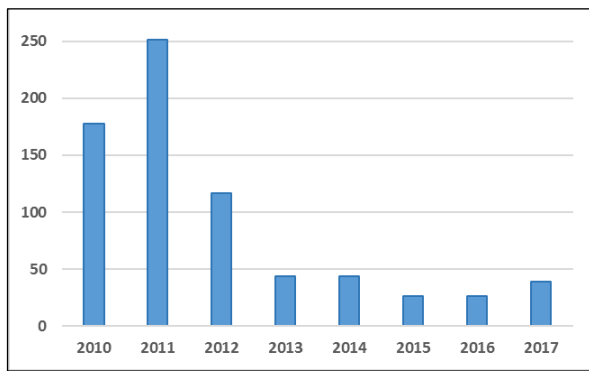




Drug Shortages: Causes, FDA Authority, and Policy Options

Drug shortages have remained a serious and persistent public health concern, despite the prevention and mitigation efforts of Congress, the Food and Drug Administration (FDA), and health care providers. While the number of new drug shortages has declined since its peak in 2011, many medically necessary products, such as sterile saline solution and sodium bicarbonate, remain in shortage. According to FDA, some active drug shortages have persisted for more than eight years.

Figure 1. Number of New Drug Shortages, 2010-2017



Source: FDA annual reports on drug shortages for calendar years 2015, 2016, and 2017. Presentation from November 27, 2018, public meeting, “Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions,” https://healthpolicy.duke.edu/sites/default/files/atoms/files/duke-fda_drug_shortages_presentation_slides__0.pdf.

Causes of drug shortages include manufacturing and quality issues (e.g., contaminants); lack of transparency (e.g., lack of information about drug quality and supply reliability); and business decisions made by individual firms (e.g., low profit margins leading to market exit and mergers resulting in a limited number of manufacturers).

Current Law Requirements

The Federal Food, Drug, and Cosmetic Act (FFDCA) and corresponding regulations require that drug manufacturers submit to FDA certain information pertaining to shortages. More specifically, FFDCA Section 506C requires that the manufacturer of a prescription drug that is life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, as specified, notify FDA of any permanent discontinuance or interruption in the manufacture of a drug that is likely to disrupt its United States supply. The manufacturer is required to notify FDA at least six months prior to such interruption, or, if not possible, as soon as practicable, which FDA regulation specifies to be no later than five business days after the permanent discontinuance or interruption occurs.

FDA must maintain and make public an up-to-date list of drugs that are in shortage (FFDCA §506E). The list must include

- the name of the drug in shortage,
- the name of the drug manufacturer,
- the estimated duration of the shortage, *as determined by FDA*, and
- the reason for the shortage, *as determined by FDA*, selecting from the following reasons: (1) requirements related to complying with good manufacturing practices, (2) regulatory delay, (3) shortage of an active ingredient, (4) shortage of an inactive ingredient component, (5) discontinuance of the drug’s manufacture, (6) delay in drug’s shipping, or (7) demand increase for the drug.

FDA maintains its list in the form of a searchable database on its website that provides information about current and resolved drug shortages and discontinuations reported to the agency. FDA maintains a separate list for biologics that are in shortage. The agency also is required to submit to Congress an annual report on drug shortages, which must include the number of actual and prevented shortages and manufacturer notifications; FDA communication procedures; and specified details of FDA shortage prevention and mitigation actions, among other things. (FFDCA §506C-1).

Like FDA, the American Society of Health-System Pharmacists (ASHP) also tracks drug shortages, although there are differences in how the two track and report information. FDA’s list is generally targeted toward the public, while ASHP’s audience is health care providers. In addition, among other differences, FDA’s list is based on manufacturer-provided information, while ASHP’s list is based on voluntary reports from health care providers, patients, and others, and is updated more frequently.

Actions to Prevent Drug Shortages

In 2012, Congress passed legislation to address drug shortages. Title X of the FDA Safety and Innovation Act (FDASIA, P.L. 112-144) expanded reporting requirements related to drug shortages; explicitly authorized FDA to expedite inspections and review of applications to help mitigate or prevent shortages; required FDA to submit annual reports to Congress; required FDA to establish a task force to develop and implement a strategic plan regarding its response to preventing and mitigating shortages; and required GAO to “examine the cause of drug shortages and formulate recommendations on how to prevent or alleviate such shortages.” In 2016, Section 3016 of the 21st Century Cures Act (P.L. 114-255) authorized

FDA to “award grants to institutions of higher education and nonprofit organizations for the purpose of studying and recommending improvements to the process of continuous manufacturing of drugs and biological products and similar innovative monitoring and control techniques.”

In the past year, FDA has announced a series of actions related to drug shortages. On July 12, 2018, FDA announced the availability of a new Drug Shortages Task Force, charged with looking for “holistic solutions to addressing the underlying causes for these shortages.” On November 9, 2018, FDA announced the availability of a new tool—the New Inspection Protocol Project (NIPP)—to be applied to the agency’s inspection of facilities that manufacture sterile injectable drugs, which have been the subject of sterility problems and shortages in the past. On November 27, 2018, FDA held a public meeting with various stakeholders to identify the root causes of drug shortages and recommend solutions.

Policy Options

Congress, FDA, and health care providers have remained concerned about persistent drug shortages, and may consider a range of policy options to address those concerns. This section provides examples of policy options that have been proposed by stakeholders.

Penalties for Failure to Report

Under current law, if a manufacturer fails to report a permanent discontinuance in or interruption of the manufacture of a drug, FDA issues a letter to which the manufacturer has 30 days to respond, providing the reason for noncompliance and the required information. FDA must make its letter and the manufacturer’s response public, unless the manufacturer has a reasonable basis for not notifying FDA. Congress may consider strengthening penalties for failure to report the required information.

Development of Contingency Plans

While manufacturers are required to report to FDA discontinuations or interruptions in the production of certain drugs, they are not required to have contingency plans in place, and preparing for disruptions caused by natural disasters is difficult. Congress may consider authorizing FDA to require or incentivize companies to establish contingency plans, particularly for drugs with a limited number of manufacturers or drugs that are frequently in shortage. Relatedly, Congress also may consider expanding FDA’s authority to require manufacturers of certain drugs (e.g., sterile injectable drugs) to conduct a risk assessment to identify the vulnerabilities in their drug supply, including vulnerabilities that could cause a shortage, and to establish risk mitigation plans to address those risks.

Supporting Manufacturing Improvements

As most shortages are the result of manufacturing and quality issues, supporting and incentivizing companies to develop and maintain robust manufacturing processes could help address drug shortages. In March 2015 congressional testimony, the then FDA Commissioner spoke of new manufacturing technologies that could eventually “lower costs, limit drug shortages, and reduce supply chain

vulnerabilities.” For example, continuous manufacturing has been characterized as safer and more reliable than batch manufacturing and may enable manufacturers to better prevent and respond to drug shortage and recall events. In contrast to batch manufacturing, continuous manufacturing uses an uninterrupted process, decreasing the possibility of introducing human error during the stops and starts of the batch process. FDA has awarded grants to several institutions to study and recommend improvements to continuous manufacturing of drugs and biologics, pursuant to its authority under Section 3016 of the 21st Century Cures Act. Congress may consider establishing incentives for manufacturers to invest in new technologies and to develop and maintain high-quality manufacturing practices.

Increasing the Role of 503B Outsourcing Facilities

The term *outsourcing facilities* applies to entities that compound drugs in large quantities, such as for use in hospitals (FFDCA §503B). Compounded drugs are not evaluated for safety and effectiveness by FDA prior to use. As such, they are generally considered higher risk than FDA-approved drugs. An entity that elects to register as an outsourcing facility is subject to FDA inspection and must notify the agency whether it intends to compound products on the drug shortage list. In most cases, pharmacy compounding of a drug that is essentially a copy of one or more approved drugs is not allowed. However, an outsourcing facility may compound a drug that is essentially a copy of an approved drug if the compounded drug is identical or nearly identical to an approved drug on the shortage list. However, few data are available on the quality of 503B-compounded drugs, and health care practitioners may be hesitant to rely on them. FDA and Congress could explore the feasibility of sharing information about the quality of drugs produced by outsourcing facilities with certain health care entities.

Incentivizing Manufacture of Drugs in Shortage

FDA cannot require a manufacturer to make a drug or to make more of a drug. Congress could, however, authorize FDA to provide incentives to drug manufacturers and outsourcing facilities to make drugs that are on the shortage list or at risk of being in shortage. For example, Congress could allow FDA either to waive generic drug user fees or to reimburse fees to a generic manufacturer who submits an application for a drug on the shortage list and subsequently markets the drug. Other incentive options that have been proposed include tax credits, federal grants, and revised reimbursement policies for certain generic drugs. Sterile injectable drugs, in particular, are complex to manufacture and have relatively low profit margins. Commissioner Gottlieb has announced that FDA will be working with the Centers for Medicare & Medicaid Services (CMS) and other payers to evaluate reimbursement policies.

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