

Report to Congress

Drug Shortages for Calendar Year 2020

(Required by Section 506C-1 of the Federal Food, Drug, and Cosmetic Act)



U.S. FOOD & DRUG
ADMINISTRATION

Executive Summary

This annual report to Congress summarizes the major actions taken by the U.S. Food and Drug Administration (FDA or the Agency) during calendar year (CY) 2020 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, drug shortages remain a top priority for FDA.

During the Coronavirus Disease 2019 (COVID-19) pandemic, FDA continued to closely monitor the medical product supply chain. As FDA expected, the supply chain was impacted by the pandemic, leading to supply disruptions or shortages of drug products in the United States. FDA understands the significant impact this can have on patient care and is doing everything within its authority to help prevent and alleviate these disruptions and shortages. As a result of presidential, congressional, and Agency actions, manufacturers are notifying FDA earlier than in the past about certain manufacturing interruptions and discontinuances that can lead to shortages. These early notifications give 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 199 drug shortages during CY 2020. In addition, the number of new shortages tracked by CBER and CDER during this same period was 43, compared to a peak of 251 new shortages during CY 2011.²

Based on FDA's experience to date and the data on drug shortages presented in this report, the Agency believes that the requirements related to an early notification of interruptions and discontinuances in manufacturing 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, including adequate supplies of drugs needed to treat patients with COVID-19.

¹ In this report, the phrase "drug shortages" includes shortages of human drug and biological products. This report individually refers to shortages tracked by FDA's Center for Drug Evaluation and Research or FDA's Center for Biologics Evaluation and Research when the context requires distinguishing between these Centers.

² This eighth annual report to Congress addresses all covered drug and biological products, including all drugs within the meaning of section 506C(h)(1) of the Federal Food, Drug, and Cosmetic Act. As permitted by section 506C(h)(i)(3), FDA included in this definition all biological products licensed under section 351 of the Public Health Service Act, except source plasma and those that also meet the definition of a "device." See *Final Rule: Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products*, 80 FR 38916 at 38918 (July 8, 2015). See Appendix 3 for a breakdown of CBER's and CDER's CY 2020 numbers.

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Introduction

The Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted on July 9, 2012.³ 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 adding section 506C-1, which requires the Food and Drug Administration (FDA or the Agency) to file an annual report to Congress on drug shortages.⁴ FDA is submitting this annual report to fulfill its obligations under section 506C-1.

Specifically, this report:

- Provides a background on drug shortages and FDA’s efforts to address them
- Responds to the specific issues listed under section 506C-1
- Includes analyses that reflect data collected and evaluated by FDA’s Center for Biologics Evaluation and Research (CBER) and FDA’s Center for Drug Evaluation and Research (CDER) during calendar year (CY) 2020
- Summarizes some important ongoing activities FDA believes will help address drug shortages in the future
- Includes a list of definitions in one appendix, as well as three additional appendices that include the statutory language regarding annual reporting on drug shortages and a breakdown of data supplied by CBER and CDER, at the end of this report

Background

Drug shortages can have serious and immediate effects on providing needed therapies to patients, therefore 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.

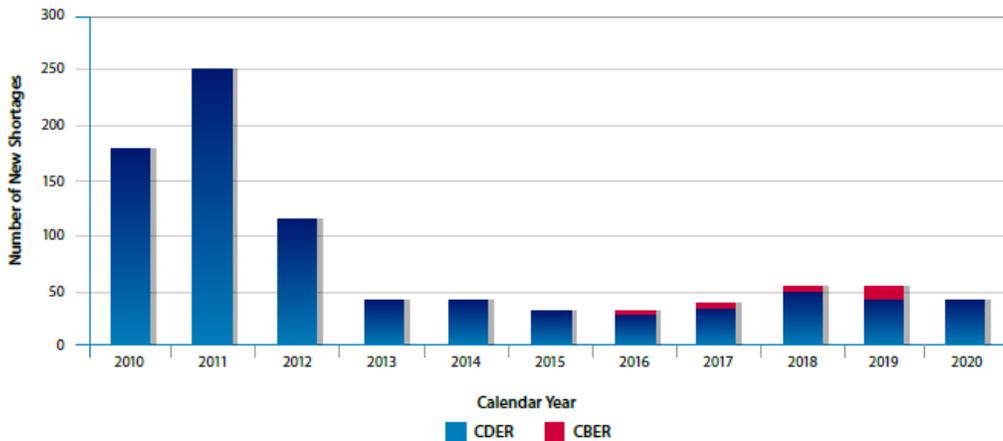
³ Pub. L. 112-144, 126 Stat. 994 (July 9, 2012).

⁴ 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 3 quarters of the calendar year. The 21st Century Cures Act, which was enacted on December 13, 2016, amended section 506C-1 to require that

[n]ot 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

Figure 1 shows the number of new drug shortages identified by calendar year from 2010 through 2020. The number of new drug shortages per calendar year has declined from a high of 250 in 2011 to 43 in 2020.

Figure 1. Number of New Drug Shortages Per Calendar Year, 2010 to 2020.⁵



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 the shortage involves a critical drug to treat cancer, to provide parenteral nutrition, or to address another serious medical condition, such as a shortage of blood pressure medications. Although there has been a leveling off in new shortages over the past few years, CY 2020 has been a challenging year for shortages. FDA continues to see the residual effects from the closing of two manufacturing facilities in 2017 and 2018 by major drug manufacturers for remediation purposes, which resulted in the loss of the manufacturing capacity needed for the supplies of numerous drugs. In addition, the COVID-19 pandemic has greatly affected the pharmaceutical supply chain in CY 2020, such as through the increase in demand for many 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 compared to the drug in shortage. As summarized below, to prevent these situations from occurring, FDA has used a variety of methods to prevent shortages, working within the statutory and regulatory framework in place and in partnership with

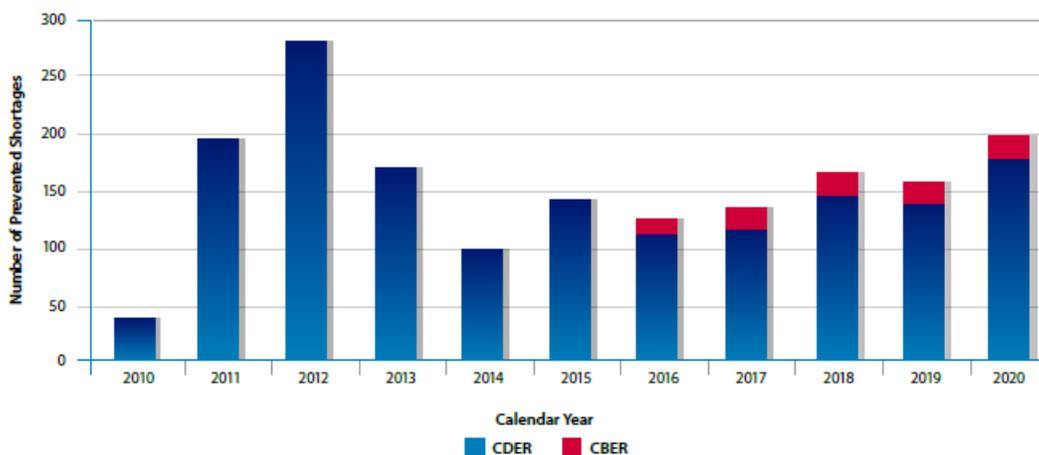
⁵ This eighth annual report to Congress is the fifth to include reporting for both drug and biological products, which include all drugs within the meaning of section 506C(h)(1) of the FD&C Act; other products tracked by CDER's Drug Shortage Staff, such as certain therapeutic biological products licensed under section 351 of the Public Health Service Act (PHS Act); and biological products licensed under section 351 of the PHS Act that are tracked by CBER's Office of Compliance and Biologics Quality, such as vaccines and blood products. See Appendix 3 for a breakdown of CBER's and CDER's CY 2020 numbers.

manufacturers and other stakeholders. FDA’s investigation into nitrosamine impurities is an example of how the Agency has taken steps to ensure the safety of drug products while also working to both mitigate and prevent future shortages using tools such as expedited reviews and inspections.⁶

As tracked by CDER, FDA helped prevent 282 drug shortages in CY 2012, 170 shortages in CY 2013, 101 shortages in CY 2014, and 142 shortages in CY 2015. As tracked by CBER and CDER, FDA helped prevent 126 shortages in CY 2016, 145 in CY 2017, 160 in CY 2018, 154 in CY 2019, and 199 in CY 2020.⁷

Figure 2 shows the number of prevented drug shortages, identified by calendar year, from 2010 through 2020. FDA helped prevent large numbers of drug shortages, most recently 154 in CY 2018 and 199 in CY 2020. The highest number of shortages prevented was 282 in CY 2012.

Figure 2. Number of Prevented Drug Shortages Per Calendar Year, 2010 to 2020.



Many actions, including the following four, are helping FDA address drug shortages.

1. Executive Order 13588 – Reducing Prescription Drug Shortages

In response to a dramatic increase in shortages, the President issued Executive Order 13588 on October 31, 2011, 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.”⁸ 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

⁶ See <https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications>.

⁷ See supra n. 2.

⁸ Executive Order 13588, available at <https://obamawhitehouse.archives.gov/the-press-office/2011/10/31/executive-order-13588-reducing-prescription-drug-shortages>.

and reduce current and future disruptions in the supply of life-saving medicines, including notifications and expedited reviews, as appropriate.

2. *The Food and Drug Administration Safety and Innovation Act*

With the enactment of FDASIA on July 9, 2012, FDA was given important new authorities related to drug shortages. For example, section 1001 of FDASIA amended the FD&C Act to broaden the scope of the early notification provisions by requiring manufacturers of most 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 that is likely to lead to a meaningful disruption in supply of the drug in the United States. The FD&C Act as amended by FDASIA also allowed FDA to require, by regulation, early notification of such discontinuances or interruptions in the manufacturing of biologics.⁹

The FD&C Act as amended by FDASIA requires FDA to send a non-compliance letter to firms that fail to notify FDA in accordance with section 506C of the FD&C Act.¹⁰ FDA sent the first two such letters in 2014, an additional two such letters in 2016, three in 2018, and one in 2019.

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. *The Coronavirus Aid, Relief, and Economic Security Act (CARES Act)*

The CARES Act was signed into law on March 27, 2020, to aid response efforts to the COVID-19 pandemic and to ease the economic impact of COVID-19. In addition, the CARES Act amended the FD&C Act to include authorities intended to enhance FDA's ability to identify, prevent, and mitigate possible drug shortages by, among other things, enhancing FDA's visibility into drug supply chains. Specific authorities to enhance FDA's ability to identify, prevent, and mitigate drug shortages include the following:

- Amendments to section 506C(a) of the FD&C Act to expand the requirement for manufacturers of certain drugs to provide information on permanent discontinuances and interruptions in manufacturing that may lead to a meaningful disruption in supply to FDA.
- Amendments to section 506C(g) of the FD&C Act to require FDA to prioritize and expedite, as appropriate, the review of certain applications and inspections that could help

⁹ See section 506C(i)(3) of the FD&C Act; see also 21 CFR 600.82 and 80 FR 38915 (July 8, 2015).

¹⁰ Section 506C(f) of the FD&C Act.

mitigate or prevent a shortage of a drug covered by section 506C(a).¹¹

- The addition of section 506C(j) to the FD&C Act, requiring manufacturers of drugs described in section 506C(a) of the FD&C Act or of any active pharmaceutical ingredient (API) or any associated medical device used for preparation or administration included in the drug to develop, maintain, and implement, as appropriate, a redundancy risk management plan that identifies and evaluates the risks to the supply of the drug, as applicable, for each establishment in which the drug or API of the drug is manufactured.
- Amendments to section 510(j) of the FD&C Act to require drug manufacturers registered under section 510 of the FD&C Act to annually report on the amount of each drug that they have “manufactured, prepared, propagated, compounded, or processed” for commercial distribution.

These amendments took effect on September 23, 2020. Further information about implementation of the amendments is described below in the section on Continued Drug Shortage Efforts in 2020.

4. *Inter-agency Drug Shortage Task Force*

In response to a request in June 2018 from 31 U.S. Senators and 104 members of the House of Representatives, the Commissioner of Food and Drugs established the inter-agency Drug Shortages Task Force to determine the root causes of drug shortages and develop recommendations to address them. The task force took a comprehensive look at all drivers of drug shortages and identified potential ways to prevent or mitigate them in the future. To ensure FDA did not overlook any drivers or solutions, the task force included not only senior leaders from FDA but also leaders from a number of federal agencies including 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, the Federal Trade Commission, and the Office of the Assistant Secretary for Preparedness and Response (within the U.S. Department of Health and Human Services (HHS)) were also represented on the task force.¹² The task force invited public participation through a public meeting on November 27, 2018; established a docket to receive comments; and invited stakeholders to a series of listening sessions. In October 2019, the task force issued its report *Drug Shortages: Root Causes and Potential Solutions*¹³ that identifies root causes of drug shortages and offers recommendations for government and industry to address them. The report was updated on February 21, 2020, to include a revised economic analysis about production increases and supply restoration after a shortage.

¹¹ Note that an amendment to the FD&C Act in 2017 also required the Agency to prioritize an abbreviated new drug application for a drug that had been included on the drug shortage list under section 506E of the FD&C Act. See the FDA Reauthorization Act of 2017, Pub. L. 115-52 at s. 801 (Aug. 18, 2017).

¹² The task force also consulted with officials from the Defense Advanced Research Projects Agency, the U.S. Department of the Treasury, and DEA.

¹³ The report is available at <https://www.fda.gov/media/131130/download>.

Data Sources Used in This Report

The data used to fulfill the reporting requirements of section 506C-1 of the FD&C Act are collected by several program areas within FDA. For instance, 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). CBER/OCBQ and DSS track information about drug shortage notifications and their sources (and, therefore, the number of reporting manufacturers).

In contrast, section 506C-1 reporting requirements related to FDA's expedited review are tied to specific *submissions* by manufacturers that are experiencing production disruptions or by manufacturers that are adding or expanding their production capabilities to address a specific shortage. CBER's and CDER's offices reviewing these submissions track which reviews and related inspections they have expedited as a part of a larger set of activities related to their review of submissions.

Other section 506C-1 reporting requirements for this report relate to instances of regulatory flexibility and discretion. These specific instances, all requiring separate regulatory and scientific evaluations and justifications, are tracked by CBER/OCBQ and CDER's Office of Compliance (CDER/OC).

Annual Reporting Requirements Per Section 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 this congressional report and the data addressing those requirements are as follows.

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

For CY 2020, FDA was notified of 512 potential drug and biological product shortage situations by 120 different manufacturers.¹⁴

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

CDER/OC and FDA's 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

¹⁴ No notifications were received regarding a permanent discontinuance or interruption in manufacturing of an API between September 23, 2020 (the effective date of the CARES Act amendments to section 506C(a) of the FD&C Act requiring such notifications) and December 31, 2020.

respect to drug shortages. First, CDER/OC communicates with DSS on warning letter and enforcement action recommendations being reviewed within that office. Second, FDA's 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's 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 would have 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 identified during an inspection or other field activities that has the potential to lead to a product shortage. Also, FMD #15 clarified communication roles, responsibilities, and expectations between ORA and the centers related to potential and current product shortage situations. In addition, consistent with section 704(b)(2) of the FD&C Act, added by the CARES Act, DSS routinely receives access to the FDA Forms 483 presented to drug establishments.

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

Mitigation efforts begin once FDA confirms that a shortage exists or may occur. The actions FDA can take to prevent or mitigate a shortage include, as appropriate, the following:

- 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's inspections and reviews of submissions submitted by affected manufacturers attempting to restore production;
- Expedite FDA's 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 CDER;¹⁵
- Review requests for extensions of expiration dating;

¹⁵ FDA may require manufacturers to submit for review, as well as for confirmatory testing, samples of any lot of any licensed biological product, together with the protocols showing the results of applicable tests when deemed necessary for the safety, purity, or potency of the product. See 21 CFR 610.1 and 610.2.

- Exercise temporary regulatory flexibility for new sources of medically necessary drugs;
- Work with the affected manufacturers to ensure adequate investigations 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 manufacturers to tailor their responses to the specific situations. 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 489 submissions in CY 2020.¹⁶

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.¹⁷

FDA prioritized 19 establishment inspections to address drug shortages in CY 2020.¹⁸

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 DEA in efforts to prevent or mitigate the shortage. Among other duties, DEA is responsible both for setting aggregate limits on the amount of certain controlled substances that may be manufactured and for allocating to each manufacturer a specific percentage of the aggregate limit (a quota). This tight control over such 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 of a controlled substance if this step would help avoid a shortage of the product.

¹⁶ See Appendix 4 for a breakdown of submission types.

¹⁷ This includes prioritized inspections or site reviews for new applications or supplements that were granted an expedited review due to a drug shortage.

¹⁸ Note that not all submissions to FDA require inspections, but some submissions may involve multiple sites that require multiple inspections.

Recognizing this need, FDASIA amended the FD&C Act to include 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.¹⁹ DSS has reached out to DEA on four occasions during CY 2020 regarding 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 that also meet the appropriate quality, safety, and efficacy standards. However, FDA recognizes that there can be risks to patients if treatment options are not available for critical conditions.

The Agency 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 helping to alleviate a drug shortage and to ensure access to treatment options for patients in critical need.

During CY 2020, FDA exercised regulatory flexibility and discretion in 110 instances, affecting 78 products.²⁰ 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. For example:
 - 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

¹⁹ The MOU is available at <https://www.fda.gov/about-fda/domestic-mous/mou-225-15-11>.

²⁰ One instance of regulatory flexibility may affect more than one product. Conversely, a shortage of one product may involve multiple instances of regulatory flexibility to mitigate the issue.

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.

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 issuing the letter, FDA is required to post a copy of the letter and any response received on FDA's website,²¹ with appropriate redactions to protect trade secrets or confidential commercial information, unless FDA determines that the letter was issued in error or, 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 eight non-compliance letters under section 506C(f). The letters sent by FDA and the responses received from the manufacturer are available on FDA's website. In CY 2020, no non-compliance letters were sent.

Requirement 7: Specify the number of drug shortages occurring during 2020.

The data from CDER's drug shortage database²² shows that the number of new shortages significantly decreased between 2012 and 2016, with 117 in CY 2012, 44 in CY 2013, 44 in CY 2014, 26 in CY 2015, and 26 in CY 2016. Unfortunately, this downward trend did not continue in subsequent years. Two large drug manufacturers closed manufacturing facilities for remediation purposes in 2017 and 2018, and these closures resulted in the loss of the manufacturing capacity needed for the supplies of numerous drug products. In CY 2017, there were a total of 39 new CBER- and CDER-tracked shortages identified; in CY 2018, 54 were identified, in CY 2019 there were 51 new shortages, and in CY 2020 there were 43 new shortages.²³

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, 41 ongoing CBER- and CDER-tracked shortages at the end of CY 2017, 67 ongoing shortages for CY 2018,

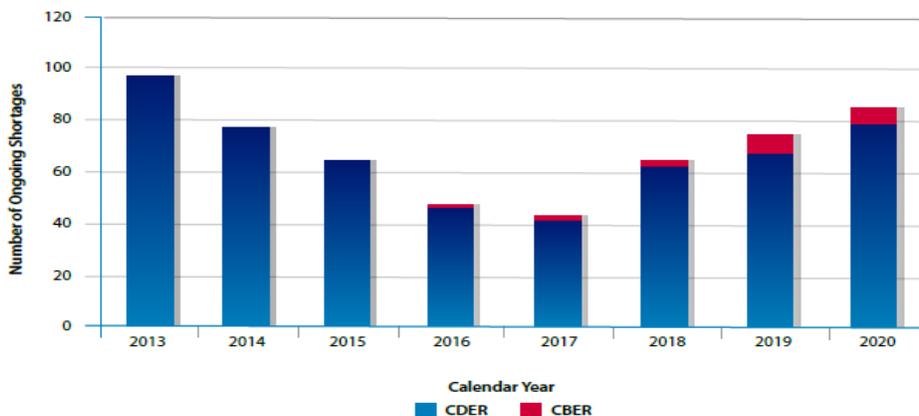
²¹ Links to letters of non-compliance with notification requirements are available at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm403902.htm>.

²² CDER's drug shortage statistics can be found at: <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm>.

²³ See Appendix 3 for a breakdown of CBER's and CDER's CY 2020 numbers.

and 76 ongoing shortages for CY 2019. As of December 31, 2020, there were 86 ongoing CBER- and CDER-tracked shortages. This increase of ongoing shortages at the close of CY 2020 as compared to the close of previous calendar years is due to the previously discussed closures of manufacturing facilities for remediation purposes, as well as the increase in demand for many drug products due to the COVID-19 pandemic.

Figure 3. Number of Ongoing Drug Shortages Per Calendar Year, 2013 to 2020.



Continued Drug Shortages Efforts in CY 2020

FDA’s COVID-19 pandemic response in CY 2020 included the following activities:

- In January 2020, prior to the World Health Organization declaring COVID-19 to be a global pandemic, CDER DSS began proactively reminding manufacturers of CDER-regulated products to notify FDA of permanent discontinuances or interruptions in manufacturing related to the spread of the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). CBER similarly reached out to manufacturers of CBER-regulated products. There have been many new challenges impacting the supply of needed medications, including transportation issues, employee absenteeism due to outbreaks of COVID-19 at manufacturing plants, and unprecedented increased demand for certain drugs needed for hospitalized patients with COVID-19. As with all shortages, a team effort is required to mitigate and resolve these shortages. CBER’s and CDER’s shortage staffs work closely with manufacturers to mitigate the shortage risk and coordinate with all relevant CBER or CDER offices on activities related to restoring full supply.
- The COVID-19 pandemic has also increased the risks of shortages due to sudden increases in demand for drugs used in hospitalized patients, particularly the most critically ill. To respond to this risk, DSS asked manufacturers to evaluate their entire supply chain, including key starting materials, APIs, packaging components, and finished dosage forms.

- As discussed above, manufacturers are required to notify FDA of certain permanent discontinuances and interruptions in manufacturing. In response to the COVID-19 pandemic, during CY 2020, FDA also requested, on a voluntary basis, additional information, including inventory levels, production plans, and distribution quantities, to better understand the supply chain. Although the manufacturers are not required to provide this information, it has been extremely valuable for FDA’s work to prevent drug shortages.
- In CY 2020, to increase patient access to critically needed medications in shortage, or to prevent potential shortages, FDA leveraged all its regulatory tools.
 - CDER expedited reviews for more than 100 original abbreviated new drug applications (ANDAs) for drugs for the treatment of patients with COVID-19 and more than 150 ANDA supplements under the COVID-19 prioritization programs.
 - CDER expedited assessments of manufacturing supplements to facilitate the manufacturing capacity for COVID-19 therapeutic biologics.
 - CDER exercised regulatory flexibility and discretion in 45 instances to increase supplies of heparin, albuterol, etomidate, midazolam, propofol, and many other critically needed medications.
 - CDER issued a total of 6 guidance documents related to the temporary enforcement discretion for the compounding of drugs needed to treat hospitalized COVID-19 patients.
 - CDER issued a guidance for industry for immediate implementation entitled [“Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act.”](#)²⁴ requesting that manufacturers not only report permanent discontinuances and interruptions in manufacturing, but also report disruptions due to increased demand.
- During CY 2020, FDA approved 48 original ANDAs and 94 supplemental ANDAs for drug products frequently used in hospital intensive care units for treatment of COVID-19 patients. These approvals help ensure the adequate supply of these essential products during this time of heightened demand and represent the dedicated efforts of review staff from many offices within FDA.
- FDA continues to work closely with manufacturers to mitigate and prevent shortages as the COVID-19 situation evolves. DSS is currently focusing its shortage efforts on the drugs used in the hospital intensive care unit setting for patients on ventilators, including sedatives, opioid analgesics, neuromuscular blocking agents, vasopressors, anticoagulants, dialysis agents, antibiotics, beta-2 agonist inhalers, and intravenous fluids. FDA is working with manufacturers to increase supplies to meet current demand by

²⁴ This guidance is available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/notifying-fda-permanent-discontinuance-or-interruption-manufacturing-under-section-506c-fdc-act>.

expediting its review of applications and utilizing regulatory flexibility and discretion for additional supplies, including, in rare instances when all alternatives are exhausted, imports from FDA-registered sources approved in other countries.

- Manufacturers of drugs and biological products are required to report certain anticipated supply disruptions to FDA. Importantly, manufacturers are encouraged to report any issues related to COVID-19 or other disruptions to FDA as soon as possible so the Agency can work to prevent these issues from leading to shortages. For products regulated by CDER, manufacturers should submit initial notifications either via email at drugshortages@fda.hhs.gov or through the CDER Direct NextGen Portal²⁵ at <https://edm.fda.gov/wps/portal/>. Initial notifications regarding products regulated by CBER should be submitted to FDA electronically via email at cbershortage@fda.hhs.gov. All additional updates should be submitted by email to the applicable center (CDER or CBER), not through the NextGen Portal.
- To provide the most current information to patients and caregivers, FDA maintains a public, up-to-date list of drugs and biological products that the Agency has determined to be in shortage, including those related to COVID-19.²⁶
- In addition to the efforts described above, FDA has been working to implement the authorities and requirements added by the CARES Act (described in the Background section) and plans to issue guidance on these topics, including on reporting manufacturing discontinuances and interruptions to FDA, risk management plans, and reporting the amount of drugs manufactured.

Conclusion

Drug shortages remain a significant public health issue in the United States and a top priority for FDA, particularly during the COVID-19 pandemic.

The Agency notes that FDA's response to the COVID-19 pandemic has highlighted the following needs that require ongoing work to address fully:

- **Need to gain better insight into the supply chain.** Interruptions or problems in the drug supply chain can create or worsen drug shortages. As mentioned earlier in this report, the CARES Act includes authorities meant to enhance FDA's ability to identify, prevent, and mitigate possible drug shortages by improving the Agency's visibility into the drug supply chain. Such authorities include additional notifications to FDA of manufacturing discontinuances or interruptions and a requirement for firms to report the amount of drugs they manufacture.
- **Need to increase the resilience of the supply chain.** Redundancy in the supply chain (as opposed to reliance on a single facility or geographic region) increases agility and

²⁵ The NextGen Portal is available at <https://edm.fda.gov/wps/portal/>.

²⁶ This list is available at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm>.

potential solutions to alleviate shortages that occur due to regional or localized supply disruptions and that could ultimately create or exacerbate a drug shortage. For example, if a manufacturing facility needs to temporarily close or its operations are curtailed by factors such as travel restrictions, quarantines, or social distancing requirements, it is important to have alternative facilities available to manufacture the drug or its API. In addition, as noted above, the CARES Act includes a provision requiring certain manufacturers to develop a redundancy risk management plan that identifies and evaluates the risks to the drug supply at establishments manufacturing the drug or its API.

To address shortages, including those related to the COVID-19 pandemic, 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. Early and open dialogue between FDA and manufacturers is critical to the success of this work. Because of important presidential, congressional, and FDA actions, FDA has been able to learn of possible shortages before they occur and take steps to prevent or mitigate them. During CY 2020, there were 43 new shortages, and FDA helped prevent 199 potential shortages. While important progress has been made in preventing drug shortages from occurring, FDA continues to work to ensure that patients in the United States have access to the medicines they need. This report reflects FDA's commitment to continue its important work to prevent and mitigate drug shortages.

Appendix 1

Drug Shortage: A *drug shortage* means a period when the demand or projected demand for a 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 a 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 the 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's and CBER's Shortage Numbers, CY 2020

	CDER	CBER
New Shortages	43	0
Prevented Shortages	179	20
Ongoing Shortages	78	8
Notifications	473	39
No. of Manufacturers Notifying	93	29
ACTIONS TAKEN TO MITIGATE SHORTAGES		
Regulatory Flexibility and Discretion	110	1
Expedited Reviews	471	18*
Expedited Inspections	19	0

* This number includes expedited reviews for nine biologics license application (BLA)/BLA supplements and nine lot-release submissions for CBER-regulated products.

Appendix 4

Breakdown of Expedited Reviews by Submission Type

	EXPEDITED REVIEWS
CDER NDA/NDA Supplements	170
CDER ANDA/ANDA Supplements	296
CDER BLA/BLA Supplements	5
CBER BLA/BLA Supplements	9*

* This number does not include expedited reviews for the nine lot-release submissions for CBER-regulated products.