Report to Congress

Drug Shortages

CY 2024

(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 the Agency) during calendar year (CY) 2024 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 and any impacts that may lead to supply disruptions or shortages of drug products in the United States. FDA understands the significant impact disruptions or shortages can have on patient care and is doing everything within its authority to help prevent and alleviate them. 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 to identify ways to maintain treatment options and prevent shortages. During CY 2024, FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) worked with manufacturers to successfully prevent 283 drug shortages using a range of available tools, including regulatory flexibility and discretion when appropriate. During this same period, 15 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. Unexpected events, such as natural disasters, shutdowns at facilities, and closures of facilities, also put increased strain on the supply chain and drug supply. FDA has worked to address acute shortages, shortages due to current good manufacturing practice violations, and other manufacturing challenges over the past calendar year.

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[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 Center for Biologics Evaluation and Research when the context requires distinguishing between these Centers.

[2] This twelfth 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 products 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 CDER's and CBER's CY 2024 numbers.

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 are helping to reduce the threat and impact of drug shortages, as are FDA's own actions. 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.

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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 the 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:

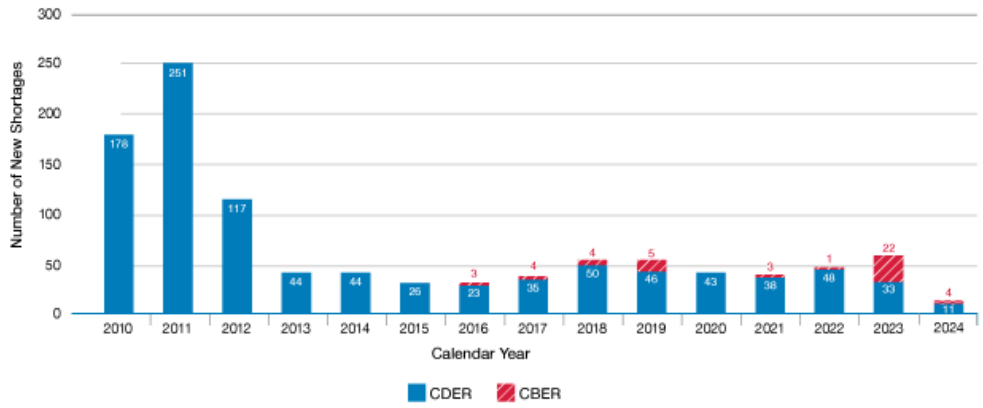
- Provides a background on drug shortages and FDA's efforts to address them;
- Responds to the specific issues listed under section 506C–1;
- Includes analyses that reflect data collected and evaluated by FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) during calendar year (CY) 2024;
- 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 2024. The number of new drug shortages per calendar year has declined from a high of 251 in 2011 to 15 in 2024.

Figure 1. Number of New Drug Shortages Per Calendar Year (from CY 2010 to CY 2024).[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 the number of new shortages has leveled off over the past decade, CY 2024 has been a challenging year for shortages. As a result of Hurricane Helene in the fall of 2024, the facility of a major manufacturer was significantly damaged and shut down for reconstruction and remediation, resulting in loss of manufacturing capacity needed for the supplies of numerous products. This caused delays in the release of some products, resulting in

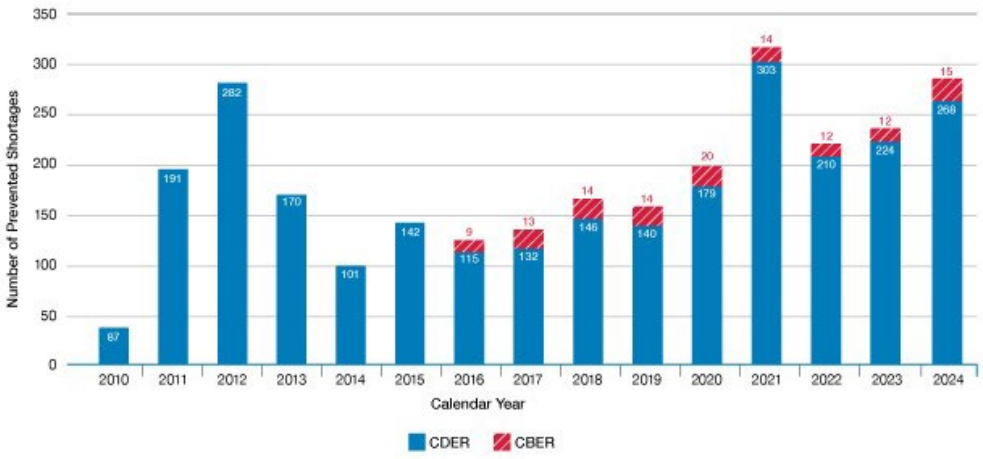
[1] This twelfth annual report to Congress is the ninth to include reporting for both drug and biological products, which include all drugs within the meaning of section 506C(h)(1) of the FD&C Act; other products tracked by CDER's Drug Shortage Staff, such as certain therapeutic biological products licensed 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 CDER's and CBER's CY 2024 numbers.

new shortages and worsening of existing shortages. FDA's efforts to respond to Hurricane Helene are summarized later in the report. In general, FDA continues to see manufacturers in the United States and abroad experiencing quality issues and struggling 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 others. FDA's ongoing 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 2024, FDA worked with manufacturers to successfully avoid a large number of drug shortages, helping to prevent 283 shortages. For a comparison to recent years, FDA helped prevent 222 shortages in CY 2022 and 236 in CY 2023. 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 2024.

Figure 2. Number of Prevented Drug Shortages Per Calendar Year (from CY 2010 to CY 2024).



[2] See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits.

Many actions, including the following, 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 OF 2022 (FDORA)

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."[3] 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

[3] 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 biological products.[4]

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.[5] FDA has sent 11 such letters since 2014.[6]

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. 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).[7]

- 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

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

[5] See section 506C(f) of the FD&C Act.

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

[7] 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 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 (CDER/OC), and CDER's Drug Shortage Staff (DSS). This coordination includes sharing field investigators' inspection reports with DSS 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/OC, and the DSS and (2) data on the number of inspection reports shared with DSS.

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 DSS and CBER's Office of Compliance and Biologics Quality (CBER/OCBQ). DSS and CBER/OCBQ 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. CDER's and CBER'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 CDER/OC and CBER/OCBQ.

IV. Annual Reporting Requirements Per Section 506C–1

Section 506C–1 of 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 2024, FDA was notified under section 506C(a) of 1459 potential drug and biological product shortage situations by 151 different manufacturers. FDA continues to see a greater adherence to notification requirements than in past years.

> ***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 Inspections and Investigations (OII, formerly the Office of Regulatory Affairs) and the medical product centers, which include CDER and CBER, OII issued Field Management Directive (FMD) #15 in July 2012. FMD #15 established drug shortage coordinators in OII so that each FDA field district would have a District Drug Shortage Coordinator who serves as the point of contact between OII 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 OII and the Centers related to potential and current product shortage situations.

For more details on how CDER and OII coordinate their communications on a regular basis pertaining to shortages, as originally informed by FMD #15, see the 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 OII 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, OII'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 OII. DSS receives access to the Form FDA 483s for all drug establishment inspections (i.e., not only when a drug is on the shortage list, but also 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 OII. By sharing all these forms, OII has met the requirement to share the subset of reports referenced in 506D(g). In CY 2024, DSS was provided with 2,367 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;[8]

- Reviewing requests for extensions of expiration dating;

- Exercising temporary regulatory flexibility and discretion 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 support the distribution of specific batches of a drug product; and

- Establishing communication channels with 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 225 submissions in CY 2024.[9]

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.[10]

[8] 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.

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

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

FDA prioritized 20 inspections to address drug shortages in CY 2024.[11]

> ***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 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.[12] DSS reached out to DEA on 90 occasions during CY 2024 regarding potential shortage situations.

As an example of the impact of increased coordination, DEA publicly noted that in July 2024 they received written correspondence from FDA regarding the domestic drug shortage of lisdexamfetamine, a Schedule II stimulant used to treat attention-deficit/hyperactivity disorder (ADHD) and other conditions. DEA further noted that FDA's letter requested an increase in lisdexamfetamine quota, which DEA subsequently granted in September 2024.

> ***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,

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

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

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 2024, FDA exercised regulatory flexibility and discretion in 107 instances, affecting 114 products.[13] 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 was completed before releasing the product into the marketplace,
  - Third-party oversight of manufacturing was instituted to detect and 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 manufacturing issue 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).*

[13] A single instance of regulatory flexibility and discretion may affect more than one product. Conversely, a shortage of one product may involve multiple instances of regulatory flexibility and discretion 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, 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.[14] In CY 2024, FDA did not issue any non-compliance letters. All non-compliance letters and the responses FDA received from the manufacturers are available on FDA's website.[15]

Requirement 9: *Specify the number of drug shortages occurring during 2024.*

The data from CDER's drug shortage database[16] 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.[17] 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 49 new drug shortages in CY 2022, 55 new drug shortages in CY 2023, and 15 new drug shortages in CY 2024.[18]

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

[15] Ibid.

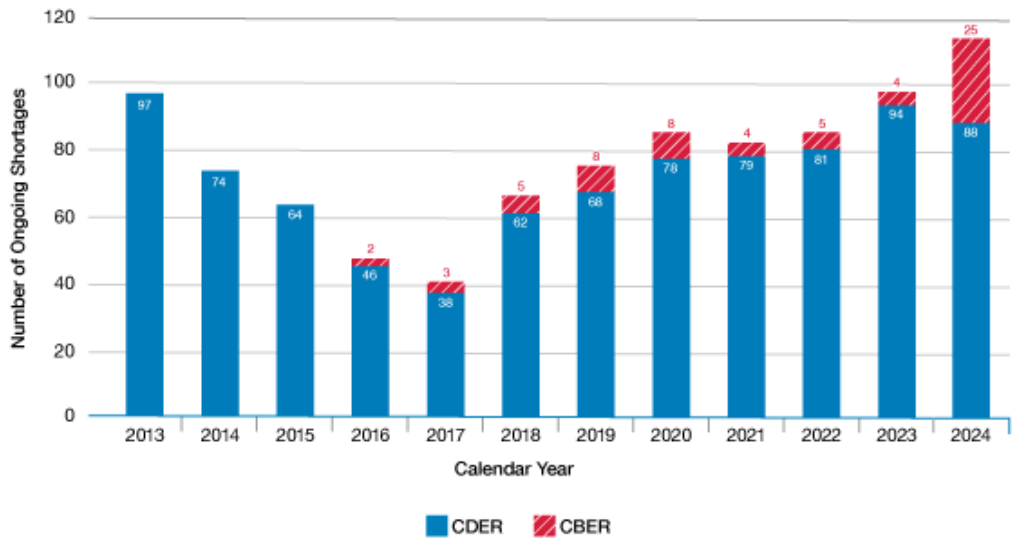
[16] CDER's drug shortages can be found at https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

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

[18] See Appendix C for a breakdown of CDER's and CBER's CY 2024 numbers.

Another data point to note is the number of ongoing shortages yet to be resolved from previous years. As of December 31, 2024, FDA had identified 113 ongoing CDER- and CBER-tracked shortages.

Figure 3. Number of Annual Ongoing Drug Shortages Per Calendar Year (from CY 2013 to CY 2024).



V. Continued Drug Shortage Efforts in CY 2024

In CY 2024, FDA worked diligently to address and prevent drug shortages, including by implementing actions to, among other things, incentivize drug manufacturing establishments' use of more advanced quality management practices, collaborate with foreign regulatory authorities, and expand communication between field investigators, CDER/OC, and DSS in advance of and during certain inspections. These 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 a QMM Program

CDER continues to develop a program to promote quality management maturity (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 more advanced quality management practices supports a more reliable drug supply chain. Specific CY 2024 accomplishments include the following:

- CDER developed a prototype assessment protocol covering the five practice areas described in the White Paper published in 2023 titled *CDER's Quality Management Maturity Program: Practice Areas and Prototype Assessment Protocol Development*[19].

- In January 2024, CDER published a *Federal Register Notice*[20] to solicit volunteers to participate in the 2024 Voluntary Quality Management Maturity Prototype Assessment Protocol Evaluation Program.

- CDER evaluated nine establishments as part of the voluntary Quality Management Maturity Prototype Assessment Protocol Evaluation Program. Following each assessment, CDER provided the establishment with a QMM report that highlighted areas of strength and opportunities for improvement.

[19] https://www.fda.gov/media/171705/download

[20] https://www.federalregister.gov/documents/2024/01/25/2024-01423/voluntary-quality-management-maturity-prototype-assessment-protocol-evaluation-program

B. FDA Public Communications Regarding Drug Shortages

In March 2024, FDA launched a new portal for patients, consumers, and health care professionals to report potential new drug shortages directly into CDER's NextGen reporting system. Since 2017, NextGen has been a way for regulated industry to communicate with the FDA, including submitting information on shortages, discontinuations, and anticipated supply disruptions.

The new public portal allows anyone outside regulated industry, including health care professionals, patients/consumers, and professional organizations, to submit shortage information through an online form directly into NextGen. Expanding access to NextGen's shortage reporting beyond regulated industry will allow for greater consistency and ease of reporting by outside stakeholders, improving the reporting process.

Early notification about drug shortages or potential supply challenges can help FDA staff take action to quickly resolve or mitigate the shortage. FDA staff investigate every notification submitted through NextGen to determine if the nationwide demand for the drug exceeds available supply.

C. Control of Nitrosamine Impurities in Human Drugs

In September 2024, FDA published the second revision of the guidance, *Control of Nitrosamine Impurities in Human Drugs*[21], which provides recommendations for steps manufacturers and applicants of active pharmaceutical ingredients and drug products should take to detect and prevent unacceptable levels of nitrosamine impurities in drug products. In doing so, this guidance aims to help mitigate the risk of nitrosamine impurities in drug products while maintaining the availability of critical drugs. The guidance includes information about nitrosamine drug substance-related impurities, recommends implementation of new nitrosamine control strategies, and provides an updated recommended timeline for manufacturers to implement these recommendations.

When recommending implementation timelines, FDA may consider factors such as the potential risk to public health, the state of scientific knowledge, the scope of the problem, the feasibility and complexity of implementing effective prevention or mitigation strategies, and the risk of drug shortages.

One of the key features of the updated guidance is an incorporated web page that will

[21] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs

be updated, as appropriate, when new information becomes available.[22]

FDA has been investigating the presence of nitrosamine impurities in certain drug products since 2018. FDA is providing additional recommendations regarding risk and appropriate actions for manufacturers to take to help ensure drug products continue to be safe. This will help prevent potential disruptions in drug supplies and shortages that can result from unacceptable levels of nitrosamine impurities in drug products.

D. Hurricane Helene

On September 28, 2024, FDA was made aware of the devastating impact Hurricane Helene had on Baxter International's North Cove manufacturing facility in Marion, North Carolina. This facility is one of the largest manufacturers of intravenous and peritoneal dialysis solutions in the United States, some of which have been on FDA's shortage list. A massive effort by FDA and federal partners supported infrastructure repairs and enabled operations to resume quickly. In just over 60 days, new product was being released from this facility.

FDA's engagement included reviews of requalification protocols that were designed to ensure the quality, safety, efficacy, and purity of products when restarting manufacturing lines. These protocols included cleaning and qualification of impacted manufacturing lines and areas, enhanced monitoring and testing for the facility environment, and sterility assurance activities. FDA conducted regulatory oversight activities at Baxter North Cove once the manufacturing lines successfully restarted to provide additional assurance, beyond testing, of the quality and safety of the products manufactured. Products manufactured after the requalification activities undergo testing before distribution and are released if all regulatory requirements are met to ensure the quality and safety of the products. FDA also exercised enforcement discretion for temporary importation to provide treatment options for patients in critical need during the shortage. FDA worked closely with Baxter to safely import millions of units of product from at least four different international facilities.

[22] See the FDA/CDER Nitrosamine Impurity Acceptable Intake Limits web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related.

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 permanent discontinuances and interruptions in manufacturing before they occur provide 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 FD&C Act, as amended by the CARES Act, requires manufacturers to notify FDA of API manufacturing discontinuances or interruptions and requires firms to report annually on the amount of drugs they manufacture.

- **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.

- **Facilitating the adoption of advanced manufacturing.** Advanced manufacturing is a collective term for new medical product manufacturing technologies that can improve drug manufacturing reliability, minimizing deviations from good manufacturing practices, address shortages of medicines, and speed time-to-market. FDA can help reduce our reliance on foreign manufacturing by facilitating the adoption of advanced manufacturing for companies that are willing and able to make the investment. Advanced manufacturing technologies may help domestic companies operate with lower costs and fewer quality manufacturing deviations in smaller facilities, improving the global competitiveness of U.S. manufacturing. FDA has a strong record in

advanced manufacturing, and FDA has a number of initiatives[23] to encourage the development and adoption of advanced manufacturing that could make reshoring of drug manufacturing facilities more competitive.

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 2024, there were 15 new drug shortages, the lowest in a decade. 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 283 potential shortages. Fundamentally, these substantial efforts reflect FDA's commitment to continue its important work to prevent and mitigate drug shortages.

[23] https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-manufacturing

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.

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 2024

	CDER	CBER
NUMBER OF SHORTAGES		
New Shortages	11	4
Prevented Shortages	268	15
Ongoing Shortages	88	25
Notifications	1420	39
Number of Manufacturers Notifying	129	28
ACTIONS TAKEN TO MITIGATE SHORTAGES		
Regulatory Flexibility and Discretion	106	1
Expedited Reviews	206	19*
Expedited Inspections	20	0

* This number includes expedited reviews for 6 biologics license application (BLA)/BLA supplements, 1 regulatory discretion request and 12 lot-release submissions for CBER-regulated products.

Appendix D: Breakdown of Expedited Reviews in CY 2024 by Submission Type

Submission Type	Expedited Reviews
NDA/NDA Supplements (CDER)	47
ANDA/ANDA Supplements (CDER)	149
BLA/BLA Supplements (CDER)	10
BLA/BLA Supplements (CBER)	6*

* This number does not include the expedited reviews for the 12 lot-release submissions for CBER-regulated products.

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