



**U.S. FOOD & DRUG
ADMINISTRATION**

Report on Drug Shortages for Calendar Year 2018

Required by

Section 506C-1 of the Federal Food, Drug, and Cosmetic Act

Food and Drug Administration
Department of Health and Human Services

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EXECUTIVE SUMMARY

This sixth annual report to Congress summarizes the major actions taken by the Food and Drug Administration (FDA) during calendar year (CY) 2018 to prevent or mitigate drug shortages¹ in the United States. Because drug shortages can pose a significant public health threat that can delay, and in some cases even deny, critically needed care for patients, shortages remain a top priority for FDA. As a result of actions by the President, Congress, and FDA, manufacturers are notifying FDA about potential shortages earlier than in the past. Early notification of potential shortages gives FDA additional time to work with manufacturers and other stakeholders to identify ways to maintain treatment options and prevent a shortage. Using a range of available tools, including regulatory flexibility and discretion when appropriate, FDA's Center for Biologics Evaluation and Research (CBER) and FDA's Center for Drug Evaluation and Research (CDER) worked with manufacturers to successfully prevent 160 shortages from January 1 to December 31, 2018. In addition, the number of new shortages tracked by CBER and CDER for this same period in 2018 was 54, compared to a peak of 251 new shortages during calendar year 2011.²

Based on our experience to date and the data on drug shortages presented in this report, FDA believes that the requirements related to early notification of potential shortages and FDA's own actions are helping to reduce the threat and impact of drug shortages. FDA will continue to prioritize this important public health issue, working to ensure the availability of necessary drugs and biological products for the American public.

¹ For purposes of this report, the term "drug shortage" includes shortages of human drug and biological products. The report may individually refer to shortages tracked by FDA's Center for Drug Evaluation and Research or FDA's Center for Biologics Evaluation and Research, if the context requires distinguishing between these.

² This sixth annual report to Congress addresses all covered drug and biological products. This includes all drugs within the meaning of section 506C(h)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as well as other products tracked by CDER's Drug Shortage Staff, such as biological products approved under section 505 of the FD&C Act. This also includes biological products licensed under section 351 of the Public Health Service Act and tracked by CBER's Office of Compliance and Biologics Quality, such as vaccines and blood products. See Appendix 3 for a breakdown of 2018 CBER and CDER numbers.

INTRODUCTION

The Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted on July 9, 2012. Title X of FDASIA, which addresses drug shortages, took effect on the date of enactment and, among other things, amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301 et seq.) by updating section 506C. Section 506C sets forth the requirement that manufacturers notify FDA of a permanent discontinuance or interruption in the production of certain prescription drugs that are life-saving, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition. In addition, section 1002 of Title X of FDASIA added section 506C-1 to the FD&C Act, requiring FDA to file an annual report to Congress on drug shortages.³ FDA is submitting this annual report to fulfill its obligations under section 506C-1. The report provides background about drug shortages and FDA efforts to address them to date. FDA also responds to the specific issues listed under section 506C-1. The analyses reflect data collected and evaluated by FDA’s CBER and CDER from January 1, 2018, through December 31, 2018. This report also summarizes some important ongoing activities FDA believes will help to address drug shortages in the future. A list of definitions and three additional appendices, which include the statutory language regarding annual reporting on drug shortages and the breakdown of data supplied by CBER and CDER, are included at the end of this report.

BACKGROUND

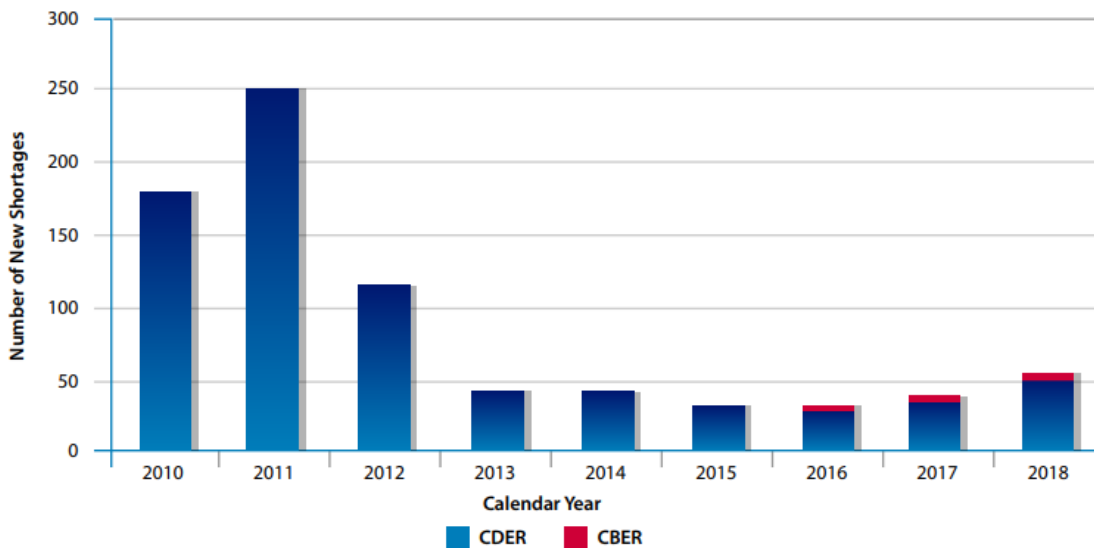
Drug shortages can have serious and immediate effects on providing needed therapies to patients, and preventing shortages is a priority for FDA. At the height of the drug shortage crisis, the number of new shortages tracked by CDER quadrupled, from approximately 61 shortages in 2005 to more than 250 in 2011.

The following figure shows the number of new drug shortages identified by year from 2010 through December 31, 2018.

³ Section 506C-1 of the FD&C Act initially required the annual report on drug shortages to be submitted to Congress “not later than the end of each calendar year.” To meet this deadline, the annual reports submitted to Congress presented data and information on drug shortages gathered during the first three quarters of the calendar year. The 21st Century Cures Act, which was enacted on December 13, 2016, amended section 506C-1 to require that “

...”

Figure 1. Number of New Drug Shortages Per Year, 2010 - 2018⁴



Although the number of new drug shortages has declined since 2011 as a result of work by many groups including FDA, shortages continue to pose a real challenge to public health. This is especially the case when a shortage involves a critical drug to treat cancer, to provide parenteral nutrition, or to address another serious medical condition, such as the shortage of intravenous saline solution. While there has been a steady decrease in new shortages over the past few years, calendar year 2018 has been a challenging year for shortages. We continue to see the trickle-down effects from the closing of a facility by a major drug manufacturer for remediation purposes in 2017, which resulted in the loss of manufacturing capacity needed for the supplies of numerous drug products.

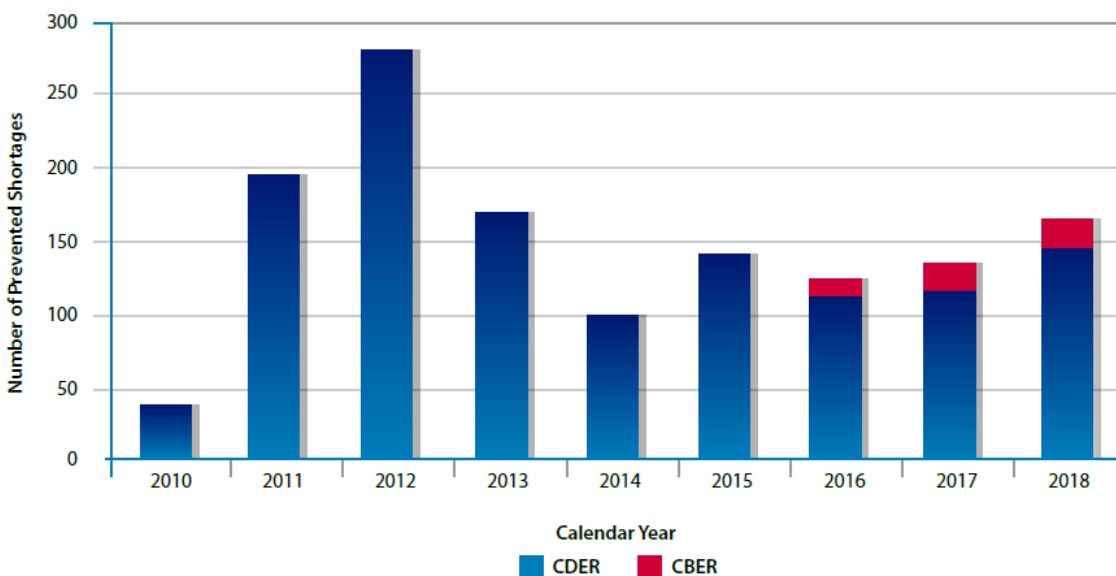
Shortages can delay or deny needed care for patients, creating a potential lapse in medical care. Shortages can also lead prescribers to use second-line alternatives, which may be less effective or pose additional risks. As summarized below, to prevent these situations from occurring, FDA has used a variety of methods to prevent shortages, working within the confines of the statutory and regulatory framework in place and in partnership with manufacturers and other stakeholders. As tracked by CDER, FDA helped prevent 282 drug shortages in 2012, 170 shortages in 2013, 101 shortages in 2014, and 142 shortages in 2015. As tracked by CBER and CDER, FDA helped to prevent 126 shortages in 2016, 145 in 2017, and 160 in 2018.⁵

The following figure shows the number of prevented drug shortages identified by year from 2010 through 2018.

⁴ This sixth annual report to Congress is the third year to include reporting for both drug and biological products. See Appendix 3 for a breakdown of 2018 CBER and CDER numbers.

⁵ See *supra* n. 2.

Figure 2. Number of Prevented Drug Shortages Per Year, 2010 - 2018⁶



Many actions have been taken that are helping FDA address drug shortages.

1. Executive Order 13588 – Reducing Prescription Drug Shortages

In response to a dramatic increase in shortages, on October 31, 2011, the President issued Executive Order 13588, recognizing that “shortages of pharmaceutical drugs pose a serious and growing threat to public health...endanger patient safety...burden doctors, hospitals, pharmacists, and patients...and increase health care costs.”⁷ The Executive Order acknowledged the need for a “multifaceted approach” to address the many different factors that contribute to drug shortages. The Executive Order directed FDA to take steps to help prevent and reduce current and future disruptions in the supply of life-saving medicines, including notifications and expedited reviews, as appropriate.

2. FDA Safety and Innovation Act

With the passage of FDASIA on July 9, 2012, FDA was given important new authorities related to drug shortages. For example, section 1001 of FDASIA broadened the scope of the early notification provisions by requiring manufacturers of *all prescription drugs* that are life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition (whether approved or unapproved) to notify FDA of a permanent discontinuance or temporary interruption in manufacturing. FDASIA also allowed FDA to require, by regulation, early notification of discontinuances or

⁶ This sixth annual report to Congress is the second year to include reporting for both drug and biological products. See Appendix 3 for a breakdown of 2018 CBER and CDER numbers.

⁷ Executive Order 13588, available at <http://www.whitehouse.gov/the-press-office/2011/10/31/executive-order-reducing-prescription-drug-shortages>

interruptions in manufacturing of biologics.⁸ FDASIA requires FDA to send a non-compliance letter to firms that fail to notify FDA in accordance with section 506C, as amended by FDASIA. FDA sent the first two letters in 2014, an additional two letters in 2016, and three more in 2018. Section 506C also authorizes FDA to expedite reviews of drug applications and supplemental applications and to expedite inspections that could help mitigate a shortage. Other FDASIA requirements with respect to prescription drug shortages include improving FDA's internal and external communications about shortages, improving communication between FDA and the Drug Enforcement Administration (DEA) regarding shortages of controlled substances, and developing a strategic plan to enhance FDA's response to preventing and mitigating drug shortages.

3. FDA Drug Shortage Task Force

In June 2018, 31 U.S. Senators and 107 Members of the House of Representatives asked the Commissioner of Food and Drugs to expand the Drug Shortage Task Force (created by FDASIA⁹) and work with stakeholders and other federal agencies to determine the root causes of drug shortages and develop recommendations to ensure that the appropriate supplies of essential medications are always available. This new task force expands upon the work FDA is already doing. With this new task force, FDA, as lead agency, is taking a comprehensive look at all drivers of drug shortages and identifying potential ways to prevent or mitigate them in the future. To ensure we are not overlooking any solutions, the task force includes not only senior leaders from FDA, but also leaders from the Centers for Medicare & Medicaid Services (CMS) and the Department of Veterans Affairs (VA). Collectively, CMS and the VA provide or pay for prescription medicines for millions of Americans. The Department of Defense (DoD), the Federal Trade Commission (FTC), and the Office of the HHS Assistant Secretary for Preparedness and Response (ASPR) are also represented on the task force.

FDA is also evaluating our current legal authorities to see what more we can do to better prevent and mitigate shortages. Moreover, we are pursuing new ways to support industry and other stakeholders' efforts to identify critical facilities and products and develop contingency plans.

1. Docket. We opened a docket in September 2018 to receive public comments on the root causes and drivers of drug shortages, as well as possible solutions.
2. Listening sessions. We held a series of listening sessions with key stakeholders in September and October 2018. Participants in these listening sessions included physicians, pharmacists, manufacturers, distributors, and staff from hospitals and Group Purchasing Organizations (GPOs). We have also spoken with academic

⁸ See section 506C(i)(3) of the FD&C Act; see also 21 CFR 600.82; 80 FR 38915 (July 8, 2015).

⁹ See section 506D(a)(1)(A) of the FD&C Act.

experts whose work focuses on drug shortages, and leaders of initiatives intended to address the shortage problem in novel ways.

3. Public meeting. We held a public meeting on November 27, 2018, with the help of the Duke-Margolis Health Policy Center. During this public meeting, we received input from a broad spectrum of stakeholders on the costs and effects of drug shortages on public health, the major drivers of drug shortages, and some potential long-term solutions intended to prevent or mitigate drug shortages.

The FDA Drug Shortage Task Force is currently analyzing the major drivers of drug shortages. FDA is on track to submit a report summarizing its findings and recommended interventions to Congress by the end of 2019, as requested.

DATA SOURCES USED IN THIS REPORT

The data used to fulfill the reporting requirements of section 506C-1 are collected by several program areas within FDA. Tracking the data for reporting requirements related to drugs and biological products (the number of products in shortage) is within the purview of CBER's Office of Compliance and Biologics Quality (CBER/OCBQ) and CDER's Drug Shortage Staff (DSS). Similarly, CBER/OCBQ and DSS track information about notifications and their source (and, therefore, the number of reporting manufacturers). In contrast, reporting requirements related to expedited review are tied to specific *submissions* by manufacturers that are experiencing production disruptions or manufacturers that are adding or expanding their production capabilities to address a specific shortage. CBER and CDER offices reviewing these submissions track which reviews and related inspections they expedite as a part of a larger set of activities related to their review of submissions. Other reporting requirements for this report relate to instances of regulatory flexibility and discretion. These specific cases, all requiring separate regulatory and scientific evaluation and justification, are tracked by CBER/OCBQ and CDER's Office of Compliance (CDER/OC).

ANNUAL REPORT REQUIREMENTS PER 506C-1

Section 1002 of Title X of FDASIA added section 506C-1 to the FD&C Act, requiring FDA to file a report to Congress on drug shortages for each calendar year.

The statutory requirements for the report and the data addressing those requirements are as follows.

Requirement 1: Specify the number of manufacturers that submitted a notification to the Secretary under section 506C(a) during such calendar year.

For calendar year 2018, FDA was notified of 575 potential drug and biological product shortage situations by 96 different manufacturers.

Requirement 2: Describe the communication between FDA field investigators and CDER/OC and DSS, including FDA’s procedures for enabling and ensuring such communication.

CDER/OC and the FDA field investigators in the Office of Regulatory Affairs (ORA) are crucial to FDA’s prompt response to a drug shortage. These two groups have separate functions with respect to drug shortages. Consistent with sections 506D(b) and (c) of the FD&C Act, CDER/OC communicates with DSS on warning letter and enforcement action recommendations being reviewed within CDER/OC. FDA field investigators in ORA typically conduct inspections at manufacturing facilities and report on their findings. For example, if the investigators identify actions or activities during an inspection that may have a detrimental impact on product availability, information regarding the observations and the products manufactured can be relayed to CDER immediately so that DSS can begin to assess the supply situation for those products. These procedures are critical to FDA’s efforts to prevent and mitigate a potential drug shortage.

To facilitate communications between ORA and FDA medical product centers, which include CBER and CDER, ORA issued Field Management Directive (FMD) #15 in July 2012. FMD #15 established drug shortage coordinators in ORA so that each FDA field district has a District Drug Shortage Coordinator who serves as the point of contact between ORA and FDA’s medical product centers. The District Drug Shortage Coordinator is responsible for notifying the relevant FDA center of any issue that has the potential to lead to a product shortage (e.g., information obtained during an inspection or other field activities). FMD #15 clarified communication roles, responsibilities, and expectations related to potential and current product shortage situations between ORA and the centers.

Requirement 3: List the major actions taken by the Secretary to prevent or mitigate drug shortages.

Mitigation efforts begin once FDA has confirmed that a shortage exists or could occur. The actions FDA can take to prevent or mitigate a shortage include, as appropriate:

- Identify the extent of the shortfall and determine if other manufacturers are willing and able to increase production to make up the gap;
- Expedite FDA inspections and reviews of submissions attempting to restore production;
- Expedite FDA inspections and reviews of submissions from competing entities who are interested in starting new production or increasing existing production of products in shortage;

- Expedite the release of lots of certain licensed biological products regulated by CBER or CDER¹⁰;
- Review requests for extensions of expiration dating (see below for further discussion of expiry extensions);
- Exercise temporary regulatory flexibility for new sources of medically necessary drugs;
- Work with the affected manufacturers to ensure adequate investigation into the root cause of the shortage;
- Develop risk mitigation measures to allow individual batches of a drug product to be released even when quality assurance requirements were not met; and
- Establish communication channels with stakeholders and other interested parties.

FDA can use one or more of these mitigation tools, or seek to develop other options, within its legal authority depending on the severity of the potential shortage and the surrounding circumstances. When selecting specific tools, FDA continues to work with the manufacturer to tailor its response to the specific situation. As a part of these actions, FDA also frequently communicates available information about a potential shortage or existing shortage to affected stakeholders and monitors the shortage until it has been resolved.

- **List the number of applications and supplements for which the Secretary expedited review under section 506C(g)(1) during such calendar year.**

FDA expedited the review of 167 submissions in 2018.¹¹

- **List the number of establishment inspections or re-inspections related to mitigation or prevention of a shortage that the Secretary expedited under section 506C(g)(2) during such calendar year.**¹²

FDA prioritized 12 establishment inspections to address drug shortages in 2018.¹³

¹⁰ FDA may require manufacturers to submit for review and confirmatory testing samples of any lot of any licensed biological product, together with the protocols showing results of applicable tests when deemed necessary for the safety, purity, or potency of the product. See 21 CFR 610.1 and 610.2.

¹¹ See Appendix 4 for a breakdown of submission types.

¹² Includes prioritized inspections or site reviews for new applications or supplements that were granted expedited review due to drug shortage.

¹³ Note that not all submissions to FDA require inspections, but some submissions may involve multiple sites that require multiple inspections.

Requirement 4: Describe the coordination between FDA and DEA to prevent or alleviate drug shortages.

If a drug at risk of shortage is a controlled substance, FDA works closely with the DEA in efforts to prevent or mitigate the shortage. Among other issues, DEA is responsible for setting aggregate limits on the amount of each controlled substance that may be manufactured and for allocating to each manufacturer a specific percentage of the aggregate limit (a quota). This tight control over controlled-substance products requires FDA and DEA to coordinate when a shortage of a controlled substance is looming. For example, FDA may work with DEA to enable a manufacturer to increase its allotted quota if this step would help avoid a shortage of the product.

Recognizing this need, FDASIA included provisions on improved coordination and communication between FDA and DEA regarding a potential shortage of a controlled substance. To help streamline and improve communications, FDA and DEA developed a memorandum of understanding (MOU). The MOU sets forth steps and procedures, including identifying contacts, for efficiently tracking and exchanging relevant information.¹⁴ DSS has reached out to DEA on five occasions this past year in regard to potential shortage situations.

Requirement 5: Identify the number of (and describe) instances in which FDA exercised regulatory flexibility and discretion to prevent or alleviate a drug shortage.

FDA's first priority is to ensure patients have access to safe, effective, and high quality drugs even when a drug is in shortage. FDA's preferred solution to any shortage situation is to help ensure that there is a supply of approved drugs and biological products sufficient to meet patient demand, as well as be able to meet the appropriate quality, safety, and efficacy standards. However, FDA recognizes that there can also be risks to patients if treatment options are not available for critical conditions. The Agency also understands the importance of using appropriate tools within its legal authority for certain situations in order to prevent or mitigate a shortage situation. In certain shortage situations, the temporary exercise of regulatory flexibility and discretion has proven to be an important tool in alleviating a drug shortage and ensuring access to treatment options for patients in critical need.

¹⁴ The MOU can be found at <https://www.fda.gov/about-fda/domestic-mous/mou-225-15-11.htm>.

During CY 2018, FDA exercised regulatory flexibility and discretion in 79 instances, affecting 52 products.¹⁵ Examples of situations in which FDA exercised regulatory flexibility and discretion to prevent or mitigate a shortage are listed below:

- FDA exercised temporary regulatory flexibility and discretion for medically necessary products that presented quality issues, as follows:
 - Filters were supplied with a product to remove particulate matter,
 - Extra testing for product quality or identity was completed before releasing the product into the marketplace,
 - Third-party oversight of production was instituted to monitor quality issues, and
 - Special instructions were provided to health care professionals and patients.
- FDA exercised temporary regulatory flexibility and discretion with respect to the continued distribution of a drug product to mitigate or resolve a drug shortage while FDA reviewed a supplement/proposed change to address a problem with the drug product.
- FDA exercised temporary regulatory flexibility and discretion with regard to new sources of medically necessary drugs, including FDA-registered foreign sources, in rare instances when all alternative approaches were exhausted.
- FDA permitted expanded access to investigational drugs for treatment use under an investigational new drug application (IND) (21 CFR 312.315(a)(3)(ii)) to mitigate a shortage of an approved drug product.

Requirement 6: List the names of manufacturers issued letters under section 506C(f).

Under section 506C(f) of the FD&C Act, if a manufacturer fails to provide notification of a discontinuance or interruption in manufacturing as required by section 506C, FDA must issue a letter to that manufacturer stating that the notification requirement was not met. The manufacturer is required to respond to FDA's letter within 30 calendar days, providing the reason for noncompliance and the required information on the discontinuance or interruption. Within 45 calendar days of its original letter to the manufacturer, FDA is required to post that letter and any response received on FDA's website,¹⁶ with appropriate redactions to protect trade secrets or confidential commercial information, unless FDA determines that the original notification was issued in error or,

¹⁵ One instance of regulatory flexibility may affect more than one product. Conversely, a shortage of one product may involve multiple instances of regulatory flexibility.

¹⁶ Links to letters of non-compliance with notification requirement can be found at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm403902.htm>.

after review of the manufacturer's response, that the manufacturer had a reasonable basis for not notifying FDA as required.

Since 2014, FDA has issued seven non-compliance letters under section 506C(f). During calendar year 2018, three letters were issued to Accord Healthcare Inc., Fresenius Kabi USA, LLC, and Teva Pharmaceuticals. The letter to Teva Pharmaceuticals is available on FDA's website. The two letters issued to Accord Healthcare Inc. and Fresenius Kabi USA, LLC were not posted to FDA's website because, after review of the manufacturers' response, FDA determined that the letters were issued in error.

Requirement 7: Specify the number of drug shortages occurring during 2018.

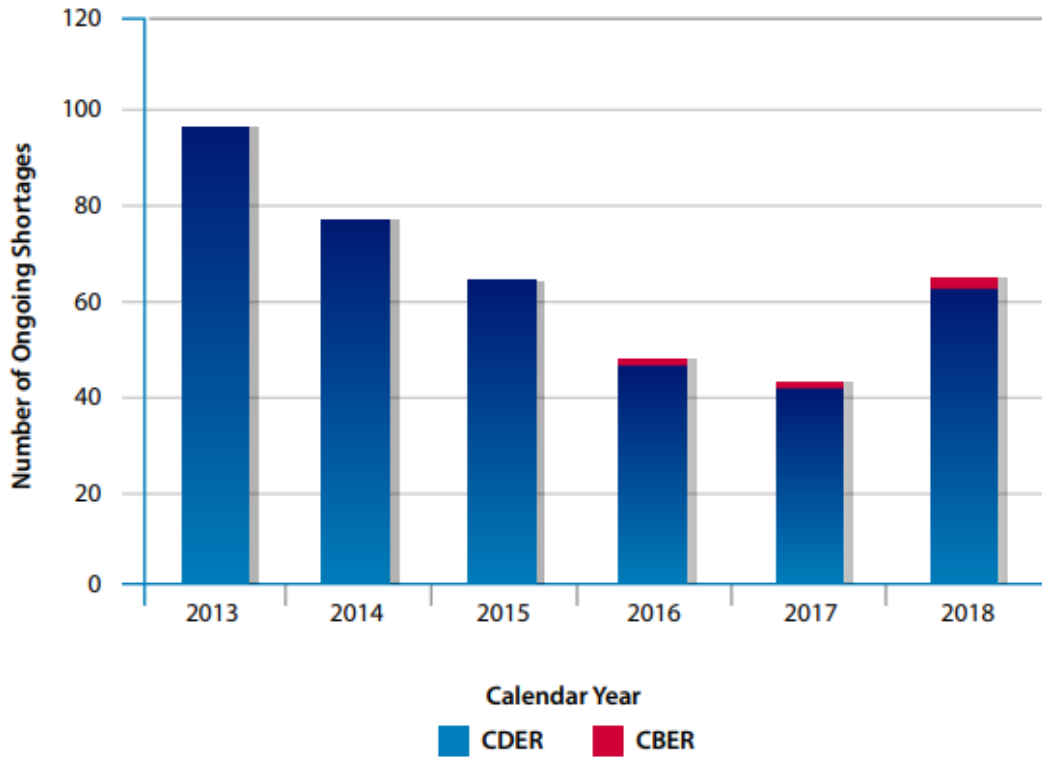
The data from CDER's drug shortage database¹⁷ shows that the number of new shortages has significantly decreased in recent years, from 117 in 2012 to 44 in 2013, 44 in 2014, 26 in 2015, and 26 in 2016. Unfortunately, this downward trend did not continue into 2017 and 2018, as previously discussed. A major drug manufacturer closed a manufacturing facility for remediation purposes in 2017, and this closure resulted in the loss of manufacturing capacity needed for the supplies of numerous drug products. In 2017, there were a total of 39 new drug and biological product shortages identified; in 2018, 54 were identified.¹⁸ In 2018, FDA prevented 160 drug and biological product shortages.

Another data point to note is the number of ongoing shortages yet to be resolved from previous years. FDA identified 97 ongoing CDER-tracked shortages at the end of CY 2013, 74 ongoing CDER-tracked shortages at the end of CY 2014, 64 ongoing CDER-tracked shortages at the end of CY 2015, 48 ongoing CBER- and CDER-tracked shortages at the end of CY 2016, and 41 ongoing CBER- and CDER-tracked shortages at the end of CY 2017. As of December 31, 2018, there were 67 ongoing CBER- and CDER-tracked shortages. This slight increase is also due to the previously discussed closure of a manufacturing facility for remediation purposes.

¹⁷ CDER's drug shortage statistics can be found at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm>.

¹⁸ See Appendix 3 for a breakdown of 2018 CBER and CDER numbers.

Figure 3. Number of Ongoing Drug Shortages Per Year, 2013 - 2018



CONTINUED DRUG SHORTAGES EFFORTS IN 2018

1. FDA Communications Regarding Expiration Dates

To ensure access to treatment options for patients in critical need, FDA has exercised regulatory flexibility and discretion by reviewing and communicating the results of studies conducted by a manufacturer that may support a patient or provider’s choice to use a drug that is or has the potential to be in shortage after its labeled expiration date. When FDA has exercised this flexibility, in order to help protect patient safety, FDA has advised that these products should have been—and should continue to be—otherwise stored as labeled.

When requesting that FDA exercise regulatory flexibility and discretion in this manner, a manufacturer submits stability data that it believes demonstrate that specific batches or lots of the drug will maintain their stability, including potency, over a longer period of time (i.e., the “extended use period”) than set forth in its labeled expiration date. Patients or providers that have product from these

specific batches or lots may choose to maintain this product in inventory and keep it available for use until the new expiration date.

Regarding the expiration dates for CDER products, please refer to the Drug Shortage Web Site found here:

<https://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>.

Regarding the expiration dates of CBER products, please refer to the Safety and Availability (Biologics) web page found here:

<https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/default.htm>.

As more data may become available from manufacturers, these lists may continue to expand. We have exercised regulatory flexibility and discretion in the manner described above with respect to multiple lots of nine different drug products.

2. FDA Drug Shortage Assistance Award

In September 2014, FDA created the FDA Drug Shortage Assistance Award¹⁹ to publicly recognize drug companies and manufacturers that have demonstrated a commitment to preventing or alleviating drug shortages of medically necessary drugs. This award recognizes efforts of drug manufacturers who, while maintaining federally mandated quality standards, have worked in cooperation with FDA and implemented strategies to help provide a steady supply of medically necessary drugs for patients at a time when critical drug shortages pose a challenge for health care providers and patients nationwide. FDA hopes that shining a spotlight on the efforts of drug manufacturers that have gone above and beyond in this area will encourage other manufacturers to follow suit.

On April 24, 2018, FDA issued a Drug Shortage Assistance Award to Teva Global Operations for its efforts in preventing a shortage of Trisenox (arsenic trioxide) Injection.

On October 22, 2018, FDA issued a Drug Shortage Assistance Award to Fresenius Kabi USA, LLC for its efforts related to mitigating the shortage of IV saline, including temporary importation of their product and ultimately submitting and obtaining approval of an abbreviated new drug application for Sodium Chloride Injection.

3. FDA Interactions with United States Pharmacopeia (USP)

FDA works closely with USP to help ensure appropriate public pharmaceutical quality standards are available. FDA is engaged with USP on an initiative to

¹⁹ Information about FDA's Drug Shortage Assistance Award can be found at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm415807.htm>.

modernize USP-NF Monographs. As we continue to refine the process, DSS is working with FDA's Compendial Operations and Standards Branch using the Drug Shortage Website to flag any possible USP changes that might affect any current shortage products. In the future, we hope to expand efforts and work together with USP to discuss not only products currently in shortage but also those vulnerable to shortage.

4. Waivers, Exceptions, and Exemptions from the Requirements of Section 582 of FD&C Act

On November 27, 2013, the Drug Supply Chain Security Act (DSCSA) was signed into law.²⁰ Section 202 of the DSCSA, which adds new sections 581 and 582 to the FD&C Act, sets forth new definitions and requirements related to product tracing. Specifically, the DSCSA outlines critical steps to building an electronic, interoperable system by November 27, 2023, that will identify and trace certain prescription drugs as they are distributed within the United States.

As part of ongoing efforts for DSCSA implementation that will ultimately result in an electronic, interoperable system by November 27, 2023, manufacturers are now required to place a unique product identifier on certain prescription drug packages.

Unfortunately, because of unique circumstances, some manufacturers were not ready to meet this requirement by November 27, 2018, but they could meet this requirement at a later date and asked FDA for assistance. FDA has authority under section 582(a)(3) to grant waivers, exceptions, and exemptions from the requirements of section 582. Using this provision, FDA has issued 12 temporary exemptions from the product identifier requirements in section 582 in cases where there were shortage concerns that the company and FDA anticipated would result from compliance with these requirements.

CONCLUSION

Drug shortages remain a significant public health issue in the United States and a top priority for FDA. To address them, FDA is working with manufacturers and other partners to help prevent shortages from occurring and to mitigate the impact of shortages that cannot be prevented. As a part of this work, early and open dialogue between FDA and manufacturers is critical to our success. Because of important actions taken by the President and Congress, FDA has been able to learn of possible shortages before they occur and take steps to prevent or mitigate them. During calendar year 2018, there were 54 new shortages, and FDA helped to prevent 160 potential shortages. While important

²⁰ Information about the Drug Quality and Security Act (DQSA) and the Drug Supply Chain Security Act (DSCSA) can be found at <https://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct/default.htm>.

progress has been made in preventing drug shortages from occurring, FDA continues to work to ensure that patients in the United States will have access to the medicines they need. This report reflects FDA's commitment to continue our important work to prevent or mitigate drug shortages.

APPENDIX 1

DEFINITIONS

Drug Shortage: A *drug shortage* means a period when the demand or projected demand for the drug within the United States exceeds the supply of the drug.

Biological Product Shortage: A *biological product shortage* means a period when the demand or projected demand for the biological product within the United States exceeds the supply of the biological product.

Meaningful Disruption: A *meaningful disruption* means a change in production that is reasonably likely to lead to a reduction in the supply of a drug or biological product by a manufacturer that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for its product. A meaningful disruption is not an interruption in manufacturing due to matters such as routine maintenance and does not include insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period.

Significant Disruption: A *significant disruption* means a change in production that is reasonably likely to lead to a reduction in the supply of blood or blood components by a manufacturer that substantially affects the ability of the manufacturer to fill orders or meet expected demand for its product. A significant disruption does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period.

Life Supporting or Life Sustaining: *Life supporting* or *life sustaining* is used to describe a drug or biological product that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.

APPENDIX 2

SEC. 506C–1. ANNUAL REPORTING ON DRUG SHORTAGES.

(a) ANNUAL REPORTS TO CONGRESS.—Not later than March 31 of each calendar year, the Secretary shall submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report with respect to the preceding calendar year on drug shortages that—

(1) specifies the number of manufacturers that submitted a notification to the Secretary under section 506C(a) during such calendar year;

(2) describes the communication between the field investigators of the Food and Drug Administration and the staff of the Center for Drug Evaluation and Research’s Office of Compliance and Drug Shortage Program, including the Food and Drug Administration’s procedures for enabling and ensuring such communication;

(3) (A) lists the major actions taken by the Secretary to prevent or mitigate the drug shortages described in paragraph (7);

(B) in the list under subparagraph (A), includes—

(i) the number of applications and supplements for which the Secretary expedited review under section 506C(g)(1) during such calendar year; and

(ii) the number of establishment inspections or reinspections that the Secretary expedited under section 506C(g)(2) during such calendar year;

(4) describes the coordination between the Food and Drug Administration and the Drug Enforcement Administration on efforts to prevent or alleviate drug shortages;

(5) identifies the number of and describes the instances in which the Food and Drug Administration exercised regulatory flexibility and discretion to prevent or alleviate a drug shortage;

(6) lists the names of manufacturers that were issued letters under section 506C(f); and

(7) specifies the number of drug shortages occurring during such calendar year, as identified by the Secretary.

APPENDIX 3

Breakdown of CDER and CBER Shortage Numbers, 2018

	CDER	CBER
NEW SHORTAGES	50	4
PREVENTED SHORTAGES	146	14
ONGOING SHORTAGES	62	5
NOTIFICATIONS	531	44
NO. OF MANUFACTURERS NOTIFYING	78	22
ACTIONS TAKEN TO MITIGATE SHORTAGES		
REGULATORY FLEXIBILITY AND DISCRETION	79	1
EXPEDITED REVIEWS	148	19*
EXPEDITED INSPECTIONS	12	0

* Includes expedited reviews for six BLA/BLA supplements and 13 lot-release submissions for CBER-regulated products.

APPENDIX 4

Breakdown of Expedited Reviews by Submission Type

	EXPEDITED REVIEWS
CDER NDA/NDA SUPPLEMENTS	40
CDER ANDA/ANDA SUPPLEMENTS	103
CDER BLA/BLA SUPPLEMENTS	5
CBER BLA/BLA SUPPLEMENTS	6*

* Does not include expedited reviews for the 13 lot-release submissions for CBER-regulated products.