Report to Congress

# Drug Shortages

## CY 2022

(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) 2022 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 continues to closely monitor the medical product supply chain, which was impacted by the Coronavirus Disease 2019 (COVID-19) pandemic during 2022, 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 2022, 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 222 drug shortages through the use of a range of available tools, including regulatory flexibility and discretion when appropriate. During this same period, the number of new shortages tracked by CBER and CDER was 49, compared to a peak of 251 new shortages during CY 2011.[2] Although the number of new drug shortages has declined since 2011 as a result of work by many groups, including FDA, shortages continue to pose a real challenge to public health, particularly when the shortage has involved a critical drug to treat cancer, to provide parenteral nutrition, or to address other serious medical conditions, such as a shortage of antibiotics. In the past 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, as well as an earlier than typical flu and respiratory virus season, FDA has seen additional strain on the pharmaceutical supply chain.

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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 FDA's Center for Biologics Evaluation and Research when the context requires distinguishing between these Centers.

[2] This tenth 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 2022 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 early notification of interruptions and discontinuances in manufacturing and FDA's own actions are helping to reduce the threat and impact of drug shortages. FDA will continue to prioritize 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.

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# I. Introduction

The Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted on July 9, 2012.[1] Title X of FDASIA, which addresses drug shortages, took effect on the date of enactment and, among other things, amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301 et seq.) by adding section 506C–1, which requires the Food and Drug Administration (FDA or Agency) to file an annual report to Congress on drug shortages.[2] 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) 2022;
- 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.

[1] Pub. L. 112-144, 126 Stat. 994 (July 9, 2012).

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

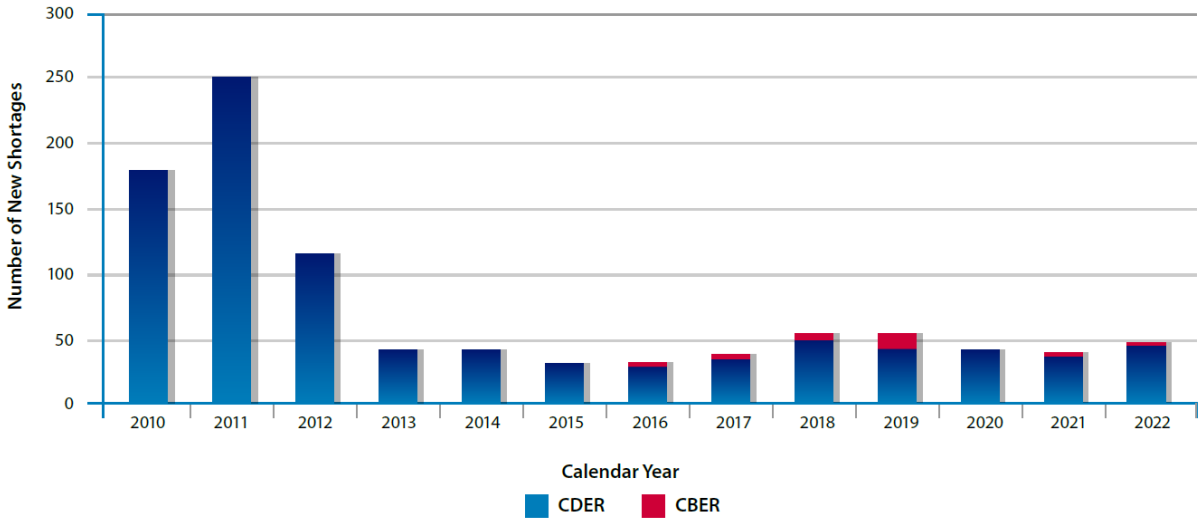
> [n]ot later than March 31 of each calendar year, the Secretary shall submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report, with respect to the preceding calendar year, on drug shortages . . .

# II. Background

Drug shortages can have serious and immediate effects on providing needed therapies to patients, therefore preventing shortages is a priority for FDA. At the height of the drug shortage crisis, the number of new 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 2022. The number of new drug shortages per calendar year has declined from a high of 250 in 2011 to 49 in 2022.

**Figure 1. Number of New Drug Shortages Per Calendar Year, (from CY 2010 to CY 2022).[3]**




Although the number of new drug shortages has declined since 2011 as a result of work by many groups, including FDA, shortages continue to pose a real challenge to public health, particularly when the shortage has involved a critical drug to treat cancer, to provide parenteral nutrition, or to address another serious medical condition, such as a shortage of antibiotics. Although there has been a leveling off of new shortages over

[3] This tenth 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 2022 numbers.

the past few years, CY 2022 has been a challenging year for shortages. FDA has seen manufacturers in the United States and abroad continue to experience quality issues and struggle with capacity constraints. Additionally, there were dramatic and rapid changes in demand for some products used to treat infectious diseases such as COVID-19, respiratory syncytial virus (RSV), and seasonal influenza, which has placed additional strain on the pharmaceutical supply chain and made it harder for FDA and manufacturers to avoid drug shortages.

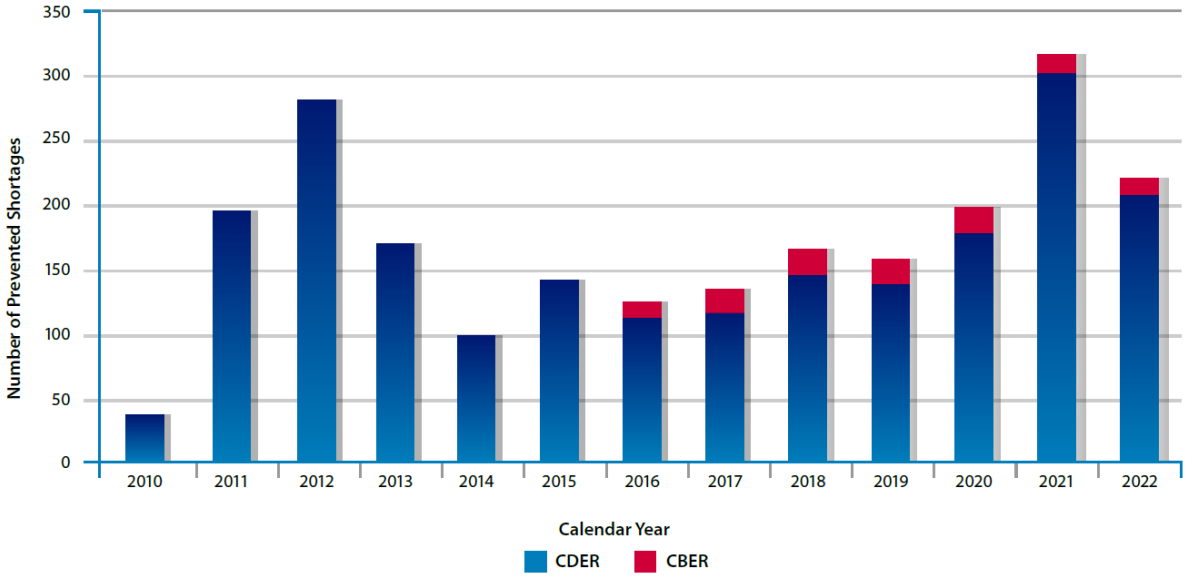
Shortages can delay or deny needed care for patients, creating a potential lapse in medical care. Shortages can also lead prescribers to use second-line alternatives, which may be less effective or pose additional risks compared to the drug in shortage. As summarized below, FDA has used a variety of 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 both mitigate and prevent future shortages by using tools such as expedited reviews and inspections.[4]

In CY 2022, FDA worked with manufacturers to successfully avoid a large number of drug shortages, helping to prevent 222 shortages. For a comparison to recent years, FDA helped prevent 199 shortages in CY 2020 and 317 in CY 2021.[5] For information on FDA's historical prevention of drug shortages, see Figure 2, which shows the number of drug shortages prevented by FDA from CY 2010 to CY 2022.

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

[5] See supra n. 2.

**Figure 2. Number of Prevented Drug Shortages Per Calendar Year (from CY 2010 to CY 2022).**




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

- Executive Order 13588 – Reducing Prescription Drug Shortages
- The Food and Drug Administration Safety and Innovation Act (FDASIA)
- The Coronavirus Aid, Relief, and Economic Security Act (CARES Act)
- The inter-agency Drug Shortages Task Force

Each of these elements 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."[6] 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

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

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 FDASIA, allows FDA to require, by regulation, early notification of such discontinuances or interruptions in the manufacturing of biologics.[7]

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.[8] FDA has sent ten such letters, including one in 2022.[9]

Other FDASIA requirements with respect to prescription drug shortages include improving FDA's internal and external communications about shortages, improving communication between FDA and the Drug Enforcement Administration (DEA) regarding shortages of controlled substances, and developing a strategic plan to enhance FDA's response to preventing and mitigating drug shortages.

## 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

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

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

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

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).[10]

- The addition of section 506C(j) to the FD&C Act, requiring manufacturers of drugs described in section 506C(a) of the FD&C Act or of any active pharmaceutical ingredient (API) or any associated medical device used for preparation or administration included in the drug to develop, maintain, and implement, as appropriate, a redundancy risk management plan that identifies and evaluates the risks to the supply of the drug, as applicable, for each establishment in which the drug or API of the drug is manufactured.

- Amendments to section 510(j) of the FD&C Act to require drug manufacturers registered under section 510 of the FD&C Act to annually report 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. The Inter-agency Drug Shortages Task Force

In response to a request in June 2018 from 31 U.S. Senators and 104 members of the House of Representatives, the Commissioner of Food and Drugs established the inter-agency Drug Shortages Task Force to determine the root causes of drug shortages and develop recommendations to address them. The task force took a comprehensive look at all drivers of drug shortages and identified potential ways to prevent or mitigate them in the future. To ensure FDA did not overlook any drivers or solutions, the task force included not only senior leaders from FDA but also leaders from several federal agencies, including the Centers for Medicare & Medicaid Services (CMS) and the Department of Veterans Affairs (VA). Collectively, CMS and the VA provide or pay for prescription medicines for millions of Americans. The Department of Defense, the Federal Trade Commission, and the Office of the Assistant Secretary for Preparedness and Response (within the U.S. Department of Health and Human Services (HHS)) were

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

also represented on the task force.[11] The task force invited public participation through a public meeting on November 27, 2018; established a docket to receive comments; and invited stakeholders to a series of listening sessions. In October 2019, the task force issued its report *Drug Shortages: Root Causes and Potential Solutions*[12] that identifies root causes of drug shortages and offers recommendations for government and industry to address them. The report was updated on February 21, 2020, to include a revised economic analysis about production increases and supply restoration after a shortage. Although the work of the task force concluded with the report and the task force itself no longer meets, FDA regularly meets internally to monitor and discuss potential and ongoing shortages.

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

[12] The report is available at https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions.

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

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

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

For CY 2022, FDA was notified of 1,293 potential drug and biological product shortage situations by 150 different manufacturers. FDA continues to see a greater adherence to notification requirements, with an increasing number of manufacturers notifying FDA annually about potential shortage issues.

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

Field investigators in CDER/OC and FDA's Office of Regulatory Affairs (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 that office 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 prevent and mitigate a potential drug shortage.

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

expectations between ORA and the centers related to potential and current product shortage situations. In addition, consistent with section 704(b)(2) of the FD&C Act, added by the CARES Act, DSS routinely receives access to the Form FDA 483 presented to drug establishments.

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

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

- Identifying the extent of the shortfall and determine 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;[13]
- 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;
- Working with the Assistant Secretary for Preparedness and Response (ASPR) on (1) their efforts under the Defense Production Act (DPA) for the development of COVID-19 vaccines and therapeutics and (2) supply chain activities;
- Developing risk mitigation measures to allow individual batches of a drug product to be released even when quality assurance requirements were not met; and

[13] 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.

- 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 the shortage until it has been resolved.

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

FDA expedited the review of 199 submissions in CY 2022.[14]

*List the number of establishment inspections or re-inspections related to mitigation or prevention of a shortage that the Secretary expedited under section 506C(g)(2) during such calendar year.[15]*

FDA prioritized 30 establishment inspections to address drug shortages in CY 2022.[16]

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

If a drug at risk of shortage is a controlled substance, FDA works closely with the 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

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

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

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

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.[17] DSS has reached out to DEA on 20 occasions during CY 2022 regarding potential shortage situations.

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

FDA's first priority is to 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 approved drugs and biological products sufficient to meet patient demand that also meet the appropriate quality, safety, and efficacy standards. However, FDA recognizes that there can be risks to patients if treatment options are not available for critical conditions.

The Agency understands the importance of using appropriate tools within its legal authority for certain situations in order to prevent or mitigate a shortage situation. In certain shortage situations, the temporary exercise of regulatory flexibility and discretion has proven to be an important tool in helping to alleviate a drug shortage and to ensure access to treatment options for patients in critical need.

During CY 2022, FDA exercised regulatory flexibility and discretion in 87 instances, affecting 76 products.[18] Examples of situations in which FDA exercised regulatory flexibility and discretion to prevent or mitigate a shortage are listed below:

- FDA exercised temporary regulatory flexibility and discretion for medically necessary products that presented quality issues. For example:
  - Filters were supplied with a product to remove particulate matter,
  - Extra testing for product quality or identity was completed before releasing the product into the marketplace,
  - Third-party oversight of production was instituted to monitor quality issues,

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

[18] 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.

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

Under section 506C(f) of the FD&C Act, if a manufacturer fails to provide notification of a discontinuance or interruption in manufacturing as required by section 506C, FDA must issue a letter to that manufacturer stating that the notification requirement was not met. The manufacturer is required to respond to FDA's letter within 30 calendar days, providing the reason for noncompliance and the required information on the discontinuance or interruption. Within 45 calendar days of issuing the letter, FDA is required to post a copy of the letter and any response received on FDA's website,[19] 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 10 non-compliance letters under section 506C(f). 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, and one in 2022.[20] In CY 2022, a letter was sent to the Bristol-Myers Squibb Company on February 2, 2022. The letter sent by FDA and the response received from the manufacturer are available on FDA's website.

*Requirement 7: Specify the number of drug shortages occurring during 2022.*

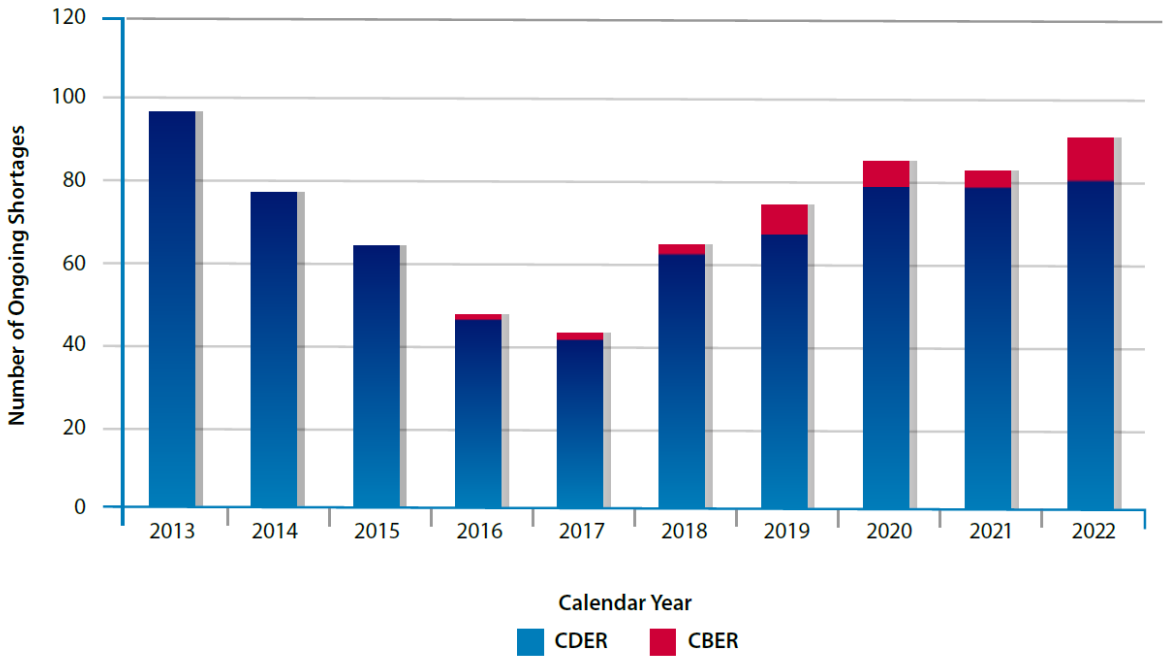
[19] Links to letters of non-compliance with notification requirements are available at http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm403902.htm.

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

The data from CDER's drug shortage database[21] show that the number of new shortages significantly decreased over time. There was a record high of 251 new shortages in 2011.[22] Since the enactment of the notification requirement under section 506C(a) of the FD&C 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 43 new drug shortages in CY 2020, 41 new drug shortages in CY 2021, and 49 new drug shortages in CY 2022.[23]

Another data point to note is the number of ongoing shortages yet to be resolved from previous years. As of December 31, 2022, FDA had identified 86 ongoing CDER- and CBER-tracked shortages. This number has continued to remain steady over the past couple years; there were 86 ongoing shortages for CY 2020 and 83 ongoing shortages for CY 2021.

**Figure 3. Number of Annual Ongoing Drug Shortages Per Calendar Year (from CY 2013 to CY 2022).**




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

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

[23] See Appendix C for a breakdown of CBER's and CDER's CY 2022 numbers.

# V. Continued Drug Shortage Efforts in CY 2022

In CY 2022, FDA worked diligently to address and prevent drug shortages, including implementing actions to, among other things, incentivize the use of quality management maturity (QMM) practices, expedite the review of monkeypox-related biologics, 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 review staff from many offices within FDA.

## A. Incentivizing QMM

CDER worked to establish a program to incentivize drug manufacturers to invest in QMM. QMM practices help drug manufacturers reduce the likelihood of supply chain disruptions (caused by a decreased supply or an increased demand) and lead to reduced costs, increased customer satisfaction, and greater operational efficiencies. CDER's specific QMM accomplishments in CY 2022 include the following:

- CDER completed two pilot programs that evaluated best practices and developed frameworks to distinguish levels of QMM.

- CDER published a white paper on QMM,[24] which highlighted the benefits of the program to different stakeholders (patients, providers, payors, purchasers, pharmacies, and pharmaceutical manufacturers) and identified key considerations that impact program development.

- CDER hosted a QMM public workshop[25] (2,000 global attendees) that shared learnings from the pilot programs and provided an opportunity for FDA to solicit feedback. Ninety-nine percent of over 400 attendees who responded to a workshop poll believed that purchasers of drug products or APIs should "consider the QMM of the facility that manufacturers them."

- Peer-reviewed journal articles on a quality benchmarking study[26] (based on

[24] This white paper, "Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals," is available at https://www.fda.gov/media/157432/download.

[25] This workshop, "Quality Management Maturity Workshop," is available at https://www.fda.gov/drugs/news-events-human-drugs/quality-management-maturity-workshop-05242022.

[26] This article, "Benchmarking the Quality Practices of Global Pharmaceutical Manufacturing to Advance Supply Chain Resilience," is available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9589742/.

collaboration with Dunn & Bradstreet and the University of St. Gallen) and lessons learned from QMM pilots[27] (domestic finished dosage form and foreign active pharmaceutical ingredient pilots) were published.

- An FDA advisory committee[28] met and voted unanimously in favor of CDER establishing a QMM program, and work is actively ongoing.

## B. Expediting the Review of Monkeypox (mpox) Biologics

In late May 2022, following reports of mpox in the United States, FDA/CBER worked with its HHS partners to expedite the submission of a manufacturing supplement, originally planned for fall 2022, to FDA to facilitate increased production of JYNNEOS, Smallpox and Monkeypox Vaccine, Live, Non-Replicating, for prevention of smallpox and mpox disease in adults 18 years of age and older determined to be at high risk for smallpox or mpox infection. After receiving a supplemental application from Bavarian Nordic, the manufacturer of JYNNEOS in May 2022, FDA immediately expedited its review, which included an inspection of the manufacturing facility in Denmark, which took place between July 1 and July 8, 2022.

Following completion of the inspection, FDA finished its evaluation of the required information to validate product quality, determined that the vaccine met its quality standards, and approved the supplemental biologics license application for JYNNEOS on July 26, 2022. Given the emerging public health need, FDA facilitated advance shipments of manufactured doses to the United States, and additional doses manufactured at a facility in Europe were distributed and administered in the United States to help address the mpox outbreak.

## C. Collaborating with Foreign Regulatory Authorities

During CY 2022, there were shortages of drug products from manufacturers in the United States and abroad, and there continues to be concern surrounding the supply chain and reliance on overseas manufacturing. 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 from Asia or other regions, although the Agency continues to monitor for any impact on supplies related to exports

[27] This article, "Lessons from CDER's Quality Management Maturity Pilot Programs," is available at https://link.springer.com/content/pdf/10.1208/s12248-022-00777-z.pdf.

[28] Information on this Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting is available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-2-3-2022-pharmaceutical-science-and-clinical-pharmacology-advisory-committee-meeting.

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.

## D. Responding to COVID-19-Related Shortage Risks

The COVID-19 pandemic has increased the risk of shortages due to sudden increases in demand for drugs used in hospitalized patients, particularly the most critically ill. In fact, in CY 2022, based on an assessment of the types of drug products that went into shortage, FDA noticed an increase in demand for certain drugs used to treat COVID-19 and other infectious diseases, especially in children.

To respond to this risk, in CY 2022, DSS requested that manufacturers not only evaluate their entire supply chain (including key starting materials, APIs, packaging components, and finished dosage forms) but also communicate about any new issues that arise. In addition, even though manufacturers are required to notify FDA of certain permanent discontinuances and interruptions in manufacturing, as discussed above, FDA also, in CY 2022, requested, on a voluntary basis, additional information from manufacturers (including inventory levels, production plans, and distribution quantities) to better understand the supply chain. Although the manufacturers were not required to provide this information, it has been extremely valuable for FDA's work to prevent drug shortages.

Due to the forward-leaning actions mentioned above, the number of new drug shortages has not increased significantly during the COVID-19 pandemic; there were 49 new drug shortages in 2022, slightly up from 41 in 2021. In addition, during CY 2022, FDA expedited the review of and approved 36 original abbreviated new drug applications (ANDAs) and 73 supplemental ANDAs for drug products that may be used in managing patients with COVID-19. These approvals have helped ensure the adequate supply of these essential products during this time of heightened demand and represent the dedicated efforts of review staff from many offices within FDA.

## E. Responding to Sudden Increases in Demand

Although the majority of drug shortages are linked to quality and GMP issues, some drug shortages are a result of increased demand. FDA generally does not receive notice or adequate information from drug manufacturers regarding sudden increases in demand (in contrast to drug shortages driven by a disruption in supply) that, if received, would position the Agency to assist in preventing or mitigating drug shortages driven by that increase in demand.

During the COVID-19 public health emergency and the recent confluence of respiratory illnesses, including COVID-19, RSV, and seasonal influenza occurring at the same time, there have been substantial increases in demand for many products needed to treat patients, resulting in shortages of some of these products, such as amoxicillin oral suspension. In addition, prior to the COVID-19 pandemic, FDA identified several demand-driven drug shortages, which FDA was not aware of until after they occurred. This delay has impacted FDA's ability to respond.

With advance notice of increases in demand that the manufacturer anticipates that it will likely be unable to meet, FDA may be able to take proactive steps to prevent or mitigate demand-driven drug shortages.

## F. Communicating About Current Drug Shortages

In CY 2022, FDA communicated with industry in multiple ways (such as by publishing guidances and 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 November 2022, FDA issued the immediately-in-effect guidance for industry Compounding Certain Beta-Lactam Products in Shortage Under Section 503A of the Federal Food, Drug, and Cosmetic Act[29] to help alleviate the shortage of amoxicillin for oral suspension. The guidance, which is geared for certain drug compounders, is intended to enable a greater supply of antibiotics like amoxicillin that are in shortage until manufacturers are able to meet the full demand.

- In July 2022, FDA issued the guidance for industry *Changes to Disposable Manufacturing Materials Questions and Answers*[30] about making changes to applications regarding disposable manufacturing materials (e.g., sterilizing filters, single use systems). The limited availability of these materials during periods of increased demand (e.g., public health emergencies or natural disasters) can affect the availability of sterile drugs and biological products. The guidance provides recommendations to applicants in determining the appropriate reporting category to communicate changes to disposable manufacturing materials.

- In May 2022, FDA issued a draft guidance for industry, *Risk Management Plans to Mitigate the Potential for Drug Shortages*,[31] intended to help manufacturers develop, maintain, and implement, as appropriate, risk management plans to

[29] This guidance is available at https://www.fda.gov/media/163367/download.

[30] This guidance is available at https://www.fda.gov/media/160300/download.

[31] The guidance is available at https://www.fda.gov/media/158487/download.

proactively assist in the prevention of human drug product and biological product shortages.

- To provide the most current information to patients and caregivers, FDA posts a public, up-to-date list of drugs and biological products that the Agency has determined to be in shortage, including those related to COVID-19.[32]

## G. Leveraging FDA's Tools to Address Shortages

To increase patient access to critically needed medications in shortage or to prevent potential shortages, FDA leveraged available tools (including the authorities and requirements added by the CARES Act (which are described in section II.C of this report)). For example, CDER:

- Expedited its reviews of approximately 80 original ANDAs and over 70 ANDA supplements.

- Expedited its assessments of manufacturing supplements to facilitate the manufacturing capacity for COVID-19 therapeutic biologics.

- Exercised regulatory flexibility and discretion in 85 instances to increase supplies of critically needed medications.

[32] These lists are available at https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm and https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages.

# VI. Conclusion

Drug shortages remain a significant public health issue in the United States and a top priority for FDA, particularly during the COVID-19 pandemic. While important progress has been made in preventing many drug shortages from occurring, FDA continues to work to ensure that patients in the United States have access to the medicines they need and to ensure a more robust supply chain.

The Agency notes that its response to the COVID-19 pandemic has highlighted the following needs that require ongoing work to be fully addressed:

- **Need to gain better insight into the supply chain**. Interruptions or problems in the drug supply chain can create or worsen drug shortages. As mentioned earlier in this report, the CARES Act includes authorities and requirements meant to enhance FDA's ability to identify, prevent, and mitigate possible drug shortages by improving the Agency's visibility into the drug supply chain. While such provisions do include a requirement for manufacturers to notify FDA of API manufacturing discontinuances or interruptions and a requirement for firms to report annually the amount of drugs they manufacture, manufacturers are not required to notify FDA of increases in demand that they are unlikely to be able to meet without meaningful shortfall or delay.

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

To address shortages, including those related to the COVID-19 pandemic, FDA is working with manufacturers and other partners to help prevent shortages from occurring and to mitigate the impact of shortages that cannot be prevented. Early and open dialogue between FDA and manufacturers is critical to the success of this work. Because of important presidential, congressional, and FDA actions, FDA has been able to learn of possible shortages before they occur and take steps to prevent or mitigate them. During CY 2022, there were 49 new shortages, and FDA helped prevent 222 potential shortages. 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. This report reflects 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.

# 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;

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

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

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

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

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

(4) 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;

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

(6) 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 2022

| | CDER | CBER |
|---|---|---|
| NUMBER OF SHORTAGES | | |
| New Shortages | 48 | 1 |
| Prevented Shortages | 210 | 12 |
| Ongoing Shortages | 81 | 5 |
| Notifications | 1267 | 26 |
| Number of Manufacturers Notifying | 133 | 17 |
| ACTIONS TAKEN TO MITIGATE SHORTAGES | | |
| Regulatory Flexibility and Discretion | 85 | 0 |
| Expedited Reviews | 193 | 11* |
| Expedited Inspections | 30 | 0 |

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

# Appendix D: Breakdown of Expedited Reviews in CY 2022 by Submission Type

| Submission Type | Expedited Reviews |
|---|---|
| NDA/NDA Supplements (CDER) | 36 |
| ANDA/ANDA Supplements (CDER) | 149 |
| BLA/BLA Supplements (CDER) | 8 |
| BLA/BLA Supplements (CBER) | 6* |

* This number does not include the expedited reviews for the five 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/.