetings with sponsors. They recommended that CDER meet with a sponsor of a drug shortage product upon request after the sponsor submits its 483 response. Industry suggested that this approach would allow for effective and timely remediation of the identified 483 issues.

FDA believes that it has adequate policies and procedures in place that address industry concerns related to communications post-issuance of a Form 483. Recently, in response to Section 806 of the FDA Reauthorization Act of 2017 (FDARA), FDA implemented processes to ensure timely reviews of responses to 483s. In addition, sponsors of drug products in shortage also already have existing mechanisms to engage the Agency through the Drug Shortages Staff, and FDA does consider all requests for meetings related to remediation, particularly if a drug is in shortage.

⁸ FDA Listening session with manufacturers, October 1, 2018.

⁹ An FDA Form 483 is issued to firm management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the FD&C Act and related Acts. (See <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions>)

Economic Incentives

Some industry stakeholders have suggested that FDA could help prevent or mitigate drug shortages by providing economic incentives such as waiving ANDA application fees or facility fees for essential medicines that have routinely been on shortage, or offering tax incentives to bring API sources and manufacturing back to the U.S.

Based on our available data, it is unlikely that waivers of ANDA application fees would provide an incentive for generic manufacturers to bring a drug to market. As highlighted in FDA's analysis, 62 percent of drugs newly in shortage between 2013-2017 resulted from issues with manufacturing quality. Addressing these issues through expanding or modernizing a manufacturing facility can cost up to \$100 million.¹⁰ In contrast, user fees for generic drugs under the Generic Drug User Fee Amendments (GDUFA) in Fiscal Year 2019 are much smaller: \$178,799 per original application; \$211,305 and \$226,305 per year for domestic and foreign finished product manufacturers; and up to \$1,862,167 per year for companies that hold more than 20 approved applications. The value of the waiver is small in proportion to the total cost of expanding, modernizing, or building new capacity.

Typically, manufacturers produce multiple drugs at a given facility and few manufacturers would dedicate a facility to manufacturing only a shortage drug or drugs. For this reason, there would be few situations in which waiving facilities fees for shortage drugs would be feasible.

As the U.S. Treasury section of the Appendix states, tax incentives often do not work and must be carefully targeted to have an impact. Although some localities may provide tax incentives for manufacturers to locate production, the cost and regulatory requirement differentials between the U.S. and locations overseas, particularly China, have provided a powerful incentive for companies to locate manufacturing there.

¹⁰ Ferriera et al., "A Comparison of Capital and Operating Costs of Aseptic Processing Facilities," *Advanced Aseptic Processing*. Edited by J. Akers and J. Agallaco, Informa Publishing (U.K.).

Appendix D: Agencies and Offices Participating in the Drug Shortages Task Force

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. In addition, the Task Force has 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. Each of these organizations has a unique perspective based on its authorities, mission, and activities.

In the course of its work, the Task Force has consulted with each of these organizations to better understand how their activities might affect drug shortages, their potential contributions to long-term solutions, and the limitations imposed by their enabling legislation and authorities. The material below provides a summary of what the Task Force has learned and was provided by the agencies themselves.

Centers for Medicare and Medicaid Services

The Centers for Medicare & Medicaid Services (CMS) pledges to put patients first in all of its programs – Medicaid, Medicare, and the Health Insurance Exchanges. To do this, the Agency strives to empower patients to work with their doctors and make health care decisions that are best for them. This means giving them meaningful information about quality and costs to be active health care consumers. It also includes supporting innovative approaches to improving quality, accessibility, and affordability, while finding the best ways to use innovative technology to support patient-centered care.

To these ends, CMS administers the Medicare program and works with state governments to administer the Medicaid program. Within Medicare, CMS administers several programs: Part A, which covers inpatient hospital, skilled nursing, and hospice care; Part B, which covers medically necessary services and supplies, including outpatient care and preventive care; and Part D, which adds prescription drug coverage to Parts A and B for beneficiaries who elect it. Part D plans are offered by private sponsors but must conform to Federal guidelines. There is also Part C, which includes Medicare Advantage Plans, whose benefits combine the coverages under traditional Medicare A, B, and potentially D as well.

Some stakeholders have suggested that Medicare and Medicaid reimbursement policies may reduce the incentive for manufacturers to market certain drugs, and thus contribute to shortages. However, drugs are reimbursed differently under each of these programs, and quantitative data about the relationship between Federal reimbursement policies and drug shortages are scarce. Some stakeholders asked if CMS had quantified how much drug shortages are costing our public programs. CMS does not collect the information needed for this analysis and indicated that HHS/ASPE is developing a report on these costs.

Medicare

Part A

Under Part A, CMS bundles payments for hospital services using a system of diagnostic related groups (DRGs). A DRG is part of a medical case classification system that standardizes prospective payment for hospitals. In general, a DRG payment covers the cost of all charges associated with an inpatient stay from the time of admission to the time of discharge, including the cost of any drugs used to treat the patient. The DRG system is intended to encourage cost containment, because hospitals whose costs exceed the DRG payment will experience a loss for the inpatient stay involved, while those whose costs are less can earn a profit. The level of DRG reimbursement varies by region and is calculated based on the average costs of hospitals in the same region, with adjustments for case intensity, so each hospital is tacitly encouraged to compete with its regional peers on cost containment.

During FDA's listening sessions and the November 2018 public meeting on drug shortages, some stakeholders raised questions about the possible impact of DRGs on drug shortages; e.g., whether the cost containment pressures they exert are incenting hospitals to buy the cheapest drug available, thus driving down generic prices to unsustainable levels. Some suggested that

changes in CMS' reimbursement policies might provide better incentives for manufacturers to market shortage drugs.

For example, some stakeholders have recommended that CMS consider a policy of paying for shortage drugs outside of the DRG. This, they believe, could ensure that their reimbursement is high enough to provide an incentive for manufacturers to market the drug. However, CMS does not have the statutory authority to move shortage drugs out of a DRG. Also, this tactic may be counter to the Administration's strategy of encouraging health care cost containment by setting reimbursement levels and allowing providers to make their own decisions about how to operate efficiently. CMS is advancing a value-based transformation of health care, with a move in emphasis from paying for individual items and services to making bundled payments for entire episodes of care, with incentives to contain costs.

Some stakeholders have noted that CMS already has a process in place for New Technology Add-on Payments or NTAPs for DRGs and pass-through payments for Ambulatory Payment Classifications (APCs, a classification system similar to DRGs for outpatient care) to supplement bundled payments. Some stakeholders have asked whether CMS might follow a similar approach for shortage drugs. However, the NTAP program is only available to new technologies that meet the definition of newness of the technology, exceed cost criterion thresholds, and demonstrate substantial clinical improvement over existing services or technologies. Due to the time needed to approve NTAPs (for DRGs) and the existing criteria, it would not be feasible for shortage drugs to be considered unless submitted applications meet all three criteria.

Stakeholders also raised the question of whether CMS could drive changes in hospitals' contracting practices through Medicare Conditions of Participation (CoP) or similar mechanisms. For example, could CMS require hospitals to enter into contracts for guaranteed supply, or exchange higher prices/reimbursement for stronger penalties when drugs go into shortage?

The statutory authority for CoP is limited to establishing health and safety standards that address systems and processes of care at a given facility. Thus, it would not be possible to use CoP as a mechanism for forcing hospitals to modify their contracting practices, which are a hospital rather than a Federal governance issue.

CMS does not have information on the fraction of shortage drugs that are reimbursed primarily by Medicare. Because Part A payments for drugs are bundled within the DRG reimbursement covering all the services provided during an episode of care, CMS cannot determine which specific drugs (active pharmaceutical ingredient/dosage form/manufacturer) have been used for specific inpatient cases. Even if CMS had this information, it would not know how much other payers, such as private insurers offering Medigap plans, have paid for shortage drugs.

Part B

Under Part B, CMS reimburses drugs based on an Average Sales Price (ASP), calculated quarterly. It is unlikely that the use of ASP has a negative financial impact on providers, because the ASP is updated quarterly. Although there is a lag between the period on which the calculation is based and the period during which the ASP is used for reimbursement (e.g., the

April-June ASP is based on sales from the previous October-December), the frequency of updates largely compensates for this lag.

Part D

Part D coverage is provided through Medicare-approved private drug plans offered by plan sponsors. Under Federal guidelines, sponsors independently negotiate pharmacy reimbursement with pharmacies and price concessions with manufacturers. Pharmacy reimbursement under Part D is based on ingredient cost, a dispensing fee, and sales tax. Ingredient costs are generally based on the Average Wholesale Price (AWP) discounted by a specified percentage or maximum allowable cost negotiated by plan sponsors.

Medicare subsidizes the cost of drugs covered under approved Part D plans. To be approved by Medicare, these plans must cover certain medications but are otherwise free to establish their own formularies, which vary and thus enable beneficiaries to have choices. Medicare Part D plans use tiered copayment systems designed to incent beneficiaries to use more cost-effective drugs. These tiered copayment systems follow CMS guidance.

Some stakeholders, citing a 2018 Avalere Health report,¹ have claimed that a 2016 CMS guidance that addresses formulary composition has led to unintended consequences by allowing both brand and generic drugs to occupy the same non-preferred tier. They believe that this policy prevents generics from competing effectively on price with brands, and as a result is responsible for reducing generic market penetration.

CMS sought comment regarding an alternative to the tier composition policy whereby plan sponsors would be prohibited from placing generics on brand formulary tiers and brand drugs on generic formulary tiers and eliminating the non-preferred drug tier. CMS analyses of formulary placement and Prescription Drug Event (PDE) data comparing generic access in 2011 to 2019 do not indicate that this alternative approach would result in the beneficiary savings asserted in the cited Avalere report. CMS has concluded that a broad prohibition of the inclusion of generic drugs on non-preferred tiers would result in preferred formulary placement of a number of generic drugs that are high cost and/or high risk for adverse events, especially in elderly patients. This could increase out-of-pocket costs for generic medications in some circumstances. For example, in order to meet actuarial equivalence, plans may raise their generic tier copayment amount in order to account for the need to add more expensive generic drugs to the generic drug tier, increasing the cost for the majority of generic drugs on the formulary. This alternative tier composition policy could also result in an increase to Part D premiums due to reduction in flexibility in plan design and reduced negotiating leverage with drug manufacturers.

However, while CMS analysis of CY 2019 formularies shows robust access to cost-effective generic medications and that Part D sponsors have been achieving very high generic dispensing and substitution rates, it notes that there are limited instances when Part D sponsors are not including generic alternatives when available. Instead, sponsors are only covering the brand drugs, which decreases generic substitution and increases beneficiary costs. Further, CMS has noted that some sponsors, despite having the generic at a more preferred formulary status than

¹ “Generic Drugs in Medicare Part D: Trends in Tier Structure and Placement.” Avalere Health. May 22, 2018.

the brand, are not achieving optimal generic substitution. While CMS is declining to change its tier composition policy at this time, it will continue to monitor beneficiary access to generic alternatives, utilization of multi-source brands when generics are available, and situations where the brand drug is situated more favorably in comparison to the generic with regards to tiering and utilization management. CMS will consider future policy changes should this trend continue.

CMS is aware of strategies that can be used to encourage generic use and has already adopted or proposed some. These include:

- Allowing certain low-cost generic drugs to be substituted onto Part D plan formularies at any point during the year, so that beneficiaries immediately have access to them and lower cost sharing;
- Requiring Part D plans to increase transparency and provide enrollees and their doctors with a patient’s out-of-pocket cost obligations for prescription drugs when a prescription is written;
- Implementing a statutory requirement signed by President Trump to prohibit pharmacy gag clauses in Part D, which prevent pharmacists from notifying consumers of lower-cost options for obtaining their medications.

Medicaid

Medicaid receives rebates on drugs provided to its beneficiaries under the Medicaid Drug Rebate Program.² The Bipartisan Budget Act of 2015 includes a provision that requires generic drug makers to pay an additional rebate to Medicaid if the prices of their generic drugs rise at a rate faster than inflation. This provision, which previously applied only to brand-name drugs, is informally known as the “CPI-U rebate” or “CPI-U penalty.”

The additional rebate for generics applies to rebate periods starting in the first quarter of 2017. The amount of the additional rebate is equal to the average manufacturer price (AMP) for the current quarter minus the baseline AMP, adjusted for inflation. Meanwhile, the adjustment for inflation is calculated as the Consumer Price Index for all Urban Consumers (CPI-U) for the month immediately before the reporting quarter, divided by the baseline CPI-U.

Some have noted that because the prices of some generics are so low, even a modest increase in price could trigger the CPI-U rebate. For example, if a company manufacturing a drug selling for \$1.00 raised its price by 5 percent to \$1.05, while the CPI-U increase is only 2.3 percent, the company would be affected by the penalty. Furthermore, some have noted that if the costs of manufacturing inputs rise faster than the CPI-U, the CPI-U rebate would undermine the ability of drug manufacturers to recoup these rising costs. As a result, the CPI-U rebate could erode the incentive for the manufacturer to continue marketing the drug and increase the likelihood of drug shortages.³

² For an explanation of the Medicaid Rebate Program, see <https://www.medicaid.gov/medicaid/prescription-drugs/medicaid-drug-rebate-program/index.html>.

³ Richard Manning and Fred Selck, Bates-White Economic Consulting, “Penalizing Generic Drugs with the CPI Rebate Will Reduce Competition and Increase the Likelihood of Drug Shortages,” September 12, 2017. Accessible

The argument that the CPI-U rebate will make it difficult for manufacturers to recoup rising input costs may be weak, however. There is little evidence that manufacturing input costs are rising faster than the CPI-U, and they are likely to be captured in the rising costs of consumer goods that the CPI-U measures.

Some state Medicaid programs offer financial incentives for pharmacists to dispense generics, as an additional strategy to encourage generic use.

at <https://www.accessiblemeds.org/sites/default/files/2017-09/Bates-White-White-Paper-Report-CPI-Penalty-09-12-2017.pdf>.

Defense Advanced Research Projects Agency and HHS Office of the Assistant Secretary for Preparedness and Response

The mission of the Defense Advanced Research Projects Agency (DARPA) is to make pivotal investments in breakthrough technologies for national security. DARPA explicitly reaches for transformational change instead of incremental advances, addressing challenges that span the spectrum from deep science to systems to capabilities. DARPA works within an innovation ecosystem that includes academic, corporate, and governmental partners to transform revolutionary concepts and even seeming impossibilities into practical capabilities. The ultimate results have included not only game-changing military capabilities such as precision weapons and stealth technology, but also such icons of modern civilian society such as the Internet, automated voice recognition and language translation, and global positioning system receivers small enough to embed in myriad consumer devices.⁴

The mission of the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) is to safeguard the Nation's health during times of disasters, emergencies, and disease outbreaks, and secondly, to strive to reduce and eliminate threats to the Nation's health security. ASPR's authorities, policies, and programs ensure that Americans have access to potentially life-saving pharmaceuticals and medical supplies for use in a public health emergency. In addition, ASPR builds relationships with Federal, state, local, tribal, and territorial government partners and the private sector to identify and mitigate risks to key systems and infrastructure so that Americans have access to quality health care every day.

Currently, ASPR and DARPA are partnering to explore novel sustainment strategies and develop point-of-need manufacturing solutions that disrupt entrenched paradigms for production and distribution of small-molecule medicines and biologics. Specifically, DARPA and ASPR are working on validating automated, portable capabilities that produce medicines and vaccines in dosage form, as either finished pills or injectables. Their partnership will ultimately provide flexible, transportable manufacturing platforms that enable response to emerging medical needs in the military or civilian populations, flexibly, on demand, and at the point of need. These systems will enable the U.S. Government to ensure supply of chemical and biological countermeasures and other medicines in austere environments, prevent or mitigate drug shortages, radically shorten the drug supply chain, and reduce U.S. dependence on overseas production and extensive distribution networks.

ASPR and DARPA are working together and with other agencies such as the FDA through various paths, including Memorandums of Understanding (MOUs) to strengthen U.S. capabilities critical to protect the Nation from 21st century health security threats.⁵ These partnerships ensure that the essential technical and policy experts are brought together to develop and navigate the core technologies and policies concurrently, ensuring that our capability and policy is compatible with a changing technology and need landscape. For example, FDA

⁴ <https://www.darpa.mil/about-us/about-darpa>

⁵ <https://www.fda.gov/about-fda/domestic-mous/mou-225-17-015>

CDER's Emerging Technology Team (ETT)⁶ is working with DARPA and ASPR to ensure that the closed manufacturing systems under development will fulfill regulatory requirements, while also assessing how the new paradigm may shift regulatory policy.⁷

⁶ <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/emerging-technology-program>

⁷ <https://www.phe.gov/ASPRBlog/pages/BlogArticlePage.aspx?PostID=318>

Department of Defense

The Department of Defense (DoD) must ensure a reliable drug supply to America's military forces so that they are adequately healthy and protected to deter war and safeguard the Nation's security. As a result, readiness is a prime concern, and DoD ensures access to drugs through a variety of mechanisms.

To help meet its service readiness sustainment requirements, the Defense Logistics Agency (DLA) Troop Support has sought various methods to garner access to pharmaceuticals. One such arrangement is the use of contingency contracts in which DLA pays its vendors a fee for access to a guaranteed quantity of specific products in a designated timeframe. Although this approach is less costly than purchasing and holding drugs in inventory, if there is an urgent need, DLA must rely heavily on vendors to meet their contractual delivery schedules.

DLA leverages the following types of contracts to ensure medical readiness:

- Industrial Base Maintenance Contracts create long term partnerships with selected manufacturers to maintain production capabilities.
- Prime Vendor War Readiness provides pre-negotiated access to prime vendor stocks.
- Vendor Managed Inventory Contracts create long term partnerships with distributors that provide guaranteed product availability.
- Corporate Exigency Contracts create long term partnerships with manufacturers providing guaranteed product availability.
- Commercial Product Visibility Contracts provide the data necessary to support critical medical IT planning and execution applications.

These contingency contracts give DoD access to approximately \$720 million worth of material, on a time-phased basis, should the DoD have a contingency that necessitates a surge in support.

Despite these efforts, DoD has experienced problems with access to certain drugs. Although it does not hold backorders in the traditional sense, the DLA does receive feedback from prime vendors on drugs that cannot be supplied due to their manufacturer backorders and strict allocations. Once a drug is unavailable, DLA urges its customers to order alternatives.

To estimate the scale of the problem, DLA used data from its Global Prime Vendor Contract for the period from October 2018 through March 2019 and examined order rejections related to Manufacturer Backorder and Manufacturer Allocation. The DoD analyzed the data and used a threshold of 50 instances or more of rejections for each National Drug Code (NDC) to determine unavailability. During this period, DLA found that approximately 1,334 NDCs were experiencing unavailability due to Manufacturer Backorder and 238 were experiencing availability issues due to Manufacturer Allocation.

DoD's access to generic drugs is also limited by the Trade Agreements Act (TAA) of 1979, a Federal law applicable to all Federal contracts. TAA prohibits Federal agencies from acquiring products made in certain countries. In the case of drugs, both the finished product and the active pharmaceutical ingredient (API) must be developed in a TAA-compliant country, unless the API undergoes substantial transformation in a compliant country. Because the APIs for many generic drugs are made in China and India, which are not TAA-compliant, DoD cannot purchase them

but must instead buy the more expensive compliant generic or brand version. In Fiscal 2018, an estimated 75 percent of the drugs DLA purchased were brands, and only 25 percent were generic.

Currently, the DoD does not maintain the data needed to determine how much more it pays for compliant drugs when TAA compliant generics are not available. However, the Department recently had an independent study conducted that estimated cost reductions based on waiving TAA compliance. The study analysts estimated that waiving TAA compliance requirements would reduce DoD's costs between \$36 million and \$83 million annually depending on the scope of the waiver.

Department of Veterans Affairs

The Department of Veterans Affairs (VA) is responsible for providing vital services, including health care services, benefits programs, and access to national cemeteries, to America's former military personnel and their dependents.

On behalf of all Federal purchasers, the VA administers several Federal Supply Schedules (FSS) under delegated authority from the General Services Administration. Included in this delegated authority is the Federal Supply Schedule for pharmaceuticals. The FSS serves multiple Federal entities including the Department of Defense (DoD), Bureau of Prisons (BoP), U.S. Public Health Service (PHS), Indian Health Service (IHS) and the VA, and covers approximately 15 million beneficiaries. The beneficiaries VA serves have low prescription co-payments and statutory authority exempts many beneficiaries from prescription co-payments based on a variety of factors, including Service Connected Disabilities and their ability to pay. Beneficiaries also have an annual cap on prescription co-payments.

Public Law 102-585 (also known as The Veterans Health Care Act of 1992) places upper limits on the prices drug manufacturers can charge "Big 4" Federal customers relative to what they charge non-Federal purchasers for drugs required to be listed in the FSS. The Big 4 Agencies are VA, the Department of Defense, the Public Health Service and the Coast Guard. Public Law 102-585 dictates that drug manufacturers may charge the Big 4 no more than 76 percent of the average price for which they sell an FSS drug to non-Federal purchasers.

The VA uses several approaches to obtain medicines for veterans, all of which are subject to established procurement hierarchies. If generic drugs are available via the FSS, the agency may buy through those contracts if a VA or joint National Contract with Other Government Agencies (OGAs) is not in place. If the needed drugs cannot be obtained through any of the contracts, VA can purchase on the open market using the Streamlined Acquisition Procedures outlined in the Federal Acquisition Regulation (FAR) or by submitting a procurement request to a warranted contracting officer.

In the event a competitively bid VA National Contract supplier lacks product to fulfill an order due to a national drug shortage, and the VA must purchase the product elsewhere, the national contract vendor may be asked to credit the VA for any purchases made in excess of what the contracted product for the same quantity would have cost. Based on back order reimbursement from the first two quarters of VA Fiscal Year 2019 where VA elected to exercise this contract clause, it is estimated that these back orders will cause an increased cost of \$2.5 million for the entire fiscal year. The magnitude of VA's actual excess cost for Fiscal Year 2019 due to procuring alternate supplies of drugs due to national shortages is estimated to be significantly larger than the amount it will recoup via contract penalties.⁸

All drugs purchased by VA must comply with the Trade Agreements Act (TAA) and the Buy American Act (BAA). A Federal Acquisition Regulation (FAR) process exists for VA to obtain a waiver to buy a non-TAA or non-BAA compliant drug, but this approach takes months to

⁸ Estimate provided in an email from Jennifer L Zacher, Assistant Chief Consultant, VA Pharmacy Benefits Management Services, to FDA on April 7, 2019.

complete for each drug shortage and does not work in practice. When no other options are available, VA allows the use of 503B compounders⁹ but strongly advises against it due to the associated risk. If VA facilities choose to outsource to a compounder, there are requirements the pharmacy must meet. VA has a growing number of contracts where they cannot find a supplier.

When drugs are in shortage in the United States, importation might enable the VA to procure them for its beneficiaries. However, importation is generally not an option since many products do not comply with the TAA and BAA. For several years, VA has advanced a legislative proposal to amend Subchapter II of Chapter 81, Title 38 of the United States Code to allow VA pharmaceutical procurements to be exempt from the TAA and BAA under certain conditions that could negatively affect the health of veteran patients. However, no legislative action has been taken on the proposal to date.

⁹ Refers to outsourcing facilities that compound consistent with section 503B of the FD&C Act (21 U.S.C. 353B).

Drug Enforcement Administration

The Drug Enforcement Administration (DEA) administers and enforces the Controlled Substances Act (CSA) to help ensure the availability of controlled substances, including certain prescription drugs, for legitimate use while limiting their availability for abuse and diversion. The CSA requires the DEA to set quotas to manage the amount of certain substances that are available in the United States. The CSA also requires those handling controlled substances to register with the DEA. In addition, the DEA works to disrupt and dismantle major drug trafficking organizations and uses confidential informants to help facilitate investigative efforts.

Controlled Substances Quota Process

The DEA sets an annual aggregate production quota (APQ) for each basic class of Schedule I and II controlled substances. The APQ is a “top line” number that specifies the maximum amount of each controlled substance that can be manufactured in the United States in a given year to provide for the estimated medical, scientific, research, and industrial needs of the United States, lawful export requirements, and the establishment and maintenance of reserve stocks. It then sets bulk and procurement quotas for individual manufacturers. Generally, the DEA sets quotas for active ingredients, not active ingredient dosage forms. Prior to the enactment of the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act enacted October 24, 2018), it could not tell individual manufacturers what prescription drugs and in what formulation to make with their quota allotment. With the enactment of the SUPPORT Act, the DEA may under specific conditions listed in the Act direct a manufacturer to utilize its allotted quota for specific formulations. 21 U.S.C. 826(a)(2).

Because of the opioid crisis, the DEA has recently been under pressure to lower several APQs, which has had a cascading effect on manufacturers. Under a provision of FDASIA that amended the DEA quota law (21 U.S.C.826(h)), any manufacturer who believes that the DEA is not giving them a sufficient quota to meet legitimate medical needs can contact the FDA to trigger the FDASIA provision. After an internal review, the FDA contacts the DEA with the information provided by the manufacturer and a synopsis of FDA’s internal assessment, the DEA then has 30 days to respond. So far, the DEA has not received any requests from the FDA under this mechanism. FDA also monitors drug shortages and if it observes a shortage of prescription drugs containing controlled substances, can also contact the DEA under the current Memorandum of Understanding (MOU) to discuss if a quota adjustment is warranted.

The DEA does not believe that it has ever contributed to a drug shortage, as manufacturers’ business decisions are beyond its control and the quotas assigned to manufacturers already have a “built in cushion.” When the DEA sets a quota for a manufacturing company, it incorporates information not only on projected needs, but also on expected, product development requirements, manufacturing losses and an inventory allowance based on 50 percent of the average current and prior year’s company’s sales. Excess quota that is not used in a given year expires and cannot be utilized to procure or manufacture new material. However, any material that was in the manufacturing process at the end of the calendar year may be completed without new quota for the new year. In addition, manufacturers can request an increase in quota at any time during the year, and as many times as needed. For approval, the manufacturer generally

must demonstrate new product development requirements or an increase in demand from the current year's sales not previously contemplated.

GAO Report on DEA Management of the Quota Setting Process

In the past 15 years, shortages of prescription drugs containing controlled substances, such as narcotics and stimulants, have increased nationwide, limiting providers' and patients' access to medications needed for treatment. In February 2015, the U.S. Government Accountability Office (GAO) reported on a study¹⁰ examining shortages of drugs containing controlled substances. The GAO report claimed that the DEA had not effectively administered the quota process managing the amount of certain controlled substances available for use in the United States, and that it needed to strengthen its coordination with FDA to prevent and mitigate shortages. The DEA raised multiple objections to the GAO report. However, during FDA's solicitation of public input into the drivers and solutions for drug shortages in 2018-2019, some stakeholders expressed a desire for better coordination between the Agency and the DEA.

In the 2015 report, GAO made seven recommendations, including that the DEA and FDA should update their MOU and agree on steps that each should take regarding drug shortages. In March 2015, the DEA implemented one recommendation to finalize an information-sharing agreement with FDA regarding drug shortages. In June 2016, the DEA implemented a second recommendation strengthening the internal controls in the quota system.¹¹ On July 16, 2018, the DEA published a final rule to strengthen the process for setting controls over diversion of controlled substances and make other improvements in the quota management regulatory system for the production, manufacturing, and procurement of controlled substances.¹²

¹⁰ "DRUG SHORTAGES: Better Management of the Quota Process for Controlled Substances Needed; Coordination between DEA and FDA Should Be Improved," GAO-15-202. February 2015.

¹¹ DRUG ENFORCEMENT ADMINISTRATION: Additional Actions Needed to Address Prior GAO Recommendations, GAO -16-737T, a testimony before the Committee of the Judiciary, U.S. Senate.

¹² Department of Justice, Drug Enforcement Administration 21CFR Part 1303 [Docket No. DEA-480] RIN 1117-AB48, Controlled Substances Quotas," Action: Final Rule, *Federal Register* Vol 83, No. 136 Monday, July 16, 2018, p. 32784.

Federal Trade Commission

The mission of the Federal Trade Commission (FTC) is to protect consumers and competition by preventing anticompetitive, deceptive, and unfair business practices through law enforcement, advocacy, and education without unduly burdening legitimate business activity. Congress has empowered the FTC to take action to prevent unfair methods of competition, such as illegal anticompetitive agreements among firms to increase prices or restrict supply, and illegal exclusionary or predatory practices. In addition to enforcing laws that prohibit unreasonable restraints of trade, the FTC is authorized to challenge mergers and acquisitions that are likely to reduce competition and lead to higher prices, lower quality goods or service, or less innovation.

Although the FTC has no authority to regulate the price of prescription drugs, nor general authority to make markets more competitive, protecting American consumers from anticompetitive activity in the health care sector has long been one of its most important responsibilities. The FTC combats high prices and drug shortages by enforcing the antitrust laws to stop anticompetitive conduct or mergers that are likely to lead to higher prices or reduced supply.¹³ The FTC's enforcement efforts and merger analysis are guided by public policy underlying the antitrust laws, namely, the promotion of consumer welfare.

Although a unilateral decision to raise prices or stop marketing a product, without more, is not actionable under the antitrust laws,¹⁴ an agreement among competitors to fix prices or reduce output is illegal.¹⁵ The FTC has the authority to prosecute anticompetitive conduct that limits consumer access to affordable prescription drugs, and in some cases, seek monetary relief for those harmed by the illegal conduct.

Complaints about drug shortages and price spikes come to the FTC from various sources including consumers, other government agencies, Congress, trade press, and news reports. Complaints are assigned to divisions in the FTC's Bureau of Competition that specialize in the pharmaceutical industry and are investigated as they arise. These efforts go back at least two decades. For example, in December 1998, the FTC filed suit against Mylan Laboratories and three other drug companies, charging them with restraint of trade, monopolization, and conspiracy to monopolize the markets for two generic drugs through exclusive dealing arrangements. The FTC alleged that Mylan and its co-conspirators agreed to deny access to the active pharmaceutical ingredients (API) needed to manufacture lorazepam and clorazepate tablets. Without access to the API, Mylan's competitors were unable to manufacture and sell the two drugs, allowing Mylan to raise prices approximately 2000-3000 percent, depending on bottle

¹³ For a list of FTC conduct and merger enforcement actions in the pharmaceutical industry, see Overview of FTC Actions in Pharmaceutical Products and Distribution (June 2019),

https://www.ftc.gov/system/files/attachments/competition-policy-guidance/overview_pharma_june_2019.pdf

¹⁴ Organisation for Economic Co-operation and Development, Excessive Pricing in Pharmaceutical Markets—Note by the United States, 28 November 2018, [https://one.oecd.org/document/DAF/COMP/WD\(2018\)111/en/pdf](https://one.oecd.org/document/DAF/COMP/WD(2018)111/en/pdf)

¹⁵ Naked agreements to fix prices or restrict output may be prosecuted criminally. Enforcement authority for criminal violations of the antitrust laws, such as price fixing and bid rigging, is vested solely in the Department of Justice.

size and dosage strength. The FTC settled the case with the defendants, returning \$100 million in illegal profits to injured consumers and state agencies.¹⁶

For nearly as long, the FTC has challenged a number of reverse payment agreements (also known as “exclusion payment” or “pay-for-delay” agreements) between branded drug companies and their generic rivals. Such agreements entail settlements of patent litigation in which the branded drug company pays its potential generic competitor to abandon a patent challenge and delay entering the market with a lower cost, generic product. Branded drug companies have used such agreements to buy more protection from competition than their patent rights provide, at the expense of competition and consumers.¹⁷

In addition, the FTC has challenged unilateral conduct by branded drug companies to illegally maintain a monopoly position by engaging in a strategy known as “product hopping”¹⁸ and through abuse of governmental processes, such as sham litigation,¹⁹ or repetitive and meritless regulatory filings (such as citizen petitions to the FDA).²⁰ The FTC also has acknowledged that misuse of restricted drug distribution programs, such as Risk Evaluation and Mitigation Strategies (REMS), may limit supply and violate the antitrust laws. Branded drug companies allegedly have used restricted distribution of drug samples to thwart efforts by generic competitors to establish bioequivalence in order to obtain FDA approval.²¹ Branded drug companies’ actions to deter generic rivals have delayed or blocked consumer access to lower cost drug products.

The second way the FTC considers how high drug prices and shortages may impact consumer welfare is through its review of mergers in the pharmaceutical industry. The FTC reviews mergers and acquisitions that may facilitate or exacerbate high drug prices or shortages where

¹⁶ FTC Reaches Record Financial Settlement to Settle Charges of Price-fixing in Generic Drug Market, <https://www.ftc.gov/news-events/press-releases/2000/11/ftc-reaches-record-financial-settlement-settle-charges-price>

¹⁷ *Federal Trade Commission v. Actavis, Inc.*, 570 U.S. 756 (2013). *In re Androgel Antitrust Litigation (No. II)*, MDL Docket No. 2084 (All Cases) 1:09-MD-2084-TWT. The FTC settled this case before trial in February 2019. <https://www.ftc.gov/news-events/press-releases/2019/02/ftc-enters-global-settlement-resolve-reverse-payment-charges>

¹⁸ *Federal Trade Commission v. Reckitt Benckiser Group PLC*, Case No. 1:19-cv-00028-JPJ-PMS (W.D. Va.), FTC File No. 131-0036 (Reckitt agreed to pay \$50 million to settle FTC allegations that Reckitt violated the antitrust laws through a deceptive product hopping scheme to thwart lower-priced generic competition to its branded Suboxone tablets. FTC’s complaint alleged that before generic versions of the tablets became available, Reckitt developed a new film version of Suboxone and misrepresented that the new film version was safer than the tablets), <https://www.ftc.gov/news-events/press-releases/2019/07/reckitt-benckiser-group-plc-pay-50-million-consumers-settling-ftc>

¹⁹ *Federal Trade Commission v. AbbVie Inc., et al.*, Case No. 2:14-cv-051510-HB (E.D. Pa.), FTC File No. 121-0028 (complaint filed seeking a permanent injunction and other equitable relief on September 8, 2014), <https://www.ftc.gov/enforcement/cases-proceedings/121-0028/abbvie-inc-et-al>

²⁰ *Federal Trade Commission v. Shire ViroPharma Inc.*, Civil Action No. 1:17-cv-00131-RGA (D. Del.), FTC File No. 1210062 (complaint filed February 7, 2017), <https://www.ftc.gov/enforcement/cases-proceedings/121-0062/shire-viropharma>

²¹ Without taking a position on the merits, the FTC filed an amicus brief in a private suit contending that Mylan’s antitrust claims are not barred as a matter of law. *Mylan Pharmaceuticals v. Celgene Corp.*, Case No. 2:14-CV-2094-ES-MAH (D. N.J. June 17, 2014), https://www.ftc.gov/system/files/documents/amicus_briefs/mylan-pharmaceuticals-inc.v.celgene-corporation/140617celgeneamicusbrief.pdf.

the parties sell competing drug products and the merged firm may be able to exercise market power post-merger.²² For branded drug companies, the focus typically is on overlaps in a therapeutic category, and for generic drug companies, the focus typically is on overlaps in specific molecules.

The FTC frequently requires divestiture of assets and related intellectual property rights as a condition of approving a merger between two pharmaceutical companies that market competing products or have competing drugs in development. For example, in July 2016, the FTC ordered Teva to divest the rights and assets related to 79 pharmaceutical products to 11 firms to address competitive concerns raised by its acquisition of Allergan, preserving competition in markets where Teva and Allergan competed or would likely have competed in the future if not for the merger.²³ Moreover, some markets, such as generic injectables, are susceptible to supply disruptions and shortages, which makes them especially sensitive to a reduction in the number of competitors.²⁴

The FTC and the FDA have a long history of working together to ensure that safe and effective drugs are accessible and affordable for consumers. For instance, on July 27, 2017, then Acting Director of the FTC's Bureau of Competition, Markus Meier, spoke on a panel with then-Commissioner of Food and Drugs Scott Gottlieb regarding Antitrust Concerns and the FDA Approval Process before the House of Representatives Judiciary Committee's Subcommittee on Regulatory Reform, Commercial, and Antitrust Law.²⁵ Mr. Meier also participated as a panelist at the FDA's Public Meeting: The Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access on July 18, 2017.²⁶ The FTC also consults industry experts and uses research and market reports related to the pharmaceutical industry to advocate for regulatory policies that encourage more competition. On November 8, 2017, the FDA joined the FTC in a public [workshop](#), "Understanding Competition in Prescription Drug Markets: Entry and Supply Chain Dynamics," in Washington DC.²⁷ This workshop considered, *inter alia*: 1) questions concerning whether generic drug companies have enough incentives to enter markets where the brand drug is off-patent; 2) the role of intermediaries such as pharmacy benefits managers

²² The FTC maintains a comprehensive merger review program to identify and prevent pharmaceutical mergers that may reduce competition and lead to higher prices for specific pharmaceutical products. For a list of merger cases in the pharmaceutical industry, see Sections IV and V in Overview of FTC Actions in Pharmaceutical Products and Distribution (June 2019),

https://www.ftc.gov/system/files/attachments/competition-policy-guidance/overview_pharma_june_2019.pdf

²³ FTC Approves Final Order Preserving Competition in Markets for 79 Pharmaceutical Products, <https://www.ftc.gov/news-events/press-releases/2016/07/ftc-requires-teva-divest-over-75-generic-drugs-rival-firms-settle>

²⁴ FTC Puts Conditions on Mylan's Proposed Acquisition of Agila from Strides, <https://www.ftc.gov/news-events/press-releases/2013/09/ftc-puts-conditions-mylans-proposed-acquisition-agila-strides>

²⁵ Antitrust Concerns and the FDA Approval Process Subcommittee on Regulatory Reform, Commercial, and Antitrust Law (Committee on the Judiciary), <https://docs.house.gov/Committee/Calendar/ByEvent.aspx?EventID=106333>

²⁶ Public Meeting: The Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access, <https://www.fda.gov/news-events/public-calendar-meetings-fda-officials/public-calendar-july-16-22-2017>

²⁷ Understanding Competition in Prescription Drug Markets: Entry and Supply Chain Dynamics, <https://www.ftc.gov/news-events/events-calendar/2017/11/understanding-competition-prescription-drug-markets-entry-supply>

(PBMs) and group purchasing organizations (GPOs); 3) how well providers and consumers understand the roles of PBMs and GPOs in the drug supply chain; and 4) how these intermediaries may impact the affordability and availability of prescription drugs in the United States.

HHS Office of the Assistant Secretary for Preparedness and Response

The mission of the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) is to save lives and protect Americans from 21st century threats. ASPR leads the Nation's medical and public health preparedness for, response to, and recovery from disasters and public health emergencies. To accomplish this mission, ASPR collaborates with the private sector; community members; health care coalitions; state, local, tribal, and territorial governments; and other partners across the country. The strength of our Nation's public health and medical infrastructure, as well as the capabilities necessary to quickly mobilize a coordinated national response to pandemics, attacks and disasters, are essential to save lives and protect all Americans.

The continuity of medical services depends on the consistency of a reliable supply chain in both steady state and response. The medical supply chain is an incredibly sophisticated system, with private sector partners working across a global market and relying on just-in-time delivery. Disruptions to the system can have critical impacts on patient care. ASPR's involvement with drug shortages is inextricably linked to its impact on health care delivery during emergencies and disasters. As a further concern, disasters can exacerbate shortage issues, such as the shortage of intravenous (IV) saline solution, which became more acute during the 2017 hurricane season. Multiple ASPR components are actively involved in supporting work on drug shortages, including the Division of Critical Infrastructure Protection (CIP); the Strategic National Stockpile (SNS); the Biomedical Advanced Research and Development Authority (BARDA); the Hospital Preparedness Program (HPP); and ASPR's Technical Resources, Assistance Center, and Information Exchange (TRACIE). ASPR authorities, policies, and programs ensure access to potential life-saving pharmaceuticals and medical supplies for use in a public health emergency.

CIP promotes resilience of the Nation's health infrastructure by leading a dynamic public-private partnership, drawing from all aspects of the Healthcare and Public Health (HPH) Sector, to manage risk and coordinate effective response to 21st century threats. Coordinating with private and public sector partners, CIP works to identify potential courses of action to both better understand and address supply chain issues, promotes resilience, and fosters connections across the sector. CIP further works to understand foreign dependencies within the supply chain and identify how policy decisions and geopolitical concerns could impact access to products in the health care delivery system. Through communication, information sharing and analysis, and policy development, ASPR is able to support the continuity of life saving and life sustaining supply chain capabilities in the Nation's Healthcare and Public Health Sector.

The SNS manages and delivers life-saving medical countermeasures (MCM) during a public health emergency. It is the largest federally owned repository of pharmaceuticals, critical medical supplies, Federal Medical Stations (FMS), and medical equipment available for rapid delivery to support Federal, state, and local response to health security threats. If a biological, chemical, radiological, or nuclear event occurred on United States soil today, the SNS is the only Federal resource readily available to respond once state and local MCM supplies are depleted. Additionally, SNS is a significant purchaser of pharmaceuticals and medical supplies, and maintains relationships with key members of the supply chain to strategically address supply availability within the United States. Together with Federal and private sector partners, the SNS

analyzes integrated procurement, storage, and delivery models to identify ways to increase supply availability within the United States, such as increasing production of key products and utilizing strategies like vendor-managed inventory and alternative distribution models.

BARDA supports the development and transition of medical countermeasures against chemical, biological, radiological, and nuclear threats, as well as pandemic influenza and other emerging infectious diseases, from research through advanced development towards consideration for approval by the FDA and inclusion into the SNS. BARDA's Division of Research, Innovation, and Ventures (DRIVE) plans to leverage new authorities under the 21st Century Cures Act to stimulate medical countermeasures innovation to solve systemic challenges. The team identifies promising new technologies across the country using an entrepreneurial approach to address public health emergencies; current focus areas include sepsis, early, pre-symptomatic detection of infection, and a variety of innovative interventions to improve MCM evaluation, production, delivery, and administration.

HPP is the nation's only source of Federal funding to support regional health care system preparedness. HPP improves patient outcomes and minimizes the need for Federal and supplemental state resources during emergencies through the development and sustainment of health care coalitions (HCCs). HCCs are comprised of diverse and often competitive health care organizations with differing priorities and objectives within a geographic area. HCCs have been active during intravenous fluid and drug shortages, including information sharing about contingency strategies and current inventories. The HCC provides a central mechanism for information sharing and management coordination between and among health care facilities to ensure the consistency of use and recommendations during shortages. The ability to share information improves situational awareness, optimizes the use of resources, and mitigates the impact of the emergency on the facilities themselves and existing and potential patients. In 2019, HPP elevated the significance of supply chain awareness and preparedness for shortages by directing coalitions to more formally identify sources for medicine and supplies and prepare to manage shortages cooperatively, when they arise.

ASPR TRACIE was created to meet the information and technical assistance needs of regional ASPR staff, health care coalitions, health care entities, health care providers, emergency managers, public health practitioners, and others working in disaster medicine, health care system preparedness, and public health emergency preparedness. ASPR TRACIE provides vetted resources for common topics of inquiry housed in a library, a centralized method to provide technical assistance for health and medical preparedness activities, and a mechanism for end users to communicate directly and share promising practices, questions, and peer-to-peer answers. ASPR TRACIE has developed and compiled resources to help stakeholders prepare for and manage drug shortages and the allocation of scarce resources. In 2017, ASPR TRACIE hosted a webinar on Clinicians and Coalitions: A Conversation about Finding Solutions for Medical Shortages.

U.S. Department of the Treasury

The U.S. Department of the Treasury's mission is to maintain a strong economy and create economic and job opportunities by promoting the conditions that enable economic growth and stability at home and abroad, strengthen national security by combating threats and protecting the integrity of the financial system, and manage the U.S. Government's finances and resources effectively.²⁸

The Treasury is organized into two major components the Departmental offices and the [operating bureaus](#). The [Departmental Offices](#) are primarily responsible for the formulation of policy and management of the Department as a whole, while the operating bureaus carry out the specific operations assigned to the Department. Taxation falls within the Treasury's jurisdiction, as its basic functions include:

- Collecting taxes, duties and monies paid to and due to the United States and paying all bills of the United States;
- Advising on domestic and international financial, monetary, economic, trade and tax policy;
- Enforcing Federal finance and tax laws;
- Investigating and prosecuting tax evaders, counterfeiters, and forgers.

Some stakeholders have suggested that tax credits might be used as a mechanism to prevent or mitigate drug shortages, e.g., by providing incentives for manufacturers:

- To invest in modern manufacturing systems, which are less prone to the quality problems that can lead to supply disruptions and shortages;
- To locate their facilities in the United States rather than overseas, which would shorten and strengthen the supply chain. Long, complex supply chains are believed to be vulnerable to disruptions resulting in shortages;
- To begin marketing, or continue to market, an unprofitable drug that otherwise would have no business case and be vulnerable to going into shortage.

According to the Treasury, there is limited evidence that tax credits are effective in achieving their goals. To be effective, a tax credit must be well designed. The industry receiving the credit needs to identify and communicate the critical factors providing levers for achieving the credit's goal, and this is often difficult to do. Furthermore, tax credits granted under highly specific conditions are often difficult to administer: e.g., it may be hard to correctly identify the parties who qualify for the credit. To the extent of a market failure, the Treasury may wish to use tax credits to address the issue, but as the Government aims to maintain stable tax revenue, credits given to one party may require that taxes be raised for another.

The Tax Cuts and Jobs Act of 2017 introduced sweeping changes to the tax code. It promised to stimulate job growth, incentivize companies to repatriate profits from abroad and invest in the U.S. economy. The Treasury is hopeful that the changes will provide an incentive for drug

²⁸ See <https://home.treasury.gov/about/general-information/role-of-the-treasury>.

manufacturers to invest in modern manufacturing systems at domestic sites. However, it is too early to assess the effect that the changes to the tax code will have on the pharmaceutical industry.

Appendix E: A Framework for Enduring Solutions to Drug Shortages

The recommendations presented in this report are non-exhaustive but as this landscape continues to evolve, policymakers may want to consider using this framework in the future. In this appendix, FDA includes a framework that policymakers can apply to determine whether an additional proposed solution (or set of solutions) to drug shortages would be enduring. Based on the root causes FDA identified earlier in the report, the Agency believes that enduring solutions to drug shortages should address the following objectives:

1. *Increasing the economic sustainability of drug manufacturing and distribution*
A solution in this area should provide predictability in production costs, pricing, and volume sold; increase flexibility in contracting and sourcing of finished drugs and raw materials; and ensure that no one group of stakeholders is favored in contracts for purchasing drugs.
2. *Enhancing supply chain resiliency*
A solution in this area should provide increased transparency to purchasers on drug manufacturing and quality maturity, while also establishing mechanisms to reward supply chain resiliency and reductions in the severity of drug shortages.

Enduring solutions should also satisfy the following broad considerations to help ensure that they would be effective and feasible to implement:

1. *Providing total benefits to society that exceed total implementation costs*
An enduring solution should effectively address the harms of drug shortages without requiring too many resources to implement. For example, it could improve treatment outcomes or the availability of drugs, reduce staffing needs for responding to drug shortages, or reduce costs for purchasing alternative treatments. Likewise, it should seek to minimize any direct costs of implementing the solution or any indirect costs for adjusting or adapting to it.
2. *Distributing net benefits to most, if not all, affected stakeholder groups*
An enduring solution should encourage stakeholders to implement it by not overly favoring or penalizing any one group. Several categories of stakeholders should be considered, including drug manufacturers; supply chain intermediaries such as GPOs, PBMs, and wholesalers; health care providers such as hospitals and pharmacies; payers (both public and private); and patients.
3. *Avoiding any major unintended consequences that could increase the total costs associated with the solution, or that could otherwise undermine its effectiveness*
Similar to the first consideration, an enduring solution should avoid generating other adverse impacts that could undermine its success once implemented. These might include discouraging drug manufacturers from remaining in the marketplace, contributing to excessive hoarding or stockpiling among drug purchasers, or disclosing commercial confidential information and trade secrets.

Appendix F: Technical Summary of FDA's Analysis

Background

To supplement FDA's review of the published literature and the feedback the Agency received from stakeholders, FDA economists and other staff carried out several additional quantitative analyses to further elucidate the root causes of drug shortages.

FDA selected quantitative analyses that met the following three criteria:

- 1) Utility – the analysis had the potential to either filter out potential root causes or evaluate the importance of what remained.
- 2) Originality – there were few to no prior analyses on the topic, or previous analyses were several years out of date.
- 3) Feasibility – there were sufficient data, methods, and time available to complete the analysis.

FDA explored analyses that would help to address each of the three criteria listed above. While it initially considered developing a predictive model to identify risk factors for drug shortages, there was not enough time available to implement this approach.¹

Table 1 below lists each of the quantitative analyses that FDA completed for the report and which of the three root causes they supported.

¹FDA is continuing to work on this predictive model as part of a longer-term project. For more information about this effort, see Appendix C.

Table 1: Quantitative Analyses Completed for the Drug Shortage Report

Analysis	Key Questions	Root Cause(s) Supported		
		1	2	3
General Characteristics of Shortage Drugs	<ul style="list-style-type: none"> - What were the reasons reported to FDA for the shortages? - How did the drugs in shortage differ from the drugs not in shortage along economic, medical, and other dimensions? - Are there any groups of shortage drugs that stand out based on these characteristics? 	X	X	X
Market Trends for Shortage Drugs	<ul style="list-style-type: none"> - What were the trends in revenues, prices, and quantities sold prior to, during, and after the shortage? - How much did the shortage drugs and manufacturing facilities comprise of a company's overall revenues? - How did these results compare to similar drugs that did not go into shortage? - How many approved but unmarketed applications were there for shortage drugs? 	X		X
Impacts of Shortages	<ul style="list-style-type: none"> - How large was the gap between previous and current production during the shortage? - How were the drugs in shortage used medically? - How did these impacts vary across the phases of the shortage lifecycle? 	X		X
Market Response to Shortages	<ul style="list-style-type: none"> - Did sustained price increases occur during shortages? - Did companies enter the market or increase production? - Did quantity sold return to previous levels once the shortage ended? 	X		X
Other Potential Drivers of Shortages	<ul style="list-style-type: none"> - Did shortages follow failed inspections or previous shortages? - Did shortages coincide with approval of newer drugs with a similar route of administration? - Were shortage drugs manufactured by someone other than the applicant? 	X	X	X

As part of the Market Trends for Shortage Drugs analysis (see above), FDA also attempted to measure trends in the profitability of specific drugs as well as the companies that made them. The Agency carried out a preliminary analysis using two separate approaches but found both to be infeasible due to limitations of the available data. For more information about these approaches and the challenges encountered, see the General Methodology section for Key Finding 2.

In the rest of this appendix, the Agency provides a more detailed summary of the data, methodology, and results that support the analysis presented in the report. Note that results were combined from several of the analyses listed above to develop each of the key findings.

Dataset Development

Sample

To construct the sample, FDA extracted monthly IQVIA National Sales Perspective (NSP) data for prescription drugs covering January 2010 to August 2018.² FDA defined a drug by grouping products by active ingredient (CombinedSalt), route of administration (ProdForm1) and dosage form (ProdForm3); it also removed drugs from this dataset based on USC and ATC codes that were unlikely to meet FDA's definition of a drug³ or therapeutic biologic, such as vaccines and biological drug products derived from blood. This yielded a total of 3,357 drugs in the dataset.

FDA then merged this IQVIA dataset with an internal FDA list of drug shortages provided by the Center for Drug Evaluation and Research (CDER) Drug Shortage Staff (DSS) and identified 130 shortages beginning between calendar years 2013 and 2017, corresponding to 163 drugs in the sample.

Metrics

For each drug in the sample, FDA calculated its price in a specific month by dividing its total revenues by its volume sold – either the number of pills (Extended Units) for tablets and capsules, or the number of dosing units (Eaches). Revenues and prices were inflation-adjusted to August 2018 using the Producer Price Index series WPU0638, which includes non-seasonally adjusted data from pharmaceutical products.⁴

FDA calculated the number of approved application holders marketing the drug in each month by first matching up each drug to the FDA Orange Book, and then removing applications that had been withdrawn from approval at the time.⁵ An approved application holder was deemed to be marketing the drug if it had: (1) an active NDC listed in FDA's NDC Directory for June 2019, and (2) positive sales in the NSP database 4 months prior to going into shortage.

FDA determined whether a drug had a generic version in the market in each month by using the Brand/Generic column in the IQVIA data to flag whether a product with a value of "generic" or

² IQVIA. National Sales Perspective. January 2010 to August 2018. Extracted: October 2018.

³ Section 201(g) of the FD&C Act (21 USC 321(g)) 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). (Source: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/classification-products-drugs-and-devices-and-additional-product-classification-issues#statutorydef>)

⁴ <https://www.bls.gov/ppi/>

⁵ <https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book>

“other” had positive sales in that month. FDA also calculated the age of the product by taking the earlier of the approval dates in the [Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations](#)⁶ and its first marketing date in the IQVIA data (Product Launch Date) for all companies that ever sold the drug during the study time period.

Finally, in many cases FDA defines these metrics at their values from “just prior to the shortage,” which refers to 4 months before the shortage start date in FDA data. This allows the analysis to account for potential delays between when the shortage first occurred and when FDA was first notified.

Summary Statistics

The 163 drugs in the sample, just prior to the shortage, tended to:

- Be administered via injection: 103 (63 percent)
- Have a generic version in the market: 109 (67 percent)
- Be older products: with a median time since first approval or marketing of 34.8 years
- Be lower price, higher volume products: 93 (57 percent) had both lower prices and higher volume sold than the median within their dosage form
- Have several more companies approved to market than were actually marketing: For the shortage drugs studied, there were, on average, three companies that were approved to market but were not doing so.

The analyses that follow are based on this set of 163 drugs in shortage, and in some cases involve comparisons against other drugs that did not go into shortage. In the remainder of this technical appendix, FDA provides an overview of the analysis and describes how it supports the findings presented in the report.

Key Findings

Key Finding 1 – Quality issues were the most common reason for disruptions that became shortages

Because the root causes of supply disruptions are likely to differ from those of demand disruptions, FDA evaluated which categories of disruptions have been most prevalent among drugs that ultimately go into shortage, i.e., when the market is unable to prevent the shortage and it is formally declared by FDA.

Methodology

In this work, FDA analyzes the reasons for drug shortages submitted to FDA by manufacturers and categorized by the Center for Drug Evaluation and Research (CDER) Drug Shortage Staff (DSS).

⁶ Id., at 3.

Under Title X of the Food and Drug Administration Safety and Innovation Act,⁷ manufacturers of certain drug products⁸ are required to submit notifications to FDA of permanent discontinuations and other meaningful supply disruptions in the United States, including the reasons for these events. This information is required to be submitted to FDA at least six months prior to the event, or if that is not possible as soon as practicable. Manufacturers that do not comply with this provision of the Act are subject to having a non-compliance letter posted on the FDA website. To this date five of these letters have been posted.⁹

For each of the 163 drugs in the sample that went into shortage, FDA identified a reason for the shortage based on information entered into FDA's databases using these notifications. FDA aggregated these reasons into five main categories, which are defined below:

- 1) Quality Issues – When there is a manufacturing problem, either with a specific product or an entire facility, that temporarily leads to unavailability of that product or a delay in shipping it to end users. For example, particulate matter in the product or unavailability of raw materials.
- 2) Product Discontinuation – When a manufacturer permanently discontinues a product from sale and there is no concurrent quality problem. It is important to note that FDA is unable to determine if this is for an economic reason.
- 3) Increase in Demand – When market-wide demand for the product has increased, and there is no other problem that is making the product unavailable to end users. For example, if a more severe than expected flu season occurs and manufacturers are unable to keep up with demand for antiviral drugs that can treat the flu.
- 4) Natural Disaster – When any problems that led to the drug shortage were solely due to a natural disaster, i.e., the drug was not already in shortage and was not experiencing these problems prior to the natural disaster. For example, when Hurricane Maria struck Puerto Rico in September 2017 and damaged the power grid, some manufacturing facilities were forced to shut down production.
- 5) Unknown – When the manufacturer provided insufficient information to FDA to categorize the shortage.

Results

Figure 1 summarizes the most prevalent reasons for disruptions among the sample of 163 drugs. FDA found that 115 of these drugs (71 percent) experienced a supply disruption (either a quality issue, a product discontinuation, or a natural disaster), and that 101 of these supply disruptions (88 percent) were specifically tied to quality issues.

⁷ See [Public Law 112-144](#).

⁸ These include products that are life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition; and which are not a radiopharmaceutical drug

⁹ <https://www.fda.gov/drugs/drug-shortages/drug-shortages-non-compliance-notification-requirement>

Among the reasons that were known, this largely followed a similar pattern to previously published data from 2011; however, 29 (18 percent) of the reasons for disruptions were unknown, which represented a notable increase from previous data.¹⁰

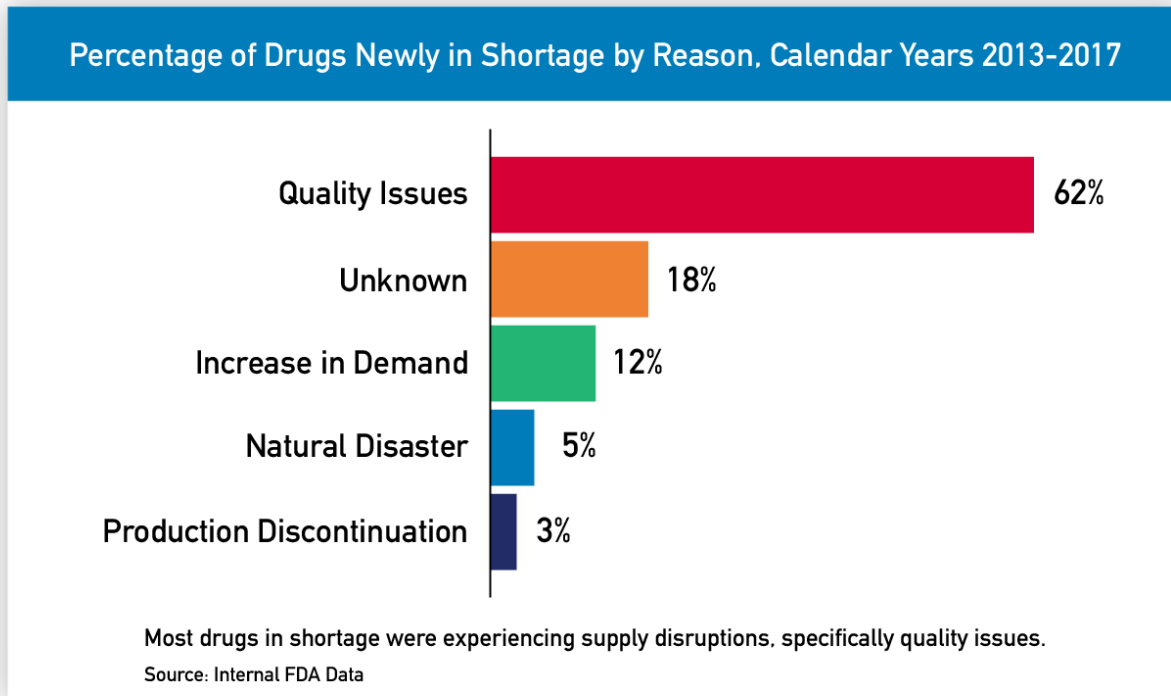


Figure A1. Most drugs in shortage were experiencing supply disruptions, specifically quality issues.

Source: Internal FDA Data

Key Finding 2 – Shortages were often associated with drugs that had a weak business case

Many stakeholders hypothesized that quality issues and shortages are more likely to occur when either the drug or the facility where the drug is made is insufficiently profitable to justify investing in improvements to manufacturing processes (i.e., it has a weak business case).

To understand how a drug’s business case may relate to the incidence of shortages, FDA examined broader economic trends for shortage drugs, as well as the relative importance of these shortage drugs and their manufacturing facilities to each company’s overall portfolio of drugs. FDA also compared these metrics against those of non-shortage drugs with similar characteristics.

¹⁰ Woodcock J, Wosinska M. Economic and technological drivers of generic sterile injectable drug shortages. Clin Pharmacol Ther. 2013;93(2):170-6

General Methodology

Framework for Determining a Drug's Business Case

Ideally, FDA would have evaluated the business case for a drug by directly measuring its profitability. However, for the reasons explained in the following paragraphs, FDA could not directly measure the profitability of shortage drugs.

The first approach for doing this attempted to estimate the overall profitability of generic drug manufacturing using financial statements (10-K forms) for publicly traded pharmaceutical companies that are reported to the Securities and Exchange Commission (SEC).¹¹ These statements capture information on gross and net profits of these firms, often separated by business segment (e.g. brand drugs vs. generic drugs). However, further review of these statements for several large- and mid-size companies revealed that pharmaceutical companies often record financial information differently, and that many companies changed their practices over time. This made it challenging to compare financial performance across companies, or to estimate trends within the same company.

The second approach attempted to estimate the profitability of individual generic drugs using data on international drug sales from IQVIA's MIDAS database.¹² The MIDAS database captures quarterly international sales and volume data that is locally recorded at the manufacturer, wholesale, or pharmacy level for over 60 countries between fourth quarter of 2012 and third quarter of 2018.

FDA attempted to use MIDAS data to estimate the profitability of individual generic drugs by assuming that drugs sold overseas in lower or middle income¹³ countries might more closely reflect the marginal cost of manufacturing.¹⁴ FDA made the distinction between lower- and middle-income countries to account for potential differences in manufacturing practices and quality maturity between drugs marketed in the United States and other countries with different regulatory requirements. For example, middle-income countries, particularly in Europe, often have differences in prices due to the significant role that the public sector plays in pharmaceutical purchasing and the use of external reference pricing.¹⁵ FDA classified countries as lower- or middle-income based on per-capita gross domestic product and retained only the countries that had the same products marketed in the U.S. Available low-income countries included India, Ecuador, Tunisia, Thailand, and the Dominican Republic. Available middle-income, European countries included Greece, Latvia, Hungary, Poland, Lithuania, Estonia, the Slovak Republic, and Turkey.

¹¹ U.S. Securities and Exchange Commission. *The Electronic Data Gathering, Analysis, and Retrieval System (EDGAR)*. <https://www.sec.gov/edgar.shtml>

¹² IQVIA MIDAS. 2012Q4 to 2018Q3. Extracted: January 2019.

¹³ FDA focused on middle income countries in Europe to identify ones that may have regulatory requirements more similar to those in the U.S.

¹⁴ FDA used this approach due to the general lack of product specific cost (and by extension, profit margin) data in public documents, including SEC financial statements; this is often considered business confidential information.

¹⁵ Souliotis K, Papageorgiou M, Politi A, Athanasiadis A. Pharmaceutical Pricing Policy in Greece: Toward a Different Path. *Front Public Health*. 2016;4:185. Published 2016 Aug 31

FDA matched products marketed overseas in at least one lower- or middle-income country with the equivalent product in the United States. The Agency then estimated gross profit margins for each matched product, one quarter prior to the shortage or in the quarter during the shortage, by first multiplying the total U.S. quantity sold by the difference between the U.S. price and the lower- or middle-income median (or lowest available) price of that product. This estimated profit was then divided by the total U.S. revenue of that product in that quarter to arrive at the gross profit margin.

FDA ultimately felt that this method did not accurately estimate profitability for several reasons. First, the standard deviation of profit margins across products and quarters was consistently large, which did not allow for easy interpretation or statistical testing. Second, estimated profit margins could not be calculated for up to 73 percent of shortage drugs – this was either because the product itself did not appear to be available in other countries, or no sales data were available in other countries during or in the months leading up to the shortage. Third, given different regulatory, manufacturing, and marketing standards between the United States and lower- and middle-income countries, FDA was unsure of whether a lower- or middle-income country's price was a useful proxy of production cost.

Due to these limitations in measuring profitability, FDA instead developed a framework to evaluate the business case that companies may have faced with the shortage drugs prior to the shortage.

The first step in this approach was to divide drugs based on whether their revenues were increasing or decreasing prior to the shortage. To do so, FDA fit univariate, linear regressions (n=154) of the drugs' revenues on the number of months from the beginning of calendar year 2010 to the starting month of the shortage.¹⁶ FDA considered those drugs with positive slopes to have had increasing revenues prior to the shortage, while those with negative slopes had decreasing revenues. Of the 154 drugs, 73 (47 percent) of them had increasing revenues prior to the shortage whereas 81 (53 percent) had decreasing revenues.

For each of these two groups, FDA examined whether there were differences among shortage drugs and similar non-shortage drugs using the following indicators:

- 1) The drug's revenues, prices, and volumes sold
- 2) The drug's share of a company's total sales
- 3) The manufacturing facility's share of a company's total sales

FDA defined similar non-shortage drugs as those that were never in shortage during the study period, and which had a comparable route of administration, age, price, and volume sold¹⁷ as of the first month with positive sales. For the route of administration, FDA matched drugs based on whether they were likely to require sterile manufacturing processes.¹⁸ For the remaining 3

¹⁶ Although there were 163 total shortages, only 154 shortages had sales prior to the shortage start date.

¹⁷ Price and volume sold were calculated as percentiles within the drug's dosage form, excluding drugs that had no sales over the previous 12 months.

¹⁸ Routes of administration that fell into this category included injection, ophthalmic, inhalation, implant, lung, vaginal, and urological.

characteristics, FDA performed a nearest neighbor match after standardizing the variables. For each shortage drug, FDA selected the 50 nearest drugs based on these 3 characteristics that also matched on the route of administration.

For each of these indicators, FDA followed a similar process. Using the sample of drugs that went into shortage and had sales prior to the shortage, FDA calculated the indicator in question for each shortage drug prior to the shortage start date. FDA then calculated the indicator in the same way for each of the 50 similar non-shortage drugs corresponding to each shortage drug. For the similar non-shortage drugs, FDA aggregated indicators across these drugs to create one comparison value for each shortage drug. Finally, FDA further aggregated both values – for the shortage drug and its aggregated comparators – across all shortage drugs and compared these results.

In aggregating these indicators, FDA used the following summarization techniques to capture the central tendency of the sample data.

- 1) Mode – In this case, the observation with the highest volume sold
- 2) Arithmetic Mean – A traditional sample mean, although this may potentially be influenced by extreme values
- 3) Median – To exclude potential extreme values, but without taking account of the full distribution of the data
- 4) Geometric Mean – To exclude potential extreme values while accounting for the full distribution of the data. Note that this measure is often similar to the arithmetic mean when extreme values are not present but has different statistical and mathematical properties.

To evaluate statistical significance when comparing results between shortage drugs and similar non-shortage drugs, FDA performed hypothesis tests for each indicator at the final level of aggregation using several methods. When FDA used a t-test, it assumed that the samples had unequal variances. When FDA used a pivot confidence interval to estimate a p-value, it carried out 1000 bootstrapped replications to estimate the error in these indicators and made no assumptions about sample distributions.

The Drug's Revenues, Prices, and Volumes Sold

Because FDA couldn't directly measure the profitability of shortage drugs, it instead indirectly explored this question by examining trends in the revenues, prices, and volumes sold of these drugs, compared with similar non-shortage drugs.

Methodology

To compare trends in these indicators, FDA first scaled these variables by their magnitude just prior to the shortage. For each shortage drug, FDA then took the geometric mean of these rescaled variables in each month before the shortage across its similar non-shortage drugs. For each month's calculation, FDA excluded similar non-shortage drugs that had a value exactly equal to zero.

To ensure that there were sufficient data for analysis, FDA excluded shortage drugs that did not have positive sales for at least one-third of their months before the start of the shortage. This left 144 of the 154 remaining shortage drugs to analyze.

For each of the remaining shortage drugs and each set of similar non-shortage drugs, FDA separately estimated the average trend in each indicator using a linear regression of the natural log of each variable on the month, from January 2010 to the start of the shortage. To compare trends between shortage and similar non-shortage drugs, FDA took the arithmetic mean of the regression coefficients for each trend within the two groups and applied a t-test to the differences in these means to evaluate statistical significance.

Results

Of the 144 drugs with sufficient data prior to the shortage, 73 (51 percent) experienced steadily decreasing revenues (see Figure 2A). Among these drugs, the magnitude of the decline was greater than similar non-shortage drugs: on average, 12.9 percent per year, compared with a 3.3 percent decline, ($p < 0.001$). During this decline in revenue, prices of these same drugs declined 2.5 percent on average per year, compared to a 2.9 percent increase in price among similar non-shortage drugs ($p < 0.01$). Despite both groups facing a declining volume of drugs sold, there was no discernable difference in this metric between drugs with declining revenue that went into shortage and similar non-shortage drugs that did not.

In contrast, 71 (49 percent) of the drugs with sufficient data prior to the shortage experienced steadily increasing revenue (see Figure 2B). Among these drugs, the magnitude of the increase was on average 23.6 percent per year, compared with a 1.0 percent increase among the similar non-shortage drugs ($p < 0.01$). While there was no statistically significant difference in price trends, the drugs that went into shortage experienced faster increases in quantity sold: a 13.6 percent increase for the drugs in shortage, compared to a 1.2 percent decline for similar non-shortage drugs ($p < 0.01$).

Comparison of Changes in Revenue, Price, and Volume Among Drugs with Decreasing and Increasing Revenues Before a New Shortage; Calendar Years 2013-2017

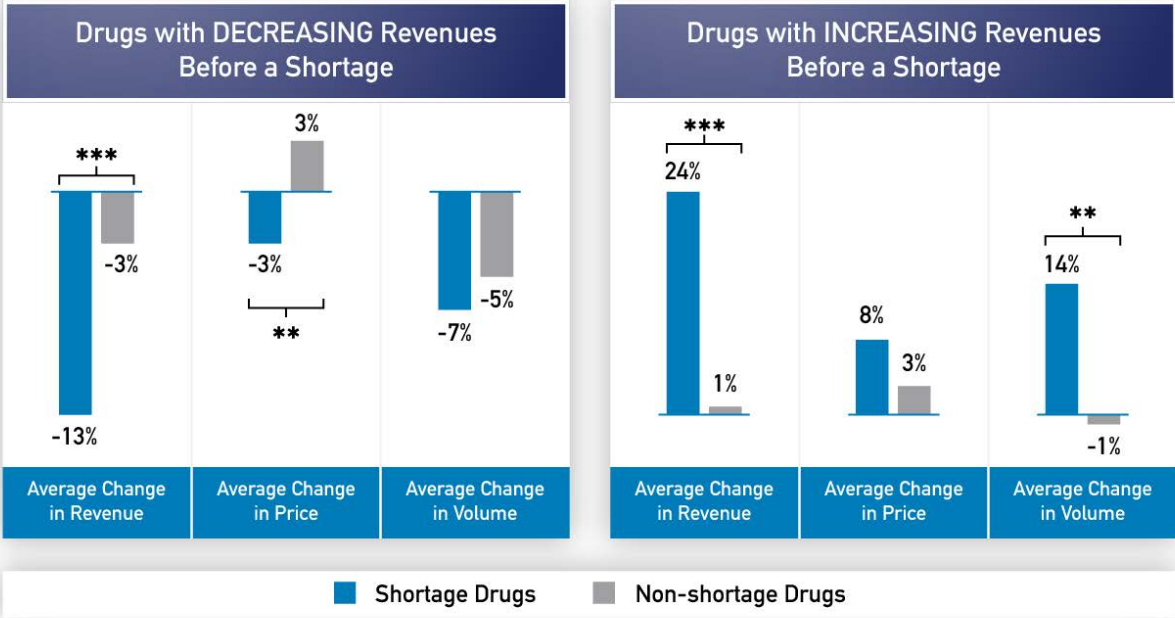


Figure A2. Drugs in shortage that faced decreasing revenues before shortage saw statistically significant differences in both their revenue and price changes compared to similar non-shortage drugs. Drugs in shortage that faced increasing revenues before shortage saw a statistically significant difference in both their revenue and volume changes compared to similar non-shortage drugs.

Sources: IQVIA. National Sales Perspective. January 2010 to August 2018. Extracted: October 2018; Internal FDA Data

Notes: ***=p<.001; **=p<.01; *=p<.05

Magnitudes of revenue changes were calculated for observations with sufficient data for analysis - 73/81 shortage drugs with decreasing revenue, 71/73 for shortage drugs with increasing revenue.

The Drug’s Share of a Company’s Total Sales

To analyze the importance of shortage drugs in a company’s portfolio relative to similar non-shortage drugs, FDA first compared the share of a company’s total sales between drugs in each group.

Methodology

For each of the 154 remaining shortage drugs, FDA calculated its share of a company’s total revenue just prior to the shortage. When a drug was sold by more than one company, FDA only considered the share of the revenue earned for the company that had the highest volume sold.

For each shortage drug's corresponding similar non-shortage drugs, FDA applied the same process as with the shortage drugs. FDA then took the geometric mean across these drugs' shares to create an analogous metric to the shortage drug.

FDA used pivot confidence intervals to estimate whether the difference between the geometric means in these two groups was statistically significant.

Results

Drugs that faced declining revenues before a shortage earned 0.16 percent of the company's total revenue just prior to the shortage, compared with 0.34 percent earned by similar non-shortage drugs ($p < .01$). However, drugs that faced increasing revenues before a shortage exhibited no statistical difference, with a 0.44 percent share of revenue earned in a company's portfolio, compared to 0.29 percent for similar drugs that did not go into shortage.

The Manufacturing Facility's Share of a Company's Total Sales

Similarly, FDA also investigated the importance of shortage drugs by examining the share of a company's revenue earned from their manufacturing facilities, comparing shortage drugs to similar non-shortage drugs.

Methodology

To compare the importance of manufacturing facilities between these two groups, the Agency first linked internal FDA registration and listing data to the dataset to identify all finished dosage form manufacturing facilities that may be producing a drug.¹⁹ This left 104 of the 154 remaining shortage drugs and 1,879 of the 3,357 drugs from the IQVIA data to analyze. FDA assumed that if multiple facilities were potentially making a product, they each produced an equal proportion of its revenue and volume sold. As a robustness check, FDA also considered only shortage drugs and similar non-shortage drugs where the available data allowed the Agency to precisely estimate the quantities and revenues of all drug products made at their respective facilities (i.e., when they were registered at only a single manufacturing facility).²⁰

For each shortage drug and company, FDA then took the revenue earned at each manufacturing facility just prior to the shortage and divided it by the total amount of revenue earned by that company in the same month. When there was more than one manufacturing facility for a particular drug and company, FDA only considered the one that had the highest volume sold.²¹

FDA then applied the same process for each shortage drug's corresponding similar non-shortage drugs. The Agency created an analogous metric by taking the geometric mean across the similar non-shortage drugs.

¹⁹ FDA's data do not capture how much of a drug is produced at each manufacturing facility

²⁰ This robustness check left 74% of shortage drugs and 66% of similar non-shortage drugs in the sample

²¹ Given the assumption of equal production across manufacturing facilities that make the same product, it is possible that there were multiple facilities that sold the same volume. In these cases, FDA took the arithmetic mean of the revenue shares across those manufacturing facilities.

As before, FDA used pivot confidence intervals to estimate whether the difference between the geometric means in these two groups was statistically significant.

Results

Manufacturing facilities that produced shortage drugs that faced decreasing revenues before a shortage earned 2.6 percent of a company's revenue just prior to the shortage, compared to 5.8 percent earned by facilities that manufactured similar non-shortage drugs ($p < .001$). Similarly, facilities that manufactured shortage drugs that faced increasing revenues before a shortage earned 3.7 percent of a company's revenue just prior to the shortage, compared to 5.9 percent earned by facilities that manufactured similar non-shortage drugs ($p < .05$).

The robustness check indicated that in both groups, the facilities that manufactured the shortage drugs still accounted for a smaller amount of their company's total revenues. However, the finding for the drugs in shortage that exhibited increasing revenues was no longer statistically significant at the 5 percent level.

Summary

The 53 percent of shortage drugs with declining revenues leading up to a shortage may have had a weak business case at both the product and facility levels. In addition to falling revenues, these drugs also faced falling prices and quantities. Likewise, these drugs and manufacturing facilities appeared to be financially less important to a company than similar products and facilities that did not go into shortage. These results suggest that the declining revenue drugs were becoming relatively less profitable over time and may have been experiencing falling demand.

The remaining 47 percent of shortage drugs with increasing revenues leading up to a shortage did not appear to have a weak business case at the product level but may have had a weak business case at the facility level. Among these drugs, both prices and volume sold were increasing, and they contributed a comparable share to a company's revenue as similar non-shortage drugs – suggesting that they may have been facing increasing demand. Yet, these drugs were potentially produced at manufacturing facilities that were less important to a company, suggesting that the business case for these drugs was not as strong as the other results may indicate.

Key Finding 3: The marketplace often fails to respond to drug shortages in a way that self-corrects shortages

Given that some of the drugs that went into shortage appeared to have a weak business case, FDA further explored market responses to drug shortages more broadly and whether shortages were self-correcting.

Methodology

Economic theory suggests that, in well-functioning markets, several milestones should occur during drug shortages that allow them to self-correct:

- 1) When demand exceeds supply, prices increase as the result of increased scarcity; these price increases continue until the market is able to close the gap between demand and supply.
- 2) With these higher prices, existing and/or new manufacturers are incentivized to increase production in this market.
- 3) Once this occurs, if the product is still useful to health care providers, quantities sold should eventually be restored to close to what they were prior to the shortage

To evaluate whether the drugs in the sample followed this pattern, FDA used three measures of the marketplace response to drug shortages corresponding to each of the milestones described above. We focused on these specific measures because they seemed appropriate in light of comments we received during listening sessions.

Measure 1: Price Increase

- At any point during the shortage, did the price of the drug increase by at least 50 percent over its level from just prior to the start of the shortage?
- Did this price increase continue for at least 6 consecutive months, or to the end of the study period if less than six months?

Measure 2: Production Increase

- At any point during the shortage, did at least one of the following occur compared with just prior to the start of the shortage?
 - An increase in the number of companies with positive sales for the drug (“entry of a new manufacturer”)
 - An increase in volume sold of at least 50 percent by a company that was already in the market just prior to the start of the shortage (“increased production from an existing supplier”)
- Did this increase continue for at least six consecutive months, or to the end of the study period if less than six months?

Measure 3: Quantity Restoration

- Calculate a baseline quantity by taking the monthly average of the volume sold between 4 and 15 months prior to the start of the shortage
- Calculate a “post-shortage” quantity by taking a similar average between four and nine months following the end of the shortage, or however much data are available if less than nine months of follow-up are available.
- If data are available from both metrics, determine whether the “post-shortage” quantity was greater than or equal to 80 percent of the baseline quantity

FDA also performed robustness checks by considering alternative thresholds for the first two measures (ranging between 5 and 50 percent), as well as an alternative time horizon of three months. In both cases, the qualitative conclusion that price increases are rare did not change.

Results

FDA's findings suggest that the marketplace often fails to respond to drug shortages in a way that allows it to self-correct (see Figure 3). Of the 163 drugs in the sample, just 4 drugs (2 percent) experienced all three milestones. Likewise, among the individual milestones:

- Only 29 drugs (18 percent) had a sustained price increase of 50 percent or more that began during the shortage.²² Of these 29, only 7 saw the entry of a new manufacturer or increased production from an existing supplier. Only 9 of the 29 had production restored to the level prior to the shortage.
- Only 54 drugs (33 percent) either experienced significant production increases (up to 50 percent or more) by companies that were already in the market, or had new suppliers enter the market. In the latter case, the median time to market entry was 13 months.
- Only 60 drugs (37 percent) had the quantity of the drug restored to within 20 percent of its amount just prior to the shortage.

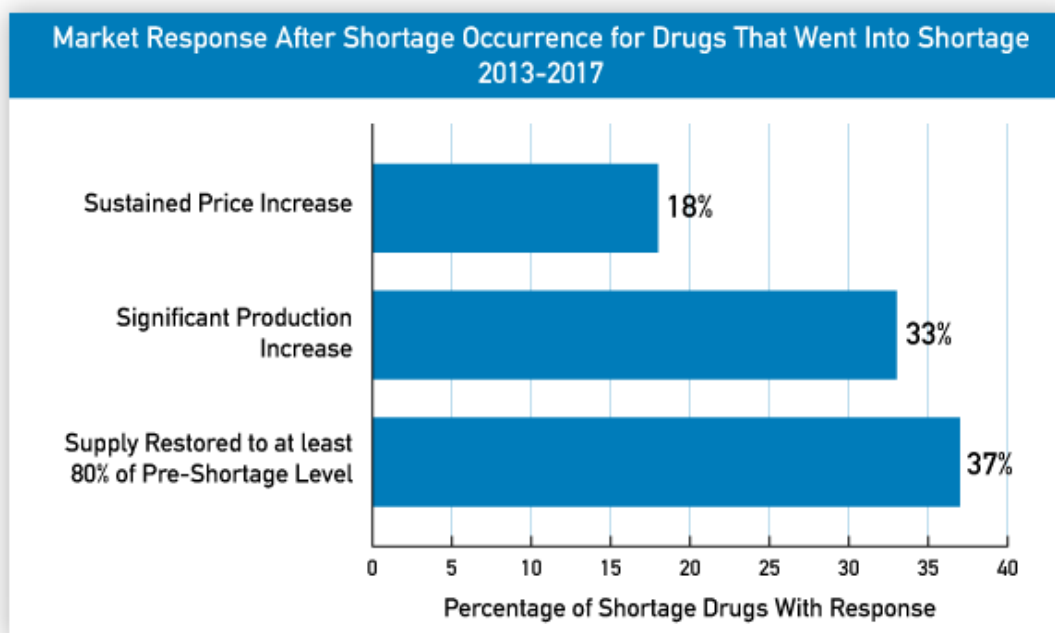
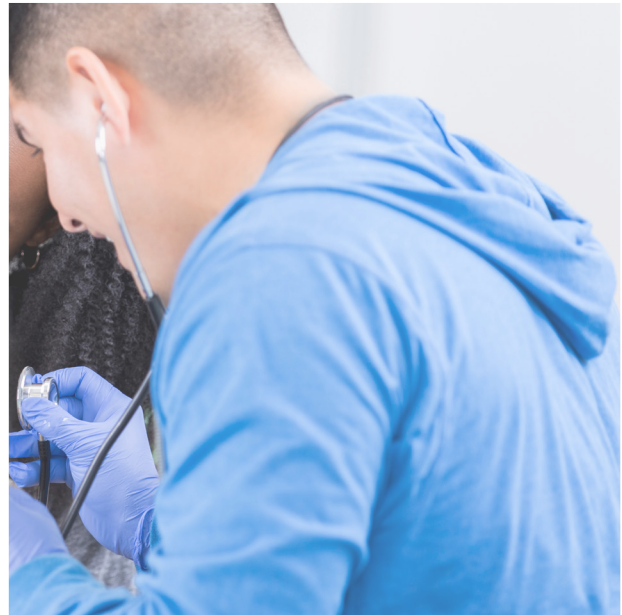


Figure A3. Few drugs in shortage experienced market response milestones that could help the shortages self-correct.

Sources: IQVIA. National Sales Perspective. January 2010 to August 2018. Extracted: October 2018; Internal FDA

²² There are two reasons why the results could also potentially overestimate the total number of sustained price increases occurring after shortage. First, roughly half of shortage drugs exhibited increasing price trends prior to going into shortage, and it is possible that their prices could have continued to increase even if they had not gone into shortage. This observation would suggest that such price increase might follow shortages without being attributable to them. Second, the analyses may also include gradual price increases that accumulated over a longer time period.



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

