

REPORT TO CONGRESS

First Annual Report on Drug Shortages
for Calendar Year 2013

Required by Section 1002 of the Food and Drug Administration Safety and
Innovation Act

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Food and Drug Administration

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First Annual Report on Drug Shortages for Calendar Year 2013

SUMMARY

This first annual report to Congress summarizes the major actions taken by the Food and Drug Administration (FDA) during the first three quarters of 2013 to prevent or mitigate drug shortages in the United States. Because drug shortages can pose a significant public health threat, delaying, and in some cases even denying, critically needed care for patients, shortages remain a top priority for FDA. As a result of recent actions by the President, Congress, and FDA, manufacturers are notifying FDA about potential shortages earlier than in the past. Early notification of potential shortages gives FDA additional time to work with sponsors and other groups to identify ways to maintain treatment options and prevent a shortage. Using a range of available tools, including regulatory flexibility when appropriate, FDA's Center for Drug Evaluation and Research (CDER) worked with manufacturers to successfully prevent 140 shortages from January 1 to September 30, 2013. In addition, the number of new shortages tracked by CDER for this same time period is 38, compared to the 117 new shortages during calendar year 2012.

Based on our experience to date and the data on drug shortages presented in this report, FDA believes that increased notifications resulting from actions by the President, Congress, and FDA are helping the agency respond more effectively to shortages and potential shortages.

INTRODUCTION

The Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted on July 9, 2012. Title X of FDASIA, which addresses drug shortages, took effect on the date of enactment and, among other things, amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) by updating section 506C. Section 506C sets forth the requirement that manufacturers notify FDA of a discontinuance or interruption in the production of certain prescription drugs that are life-saving, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition. In addition, section 1002 of Title X of FDASIA added section 506C-1 to the FD&C Act, requiring FDA to file a report to Congress on drug shortages at the end of each calendar year. FDA is submitting this first annual report to fulfill its obligations under section 506C-1.

This report reflects data collected and evaluated by the Center for Drug Evaluation and Research (CDER) beginning January 1, 2013, through September 30, 2013. To provide a

more comprehensive view of CDER's efforts to manage drug shortages, the report includes data for all products tracked by CDER's Drug Shortage Staff.¹

The statutory requirements for the report are as follows:

SECTION 506C–1 ANNUAL REPORTING ON DRUG SHORTAGES

(a) ANNUAL REPORTS TO CONGRESS.—Not later than the end of calendar year 2013, and not later than the end of each calendar year thereafter, 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 on drug shortages that—

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

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

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

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

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

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

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

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

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

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

This report provides the data requested by these provisions.

¹ Such products include all drugs within the meaning of section 506C(h)(1), as well as other products tracked by CDER's Drug Shortage Staff, such as biological products approved under section 505 of the FD&C Act. In the future, FDA's annual reports on shortages may include data on biological products tracked by the Center for Biologics Evaluation and Research, including vaccines and blood products.

KEY DEFINITIONS USED IN THIS REPORT

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

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

Life Supporting or Life Sustaining: *Life supporting* or *life sustaining* is used to describe a drug 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.

BACKGROUND

Recent experience with shortages of drugs in the United States has shown the serious and immediate effects these events can have on patients and health care professionals. While the number of new shortages tracked by CDER quadrupled from approximately 61 shortages in 2005 to more than 250 in 2011, after actions by the FDA working with stakeholders, that number significantly decreased in 2012 to 117 shortages. However, shortages continue to pose a real challenge to public health. This is especially the case when a shortage involves a critical drug to treat cancer, to provide parenteral nutrition, or to address another serious medical condition. A shortage can delay or deny needed care for patients. Shortages can also lead prescribers to use second-line alternatives, which may be less effective or pose additional risks.

Preventing drug shortages has been, and continues to be, a top priority for FDA.² Working within the confines of the statutory and regulatory framework in place at the time and in partnership with manufacturers and other stakeholders, FDA helped prevent close to 200 drug shortages in 2011 and more than 280 shortages in 2012. The following actions contributed to these successes.

1. Executive Order 13588 – Reducing Prescription Drug Shortages

In response to a dramatic increase in shortages, on October 31, 2011, the President issued Executive Order 13588, recognizing that “shortages of pharmaceutical drugs pose a serious and growing threat to public health” and that “interruptions in the supplies of

² For more information on FDA’s drug shortage efforts, see <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>.

these drugs 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 directs FDA to take steps to help to prevent and reduce current and future disruptions in the supply of lifesaving medicines, including through notifications and expedited reviews as appropriate.

2. Interim Final Rule and Draft Guidance for Industry on Drug Shortages

In December 2011, FDA responded to this Presidential directive by publishing an interim final rule (IFR)⁴ that amended existing early notification requirements. The IFR amended FDA’s regulations related to early notification to improve the likelihood of FDA receiving advance notification of a potential drug shortage, a critical step in the process of taking action that can prevent or mitigate a shortage. As a companion to the IFR, in February 2012, FDA issued a draft guidance for industry titled *Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage*.⁵ The draft guidance was issued for public comment, and: (1) further discussed the Agency’s interpretation of the mandatory reporting requirements under section 506C of the FD&C Act and FDA’s related regulations; (2) explained a policy of encouraging additional voluntary reporting; and (3) acknowledged that manufacturers play a primary role in preventing or responding to drug shortages and that many shortages arise from quality or other issues experienced during the manufacturing process. These quality issues may result in interruptions or other adjustments in manufacturing that may adversely affect market supply. Other factors affecting shortages may include delays in acquiring critical raw materials or components, import delays, or unexpected increases in demand.

3. FDA Safety and Innovation Act (FDASIA)

³ Executive Order 13588, available at <http://www.whitehouse.gov/the-press-office/2011/10/31/executive-order-reducing-prescription-drug-shortages>.

⁴ See <http://www.gpo.gov/fdsys/pkg/FR-2011-12-19/html/2011-32354.htm>. The IFR is a final rule implementing the pre-FDASIA section 506C. FDASIA significantly amended section 506C and requires FDA to initiate a new rulemaking process to implement the amended section 506C. On November 4, 2013, FDA published a proposed rule for public comment to implement the drug shortages provisions of FDASIA and withdraw the IFR (78 FR 65904, available at <https://www.federalregister.gov/articles/2013/11/04/2013-25956/permanent-discontinuance-or-interruption-in-manufacturing-of-certain-drug-or-biological-products>). Once finalized, the rule will supersede the IFR.

⁵ FDA’s guidances are available on its Guidance web site at <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>. Comments on this draft guidance are available online at <http://www.regulations.gov>, Docket No. FDA-2012-D-0140. Before publication of the IFR and draft guidance, FDA published a letter to industry on the same day the Executive Order was issued, reminding manufacturers of their obligation to notify FDA about certain issues and encouraging them to notify FDA of others, even if not required.

With the passage of FDASIA on July 9, 2012, FDA was given important new authorities related to drug shortages. For example, section 1001 of FDASIA broadened the scope of the early notification provisions by requiring all manufacturers of **all covered** prescription drugs (approved or unapproved) to notify FDA of a permanent discontinuance or temporary interruption in manufacturing. FDASIA also allowed FDA to require, by regulation, early notification of discontinuances or interruptions in manufacturing of biologics. The Act also requires FDA to send a noncompliance letter to firms that fail to notify the Agency in accordance with FDASIA. FDA can also continue to expedite reviews and inspections that could help mitigate a shortage. Other FDASIA requirements involve 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.

4. FDA Strategic Plan to Prevent and Mitigate Shortages

On October 31, 2013, FDA issued its *Strategic Plan for Preventing and Mitigating Drug Shortages*.⁶ The plan contains details on the origin of drug shortages, FDA's processes and procedures for helping to prevent or mitigate shortages, and FDA's strategy for strengthening those processes and procedures. The plan also outlines recommendations for actions other stakeholders can consider to help prevent shortages.

5. FDA Drug Shortage Proposed Rule

On November 4, 2013, FDA published a proposed rule for public comment to help implement FDASIA's expanded notification requirements. Among other things, the proposed rule would extend the notification requirement to most manufacturers of biological products.

DATA SOURCES

The data used to fulfill the reporting requirements of FD&C Act section 506C-1 are collected by several different parts of FDA, sometimes for reasons that are broader than the FDA response to drug shortages. Tracking the data for reporting requirements related to drugs (the number of drugs in shortage) is the purview of the Drug Shortage Staff. Similarly, Drug Shortage Staff track information about notifications and their source (and therefore the number of reporting manufacturers). In contrast, reporting requirements related to expedited review are tied to specific *submissions* by manufacturers that are experiencing production disruptions or manufacturers that are adding or expanding their production capabilities to address a specific shortage. CDER offices reviewing these submissions track which reviews and related inspections they expedite as a part of a larger set of activities related to their review of submissions. Other reporting requirements for this report relate to instances of regulatory flexibility and discretion.

⁶ To view the Strategic Plan and related information, visit <http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf>

These specific cases, all requiring separate regulatory and scientific evaluation and justification, are tracked by the Office of Compliance.

FINDINGS

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

For the first three quarters of calendar year 2013, FDA was notified of 202 potential shortage situations.⁷ Thirty-nine (39) different manufactures provided these notifications.

Requirement 2: Describe the communication between FDA field investigators and CDER's Office of Compliance and Drug Shortage Program and FDA procedures for enabling and ensuring such communication

CDER's Office of Compliance (CDER/OC) and the FDA field investigators in the Office of Regulatory Affairs (ORA) are both crucial to FDA's prompt response to a drug shortage. These two groups have separate functions with respect to drug shortages. CDER/OC is responsible for communicating with the Drug Shortage Staff on warning letters or enforcement action recommendations that are being reviewed within CDER/OC pursuant to sections 506D(b) and (c). FDA field investigators in ORA typically conduct inspections and report on their inspectional findings. For example, if the investigators identify actions or activities that may have a detrimental impact on product availability during an inspection at a manufacturing facility, information regarding the observations and the products manufactured can be relayed to CDER immediately so that the Drug Shortage Staff can begin to assess the supply situation for those products.

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

⁷ As noted above, this report includes data on all products tracked by CDER's Drug Shortage Staff.

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

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

- Identify the extent of the shortfall and determine if other manufacturers are willing and able to increase production to make up the gap;
- Expedite FDA inspections and reviews of submissions from manufacturers attempting to restore production;
- Expedite FDA inspections and reviews of submissions from competing manufacturers who are interested in starting new production or increasing existing production of products in shortage;
- Exercise temporary enforcement discretion for new sources of medically necessary drugs;
- Work with the affected manufacturers to ensure adequate investigation into the root cause of the shortage; and
- Develop risk mitigation measures for a batch(es) of product initially not meeting established standards.

FDA has used one or more of these mitigation tools, or has sought to develop other options, depending on the severity of the potential shortage and the surrounding circumstances. When selecting specific tools, FDA continues to work with the manufacturer to tailor its response to the specific situation. 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.

Examples of major actions that the Secretary can take to prevent or mitigate drug shortages include efforts to expedite review and inspections during this calendar year.

- **List the number of applications and supplements for which the Secretary expedited review under section 506C(g)(1) during such calendar year⁸**

Number of expedited reviews to prevent or mitigate drug shortages during the first three quarters of calendar year 2013:

- CDER's Office of Generic Drugs (OGD) expedited the review of 118 applications, including 62 abbreviated new drug applications (ANDAs) and 56 supplemental applications.
- CDER's Office of Biological Products (OBP) expedited the review of 7 supplemental applications.

⁸ Includes submissions for new applications (ANDAs) and prior approval supplements (PAS). In some cases changes being effected (CBE) supplements are also included, where FDA determined that it was appropriate for a CBE to be submitted for a change instead of as a PAS. FDA's answer to requirement 3 includes data on all products tracked by CDER's Drug Shortage Staff.

- CDER's Office of New Drug Quality Assessment (ONDQA) expedited 52 supplemental applications.
- In sum, therefore, CDER expedited the review of 177 applications in the first three quarters of calendar year 2013.
- **List the number of establishment inspections or reinspections that the Secretary expedited under section 506C(g)(2) during such calendar year⁹**

The applications and supplements that were granted expedited review due to a drug shortage resulted in 63 associated inspection requests that were prioritized.¹⁰

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

Recognizing this need, FDASIA included new 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 are developing a memorandum of understanding (MOU). The MOU sets forth steps and procedures, including identifying contacts, for efficiently tracking and exchanging relevant information. At present, FDA and DEA are working out the exact scope of information that will be tracked and exchanged and the process for implementing identified steps and procedures.

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 standards of safety, efficacy, and quality do not change in a shortage situation. FDA's preferred solution to a shortage is a supply of approved drugs that is sufficient to meet patient demand and meets the appropriate quality, safety, and efficacy standards. However, FDA recognizes that there can also be risks to patients if treatment options are

⁹ Includes prioritized inspections or site reviews for new applications or supplements, which were granted expedited review due to drug shortage

¹⁰ Note that not all submissions to OGD, ONDQA, and OBP require inspections, but that some submissions can involve multiple sites, which may require inspections.

not available for critical conditions, and understands the importance of using the appropriate tools for a given situation to prevent or mitigate a shortage. In appropriate cases, the temporary exercise of regulatory flexibility and discretion has proven to be an important tool in ensuring access to treatment options for patients in critical need.

Situations where FDA has exercised regulatory flexibility and discretion to prevent or mitigate a shortage include:

- Temporary regulatory flexibility and discretion with regard to medically necessary products that present quality issues, where measures, such as the following, mitigate the risks associated with those products when weighed against the risk to patients of not receiving the drug:
 - Filters are supplied with a product to remove particulate matter
 - Extra testing for product quality or identity is done at the manufacturing facility before release
 - Third-party oversight of production is instituted to monitor quality issues
 - Special instructions are provided to health care professionals/patients
- Temporary regulatory flexibility and discretion with regard to continued distribution of a drug to remedy a drug shortage while FDA reviews a supplement/proposed change to address a problem with the drug product; and
- Temporary regulatory flexibility and discretion with regard to new sources of medically necessary drugs – this is reserved for rare instances when all alternate approaches have been exhausted.

During the first three quarters of calendar year 2013, FDA has exercised regulatory flexibility and discretion in 76 instances, affecting 68 products.

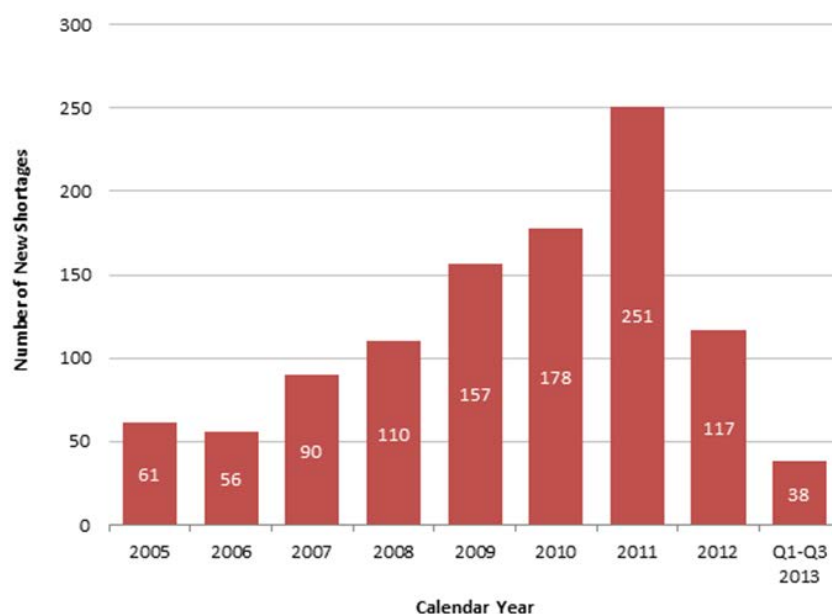
Requirement 6: List the names of manufacturers issued letters under section 506C(f)

Under section 506C(f), if a manufacturer fails to provide notification of a discontinuance or interruption in manufacturing as required by FDASIA, 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 both the reason for noncompliance and the required information on the discontinuance or interruption. Within 45 calendar days of its original letter to the manufacturer, FDA is required to post that letter and any response received on FDA's website unless FDA determines that the original notification was issued in error or, after review of the manufacturer's response, the manufacturer had a reasonable basis for not notifying FDA as required. To date, FDA has not yet issued a letter under FDASIA section 506C(f).

Requirement 7: Specify the number of drug shortages occurring during 2013 (the first three quarters of 2013)

According to information from CDER's drug shortage database,¹¹ the number of new shortages significantly decreased in 2012 to 117 (from 251 in 2011). Data indicate that this trend is continuing into 2013. By September 30, 2013, only 38 new drug shortages had been identified. The figure that follows shows the number of new drug shortages identified by year from 2005 through September 30, 2013.

Figure 1. Number of New Drug Shortages Per Year, 2005 Through September 30, 2013



Source: FDA, Drug Shortage Staff

This graph illustrates the results of the work FDA and its partners are doing to prevent drug shortages. For example, in the first three quarters of 2013, we have prevented 140 shortages.

CONCLUSION

Drug shortages remain a significant public health issue in the United States and a top priority for FDA. FDA works with manufacturers 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 our success. Because of recent important actions by the President and Congress, FDA has been able to learn of possible shortages before they occur and take steps to prevent or mitigate them. During

¹¹ CDER's drug shortage statistics can be found at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm>

the first three quarters of 2013, CDER helped prevent 140 potential new shortages. In addition, under the early notification requirements contained in FDASIA, there were only 38 new shortages for the first three quarters of 2013, compared to 117 during calendar year 2012. As outlined in FDA's *Strategic Plan for Preventing and Mitigating Drug Shortages*, a number of additional activities are underway that, along with the increase in resources FDA is devoting to drug shortages, will continue to help reduce the threat of drug shortages.