Report to Congress

Drug Shortages

CY 2023

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

Executive Summary

This annual report to Congress summarizes the major actions taken by the U.S. Food and Drug Administration (FDA or Agency) during calendar year (CY) 2023 to prevent or mitigate drug shortages[1] 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.

FDA closely monitors the medical product supply chain, which continued to be impacted by the Coronavirus Disease 2019 (COVID-19) pandemic during CY 2023, 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. During CY 2023, 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 236 drug shortages through the use of a range of available tools, including regulatory flexibility and discretion when appropriate. Despite this work, during this same period, 55 new drug shortages were identified by CDER and CBER, as compared to a peak of 251 new drug shortages during CY 2011.[2]

Although the number of new drug shortages has declined since 2011, shortages continue to pose a real challenge to public health, particularly when the shortage involves a critical drug, such as those used to treat cancer, to provide parenteral nutrition, or to address other serious medical conditions. In the past calendar year, FDA has seen manufacturers in the United States and abroad continue to experience quality issues as well as struggle with capacity constraints. Additionally, as demand increased for numerous drugs over the last several years as a result of the COVID-19 pandemic, the flu season, and the respiratory virus season, FDA has seen further strain on drug availability and the pharmaceutical supply chain. Unexpected events,

[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 eleventh 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 C for a breakdown of CBER's and CDER's CY 2023 numbers.

such as shut downs at facilities, closures of facilities, and natural disasters, also put increased strain on the supply chain and drug supply.

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 the early notification of permanent discontinuances and interruptions in manufacturing and FDA's own actions are helping to reduce the threat and impact of drug shortages. Furthermore, FDA has put forth legislative proposals in its fiscal year 2025 proposed budget that would include authorities intended to promote the Agency's response efforts, such as requirements for manufacturers both to notify FDA of an increase in demand that the manufacturer likely will be unable to meet without meaningful shortfall or delay and to provide manufacturing volume and supplier information.[3] If enacted, these proposals would greatly enhance the Agency's ongoing work to address potential drug shortages. FDA will continue to prioritize its efforts on 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 and other respiratory illnesses.

[3] See https://www.fda.gov/media/176924/download?attachment.

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I. Introduction

Section 506C–1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356c-1) requires the Food and Drug Administration (FDA or Agency) to file an annual report to Congress on drug shortages.

FDA is submitting this annual report to fulfill its obligations under section 506C–1. Specifically, this report:

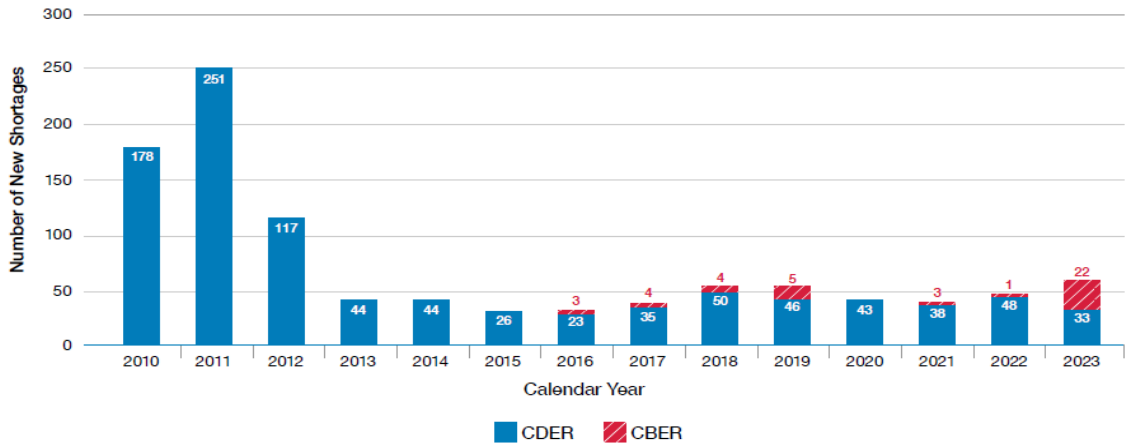
- Provides a background on drug shortages and FDA's efforts to address them;
- Responds to the specific issues listed under section 506C–1;
- Includes analyses that reflect data collected and evaluated by FDA's Center for Biologics Evaluation and Research (CBER) and FDA's Center for Drug Evaluation and Research (CDER) during calendar year (CY) 2023;
- Summarizes some important ongoing activities FDA believes will help address drug shortages in the future; and
- 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.

II. 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 drug shortages tracked by CDER quadrupled, from approximately 61 shortages in 2005 to more than 250 in 2011.

Figure 1 shows the number of new drug shortages from CY 2010 to CY 2023. The number of new drug shortages per calendar year has declined from a high of 251 in 2011 to 55 in 2023.

Figure 1. Number of New Drug Shortages Per Calendar Year (from CY 2010 to CY 2023).[1]



Due to the work of many, the number of new drug shortages has declined since 2011. However, shortages continue to pose a real challenge to public health, particularly when the shortage affects the treatment of serious medical conditions, such as with drugs to treat cancer or to provide parenteral nutrition. Although there has been a leveling off of new shortages over the past decade, CY 2023 has been a challenging year for shortages. For example, the notable increase in new shortages of CBER-regulated biological products was due to manufacturing problems and quality procedures at one manufacturer that experienced global supply chain issues related to the lack of some

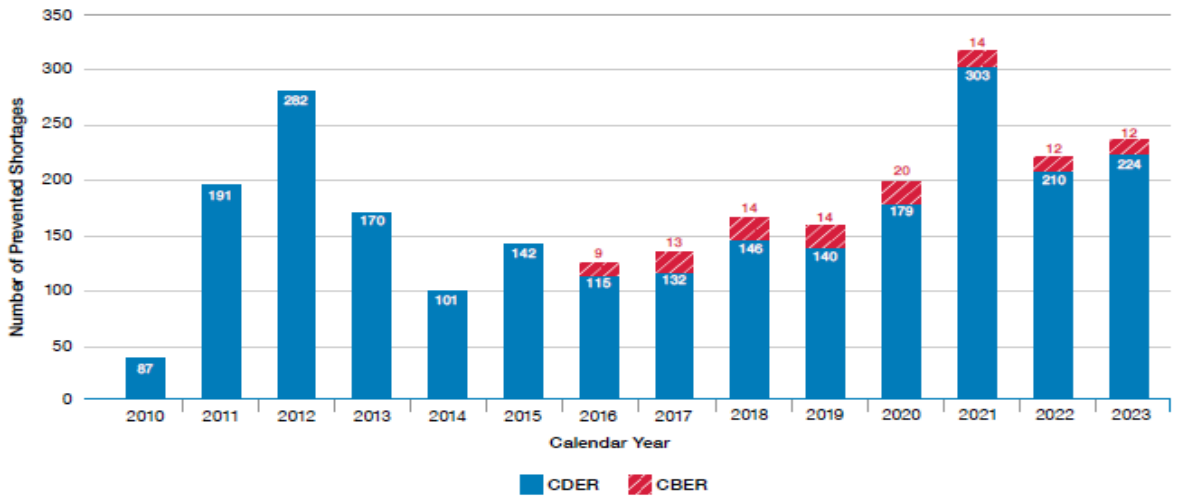
[1] This eleventh annual report to Congress is the seventh to include reporting for both drug and biological products, which include all drugs within the meaning of section 506C(h)(1) of the FD&C Act; other products tracked by CDER's Drug Shortage Staff, such as certain therapeutic biological products licensed under section 351 of the Public Health Service Act; and biological products licensed under that same section that are tracked by CBER's Office of Compliance and Biologics Quality, such as vaccines and blood products. See Appendix C for a breakdown of CBER's and CDER's CY 2023 numbers.

materials and components needed for the manufacturing process. FDA has seen manufacturers in the United States and abroad continue to experience quality issues and struggle with capacity constraints.

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, FDA has used a variety of methods to prevent shortages, working within the statutory and regulatory frameworks in place and in partnership with manufacturers and other stakeholders. FDA's investigation into nitrosamine impurities serves as an example of how the Agency has continued to take steps to ensure the safety of drug products while working to mitigate and prevent future shortages by using tools such as expedited reviews and inspections.[2]

In CY 2023, FDA worked with manufacturers to successfully avoid a large number of drug shortages, helping to prevent 236 shortages. For a comparison to recent years, FDA helped prevent 317 shortages in CY 2021 and 222 in CY 2022.[3] For information on FDA's historical prevention of drug shortages, see Figure 2, which shows the number of prevented drug shortages from CY 2010 to CY 2023.

Figure 2. Number of Prevented Drug Shortages Per Calendar Year (from CY 2010 to CY 2023).



[2] See https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications.

[3] See n. 2.

Many actions, including the following four, have helped FDA address drug shortages:

- Executive Order 13588 – Reducing Prescription Drug Shortages
- Food and Drug Administration Safety and Innovation Act (FDASIA)
- Coronavirus Aid, Relief, and Economic Security Act (CARES Act)
- Food and Drug Omnibus Reform Act (FDORA) of 2022

Each of these actions will be addressed in turn.

A. 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."[4] 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—including expediting reviews, as appropriate, and requiring manufacturers to provide advance notice of manufacturing discontinuances that could lead to a shortage of certain drugs—to help prevent and reduce current and future disruptions in the supply of life-saving medicines.

B. FDASIA

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. In addition, the FD&C Act, as amended by

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

FDASIA, allowed FDA to require, by regulation, early notification of such discontinuances or interruptions in the manufacturing of biologics.[5]

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.[6] FDA has sent eleven such letters, including one in CY 2023.[7]

Other requirements added by FDASIA with respect to prescription drug shortages include improving communication between FDA and the Drug Enforcement Administration (DEA) regarding shortages of controlled substances.

C. The Coronavirus Aid, Relief, and Economic Security (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 to FDA on permanent discontinuances and interruptions in manufacturing that may lead to a meaningful disruption in supply.

- 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 mitigate or prevent a shortage of a drug covered by section 506C(a).[8]

- 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

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

[6] Section 506C(f) of the FD&C Act.

[7] See https://www.fda.gov/drugs/drug-shortages/drug-shortages-non-compliance-notification-requirement.

[8] 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 sec. 801 (Aug. 18, 2017).

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 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.

D. FDORA

FDORA was signed into law on December 29, 2022, as part of the Consolidated Appropriations Act, 2023. FDORA included provisions regarding coordination between field investigators, CDER's Office of Compliance, and CDER's Drug Shortage Staff. This coordination includes sharing field investigators' inspection reports with the Drug Shortage Staff pursuant to section 704(b)(2) of the FD&C Act. FDORA also included related requirements for this report required by section 506C–1 of the FD&C Act to include (1) a description of the coordination and alignment activities between field investigators, CDER's Office of Compliance, and CDER's Drug Shortage Staff and (2) data on the number of inspection reports shared with the Drug Shortage Staff.

III. 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).

IV. Annual Reporting Requirements Per Section 506C–1

Section 506C–1 to the FD&C Act requires FDA to submit 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 2023, FDA was notified under section 506C(a) of 1,605 potential drug and biological product shortage situations by 159 different manufacturers. FDA continues to see a greater adherence to notification requirements, with an increasing number of manufacturers notifying FDA about potential shortage issues.

> ***Requirement 2:*** *Describe the communication between FDA's field investigators and the staff of CDER's Office of Compliance and the Drug Shortage Staff, including FDA's procedures for enabling and ensuring such communication.*

To facilitate communications between FDA's Office of Regulatory Affairs (ORA) and the 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. Each District Drug Shortage Coordinator is responsible for notifying the relevant FDA center of any issue identified during an inspection or other field activities that have 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.

For more details on how CDER and ORA coordinates its communications on a regular basis pertaining to shortages, as originally informed by FMD #15, see next section.

> ***Requirement 3:*** *Describe the coordination and alignment activities undertaken pursuant to section 506D(g) of the FD&C Act.*

FDA staff in CDER/OC and ORA are crucial to the Agency's prompt response to a drug shortage. These two groups have separate functions with respect to drug shortages. First, CDER/OC communicates with DSS on the recommendations being reviewed within CDER/OC about warning letters and other regulatory or enforcement actions; this

communication helps determine if there may be an impact on supply and if additional steps should be taken to mitigate a potential shortage when possible. Second, ORA's field investigators typically conduct inspections at manufacturing facilities and report their findings to CDER. 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 help prevent and mitigate a potential drug shortage.

In addition, consistent with section 704(b)(2) of the FD&C Act, added by the CARES Act, DSS routinely receives access to the Form FDA 483 presented to drug establishments from ORA at the close of an inspection. DSS receives access to the Form FDA 483s for all drug establishment inspections (i.e., not just those form 483s required to be provided under section 704(b)(2) when a drug is on the shortage list or when such a notification has been made available in the past 5 years), so information on the form is available to DSS as needed. In addition, when OC evaluates a case, the standard process is for OC (1) to consult with DSS to determine the potential for a meaningful disruption in supply of a drug considered to be life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition and (2) to incorporate this information into the case-handling strategy for non-compliant facilities to alleviate or mitigate the disruption in supply of such drug.

> ***Requirement 4:*** *Provide the number of reports that were required under section 704(b)(2) of the FD&C Act to be sent to the appropriate offices of the FDA with expertise regarding drug shortages, and the number of such reports that were sent.*

DSS receives access to the Form FDA 483s for all drug establishment inspections from ORA. By sharing all these forms, the requirement to share the subset of reports referenced in 506D(g) was met. In CY 2023, DSS was provided with 1,996 such forms.

> ***Requirement 5:*** *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:

- Identifying the extent of the shortfall and determining if other manufacturers are willing and able to increase production to make up the gap;

- Expediting FDA's inspections and reviews of submissions submitted by affected manufacturers attempting to restore production;

- Expediting 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;

- Expediting the release of lots of certain licensed biological products regulated by CBER or CDER;[9]

- Reviewing requests for extensions of expiration dating;

- Exercising temporary regulatory flexibility for new sources of medically necessary drugs;

- Working with the affected manufacturers to ensure adequate investigations into the root cause of the shortage;

- Developing risk mitigation measures to allow individual batches of a drug product; and

- Establishing communication channels with stakeholders and other interested parties.

Depending on the severity of the potential shortage and the surrounding circumstances, FDA can use one or more of these mitigation tools or seek to develop other options within its legal authority. 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 any such 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 259 submissions in CY 2023.[10]

[9] 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.

[10] See Appendix D for a breakdown of submission types.

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) of the FD&C Act during such calendar year.[11]

FDA prioritized 35 inspections to address drug shortages in CY 2023.[12]

Requirement 6: *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 Drug Enforcement Administration (DEA) 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.

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. This memorandum sets forth steps and procedures, including identifying contacts, for efficiently tracking and exchanging relevant information.[13] DSS reached out to DEA on 55 occasions during CY 2023 regarding potential shortage situations.

Requirement 7: *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 help 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 FDA-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.

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

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

[13] This memorandum, MOU 225-15-11, is available at https://www.fda.gov/about-fda/domestic-mous/mou-225-15-11.

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 2023, FDA exercised regulatory flexibility and discretion in 97 instances, affecting 58 products.[14] Examples of the types 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 healthcare 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 for a 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 8: *List the names of manufacturers issued letters under section 506C(f).*

[14] 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. For this year's report and moving forward, the methodology will include instances when FDA has exercised regulatory flexibility and discretion to carve out products from Import Alerts. When FDA implements a product carve-out to an Import Alert, FDA stipulates additional controls to balance any particular concern with importing such products.

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 non-compliance 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,[15] 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 11 non-compliance letters under section 506C(f) for failing to notify FDA about potential drug shortages. FDA sent the first two such letters in 2014, an additional two such letters in 2016, three in 2018, one in 2019, one in 2021, one in 2022, and one in 2023.[16] In CY 2023, FDA sent a letter to Padagis US LLC (on December 6, 2023). This letter and the response FDA received to it from the manufacturer are available on FDA's website.[17]

Requirement 9: *Specify the number of drug shortages occurring during 2023.*

The data from CDER's drug shortage database[18] show that the number of new shortages has significantly decreased since the peak in 2011. There was a record high of 251 new shortages in 2011.[19] Since the notification requirement under section 506C(a) of the FD&C Act was amended in 2012, there has been an overall trending decrease of new shortages. Despite a slight increase in numbers over the past few years, notifications have continued to help prevent shortages. There were 41 new drug shortages in CY 2021, 49 new drug shortages in CY 2022, and 55 new drug shortages in CY 2023.[20]

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

[16] See https://www.fda.gov/drugs/drug-shortages/drug-shortages-non-compliance-notification-requirement.

[17] See n. 16.

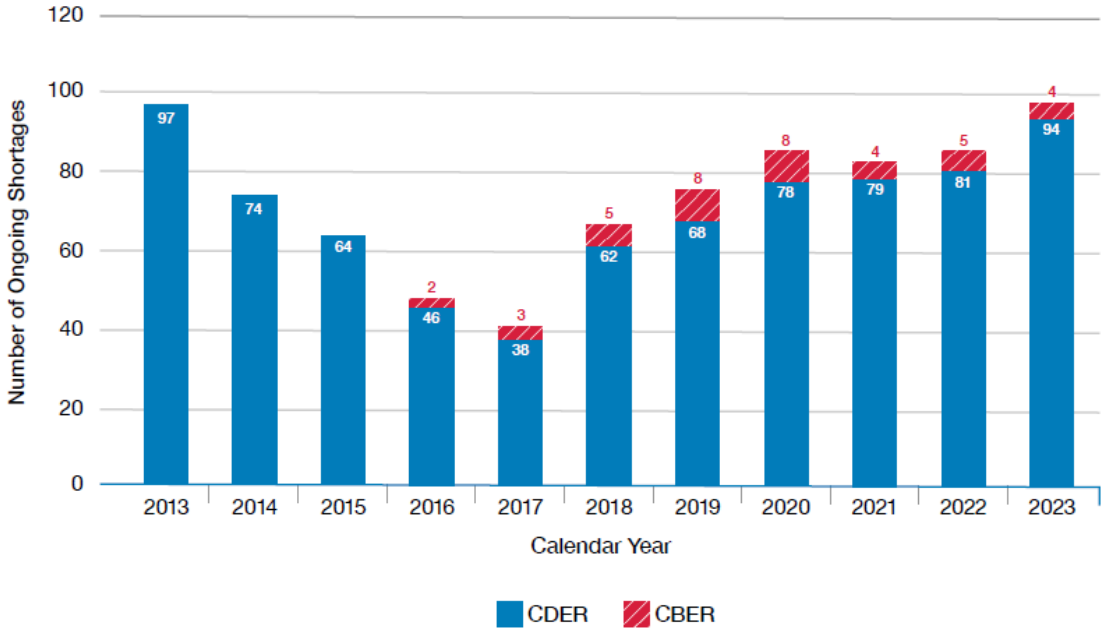
[18] CDER's drug shortages can be found at https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

[19] See Figure 1 for CBER's and CDER's new shortages per calendar year.

[20] See Appendix C for a breakdown of CBER's and CDER's CY 2023 numbers.

Another data point to note is the number of ongoing shortages yet to be resolved from previous years. As of December 31, 2023, FDA had identified 98 ongoing CDER- and CBER-tracked shortages.

Figure 3. Number of Annual Ongoing Drug Shortages Per Calendar Year (from CY 2013 to CY 2023).



V. Continued Drug Shortage Efforts in CY 2023

In CY 2023, FDA worked diligently to address and prevent drug shortages, including by implementing actions to, among other things, incentivize drug manufacturing establishments' use of quality management maturity (QMM) practices and collaborate with foreign regulatory authorities. These and other efforts, which are addressed below, have helped ensure the adequate supply of essential products, even during this time of heightened demand, and represent the dedicated efforts of staff from many offices within FDA.

A. Developing QMM

CDER continues to develop a program to promote QMM at drug manufacturing establishments. The QMM program aims to encourage manufacturers of CDER-regulated drugs to implement quality management practices that go beyond current good manufacturing practice requirements. Adopting mature quality management practices supports a more reliable drug supply chain. Specific CY 2023 accomplishments include the following:

- CDER published a white paper on QMM[21] that introduced the five practice areas in the prototype assessment protocol. This paper provided examples of elements within each practice area that may be considered during an assessment.

- A peer-reviewed journal article on lessons learned from QMM pilots[22] was published in January 2023. Between October 2020 and March 2022, CDER conducted two pilot programs with separate contractors to assess the QMM of drug manufacturers. One pilot was for domestic manufacturers of finished dosage form products, and one was for foreign manufacturers of APIs. These pilot programs provided valuable insights to CDER for developing its prototype assessment protocol.

- Following the commitment made at the Pharmaceutical Science and Clinical Pharmacology Advisory Committee on November 2, 2022, CDER engaged with over 10 stakeholder groups in 2023 through facilitated discussions to solicit their input on the perceived benefits of the QMM program, incentives that might

[21] See "CDER's Quality Management Maturity (QMM) Program: Practice Areas and Prototype Assessment Protocol Development," available at https://www.fda.gov/media/171705/download.

[22] "Lessons from CDER's Quality Management Maturity Pilot Programs," *The AAPS Journal*, January 10, 2023, https://link.springer.com/content/pdf/10.1208/s12248-022-00777-z.pdf.

encourage voluntary participation, and any potential unintended consequences of the program.

- CDER established a public docket[23] (September 15 to December 14, 2023) on CDER's QMM program that received responses from 23 individuals/entities.[24] This feedback will assist CDER in further developing its QMM program.

B. Collaborating with Foreign Regulatory Authorities

During CY 2023, there were shortages of drug products from manufacturers in the United States and abroad, and there continues to be concern surrounding the global supply chain and the United States' reliance on overseas manufacturing. There were four quarterly meetings held with the Agency's foreign counterparts. Currently, FDA continues to work closely with its colleagues in foreign regulatory authorities and directly with manufacturers to understand what the future impact on supply disruptions might be. FDA is not currently aware of shortages caused by restrictions on exports, although the Agency continues to monitor for any impact on supplies related to exports of pharmaceuticals, raw materials, and components. Should the situation change, FDA would continue to rely on its established relationships with its foreign counterparts to inform the shortage surveillance programs to inform the public and to mitigate the impact of supply constraints.

C. Responding to Increases in Demand

Although the majority of drug shortages have historically been linked to quality and GMP issues, in 2023, drug shortages also occurred as a result of increased demand. More than half of the shortages seen in CY 2023 were due, in part, to increases in demand. Due to the confluence of respiratory illnesses, including COVID-19, respiratory syncytial virus, and seasonal influenza, there have been substantial increases in demand for many respiratory products needed to treat patients, resulting in shortages of some of these products, such as cromolyn sodium concentrate. In addition, prior to the COVID-19 pandemic, FDA identified several demand-driven drug shortages, which FDA was not aware of until after they had occurred. Manufacturers are not required to notify FDA about shortages related to increases in demand, and this hampers FDA efforts to prevent or mitigate them.

[23] https://www.federalregister.gov/documents/2023/09/15/2023-20015/quality-management-maturity-program-for-drug-manufacturing-establishments-establishment-of-a-public

[24] https://www.regulations.gov/docket/FDA-2023-N-3721

D. Drug Shortage Assistance Award

As part of FDA's work to prevent and mitigate drug shortages, in 2014, the Agency created the FDA Drug Shortage Assistance Award to provide public recognition to drug companies and manufacturers that have demonstrated a commitment to preventing or alleviating drug shortages. This award recognizes efforts of drug companies and manufacturers that have worked in cooperation with FDA and have implemented strategies to help provide a steady supply of drugs for patients at a time when critical drug shortages pose a challenge for healthcare providers and patients nationwide while maintaining a commitment to quality manufacturing.

- In April 2023, FDA issued a Drug Shortage Assistance Award to Apotex. Apotex was recognized for its efforts related to alleviating a shortage of varenicline tablets.

- In November 2023, FDA issued a Drug Shortage Assistance Award to Sagent. Sagent was recognized for its efforts related to the prevention of several critical potential shortages.

E. Communicating About Current Drug Shortages

In CY 2023, FDA communicated with the public and industry stakeholders in multiple ways—including by publishing guidance documents, articles, and podcasts and by posting an up-to-date list of drugs and biological products that the Agency has determined to be in shortage—to provide information about current drug shortages. In particular:

- In March 2023, CDER published a *CDER Conversation* discussing the latest in drug shortages. In that publication, DSS talked about recent drug supply challenges and offered solutions to mitigate drug shortages.[25]

- In April 2023, FDA issued a draft guidance document for industry, Notifying FDA of a Discontinuance or Interruption in Manufacturing of Finished Products or Active Pharmaceutical Ingredients Under Section 506C of the FD&C Act, [26] to assist applicants and manufacturers in providing FDA timely and informative notifications about changes in the production of certain finished drugs, biological

[25] This piece is available at https://www.fda.gov/drugs/news-events-human-drugs/latest-drug-shortages?utm_medium=email&utm_source=govdelivery.

[26] A revision to the draft guidance document was issued in February 2024. The draft guidance document is available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/notifying-fda-discontinuance-or-interruption-manufacturing-finished-products-or-active.

products, and certain APIs that may, in turn, help the Agency prevent and mitigate drug shortages.

- In May 2023, FDA launched an episode of “Q&A with FDA” on drug shortages. The episode discussed how DSS responded to potential drug shortages by working with manufacturers to help address the shortages’ underlying causes and to enhance product availability.

VI. Conclusion

Drug shortages remain a significant public health issue in the United States and a top priority for FDA. Through important changes in FDA's authorities, and through ongoing FDA actions, progress has been made in preventing many drug shortages and quickly resolving them when they happen. Importantly, FDA's receipt of notifications of shortages before they occur provides FDA an opportunity to take steps to prevent or mitigate them. FDA also works with other stakeholders, including healthcare groups and patient organizations, to get information about specific shortages and identify opportunities to resolve them as quickly as possible.

Going forward, the Agency is working to identify opportunities to reduce the risks of drug shortages. Examples of these include the following:

- **Gaining fuller 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 requires manufacturers to notify FDA of API manufacturing discontinuances or interruptions and requires firms to report annually the amount of drugs they manufacture, but the CARES Act does not require reporting of shortages due to increased demand. Incorporating this "increased demand" requirement would greatly assist FDA's work to prevent or mitigate drug shortages.

- **Increasing the resilience of the drug supply chain**. Drug manufacturing in more than one facility and more than one geographic region can provide agility that reduces the risk of drug shortages and helps with resolution of shortages when they occur. For example, if a manufacturing facility needs to temporarily close, or its operations are curtailed by factors such as travel restrictions, quarantines, or natural disasters, it is important to have alternative facilities available to manufacture the drug or its API. FDA is ready to work with manufacturers to address these types of needs. Furthermore, an express requirement that drug manufacturers provide data identifying the suppliers they relied on to manufacture a listed drug and the extent of such reliance would help FDA identify vulnerabilities in the supply chain that may be hidden.

Overall, important progress has been made in preventing drug shortages from occurring, and FDA continues to work to ensure that patients in the United States have access to the medicines they need. Overall, during CY 2023, there were 55 new drug shortages. This report summarizes the many actions taken by the FDA to address these shortages. It also summarizes the work by FDA, manufacturers, and other groups to successfully prevent 236 potential shortages. Fundamentally, these

substantial efforts reflect FDA's commitment to continue its important work to prevent and mitigate drug shortages.

Appendix A: Definitions of Key Terms

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.

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Appendix B: Section 506C–1 of the FD&C Act

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) describes the coordination and alignment activities undertaken pursuant to section 506D(g);

(4) provides the number of reports that were required under section 704(b)(2) to be sent to the appropriate offices of the Food and Drug Administration with expertise regarding drug shortages, and the number of such reports that were sent;

(5)(A) lists the major actions taken by the Secretary to prevent or mitigate the drug shortages described in paragraph (9);

(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;

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

(7) 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;

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

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

Appendix C: Breakdown of CDER's and CBER's Shortage Numbers for CY 2023

	CDER	CBER
NUMBER OF SHORTAGES		
New Shortages	33	22
Prevented Shortages	224	12
Ongoing Shortages	94	4
Notifications	1538	67
Number of Manufacturers Notifying	136	27
ACTIONS TAKEN TO MITIGATE SHORTAGES		
Regulatory Flexibility and Discretion	97	0
Expedited Reviews	259	11*
Expedited Inspections	35	0

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

Appendix D: Breakdown of Expedited Reviews in CY 2023 by Submission Type

Submission Type	Expedited Reviews
NDA/NDA Supplements (CDER)	38
ANDA/ANDA Supplements (CDER)	210
BLA/BLA Supplements (CDER)	11
BLA/BLA Supplements (CBER)	3*

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

This report was prepared by FDA's Center for Drug Evaluation and Research and FDA's Center for Biologics Evaluation and Research. For information, please contact:

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This report is available on FDA's home page at https://www.fda.gov/.