

---

# Guidance for Industry

## Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Kalah Auchincloss at 301-796-0659 or (CBER) Stephen Ripley at 301-827-6210.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**February 2012  
Procedural**

---

---

# Guidance for Industry

## Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage

### ***DRAFT GUIDANCE***

*Additional copies are available on the Internet  
at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>  
and from these FDA Offices and Centers:*

*Office of Communications, Division of Drug Information  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Ave., WO51, Room 2201, Silver Spring, MD 20993  
Phone: 301-796-3400; Fax: 301-847-8714; Email: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

*Office of Communication, Outreach and Development  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
1401 Rockville Pike, Rockville, MD 20852-1448  
Phone: 800-835-4709 or 301-827-1800  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**February 2012  
Procedural**

---

**TABLE OF CONTENTS**

<b>I.</b>	<b>INTRODUCTION</b> .....	1
<b>II.</b>	<b>BACKGROUND</b> .....	2
	A. Public Health Impact of Drug Shortages: Why Notification to the FDA of Issues that May Lead to a Drug Shortage is Critical .....	2
	B. Overview of Current Drug Shortage Reporting.....	3
<b>III.</b>	<b>SCOPE AND LOGISTICS OF MANDATORY NOTIFICATION</b> .....	4
	A. Who is Required to Notify the Agency.....	4
	1. <i>Sole Manufacturer</i> .....	5
	2. <i>“Life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition.”</i> .....	6
	B. What Information to Report to the Agency .....	7
	C. When and How to Notify the Agency.....	9
	1. <i>Six Month Notification Period &amp; Certifications of “Good Cause”</i> .....	9
	2. <i>Procedures for Notifying the Agency of a Discontinuance and for Submitting a Certification of “Good Cause”</i> .....	9
<b>IV.</b>	<b>SCOPE AND LOGISTICS OF VOLUNTARY NOTIFICATION</b> .....	10
	A. Who Should Notify the Agency.....	10
	B. What Information to Report to the Agency .....	10
	C. When and How to Notify the Agency.....	11
<b>V.</b>	<b>WHAT FDA DOES WITH INFORMATION REPORTED</b> .....	12
<b>VI.</b>	<b>ADDITIONAL CONSIDERATIONS FOR MANUFACTURERS</b> .....	13

## **Guidance for Industry<sup>1</sup>**

### **Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage**

This guidance, when finalized, will represent the Food and Drug Administration's (FDA's or Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

#### **I. INTRODUCTION**

This document provides guidance to industry on requirements for notification to FDA of a discontinuance of certain drug products under section 506C of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as implemented by 21 C.F.R. §§ 314.81(b)(3)(iii) and 314.91. The guidance reflects amendments to the implementing regulations published as an interim final rule on December 19, 2011 (effective January 18, 2012).<sup>2</sup> This document also provides guidance to industry on voluntary notification to FDA of issues that may result in a shortage or potential disruption in supply of a prescription drug or biological product in the U.S. market, regardless of whether mandatory notification is required under section 506C.<sup>3</sup> This guidance is intended for manufacturers of prescription drug and biological products regulated by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER).

Under section 506C of the FD&C Act, “sole manufacturers” are required to report to FDA discontinuances of drug products that are “life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition.” On October 31, 2011, FDA sent a letter to manufacturers of prescription products reminding them of their mandatory reporting requirements under section 506C and encouraging them to voluntarily report to the Agency any disruptions in supply that could lead to a product shortage, even beyond those situations covered

---

<sup>1</sup> This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

<sup>2</sup> Interim Final Rule, *Applications for Food and Drug Administration Approval To Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance*, 76 FR 78530 (December 19, 2011).

<sup>3</sup> Section 506C only applies to drugs that are approved under section 505(b) or (j) of the FD&C Act. Section 506C does not apply to drugs that are biological products licensed through a biologics license application (BLA) under section 351 of the Public Health Service Act. However, drugs that are biological products are also vulnerable to shortages and are addressed in the voluntary notifications sections of this guidance. “Biological products” in this guidance refer to biological drug products.

*Draft – Not for Implementation  
Contains Nonbinding Recommendations*

by mandatory reporting.<sup>4</sup> On the same day, the President issued Executive Order 13588 directing FDA to use all available administrative tools to expand the Agency’s efforts to combat the problem of drug shortages.<sup>5</sup>

This document is intended to provide additional guidance to industry on the existing mandatory reporting requirements under section 506C, as well as additional explanation of the voluntary notification process. For both mandatory and voluntary notifications, this guidance explains why FDA should be notified, who should notify the Agency, what information should be reported, when and how to notify the Agency, and what FDA will do with reported information. The guidance also discusses certain advance planning strategies that manufacturers can consider to prevent or mitigate product shortages.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## **II. BACKGROUND**

### **A. Public Health Impact of Drug Shortages: Why Notification to the FDA of Issues that May Lead to a Drug Shortage is Critical**

FDA is concerned about the rising incidence of drug shortages in the United States, particularly those involving drugs that are manufactured by a small number of firms and for which there are no good therapeutic substitutes available. While not all drugs experience shortages, the number of drug shortages has been rising steadily over the last five years, nearly tripling from 61 in 2005 to 178 in 2010. In 2011, FDA tracked over 250 drug shortages. Drug shortages can create significant public health concerns. For example, some drug shortages delay or deny needed care for patients, because they involve drugs used to treat cancer, to fight infectious diseases, to provide required nutrition, or to address other serious medical conditions. Other shortages force providers to prescribe second-line alternatives, which can be less effective and higher risk than first-line therapies. In a survey by the Institute for Safe Medication Practices of 1,800 healthcare practitioners, a majority reported problems with drug shortages, including the use of less desirable, often more expensive alternatives and the potential for medication errors and poor patient outcomes.<sup>6</sup> Causes of drug shortages may include product quality concerns,

---

<sup>4</sup> Letter to Industry, October 31, 2011, *available at* <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm277675.htm>.

<sup>5</sup> Executive Order 13588, Reducing Prescription Drug Shortages (Oct. 31, 2011), *available at* <http://www.gpo.gov/fdsys/pkg/DCPD-201100808/pdf/DCPD-201100808.pdf>.

<sup>6</sup> Issue Brief: Economic Analysis of the Causes of Drug Shortages, ASPE, HHS (Oct. 31, 2011), *available at* <http://aspe.hhs.gov/sp/reports/2011/DrugShortages/ib.pdf> (citing Institute of Safe Medication Practices survey *available at* <http://www.ismp.org/pressroom/PR20100923.pdf>).

***Draft – Not for Implementation  
Contains Nonbinding Recommendations***

manufacturing problems, difficulty in acquiring component parts or active pharmaceutical ingredients (API), increases in demand, and shipping delays, among other things.<sup>7</sup>

FDA recognizes that some drug shortages can be neither predicted nor prevented; however, we know that effective communication and early notification from manufacturers has a significant impact on the incidence and duration of drug shortages. Manufacturers can play a critical role in decreasing the impact of shortages by reporting to the FDA circumstances that might affect their ability to supply the market and potentially lead to a drug shortage. Notifying FDA in advance of incidents that may result in a drug shortage helps FDA work with manufacturers to take early action to prevent or alleviate shortages. For example, in 2011, early notification by manufacturers allowed the FDA to help prevent shortages of 195 drugs, including 86 drugs produced by one company. However, FDA cannot begin to work with manufacturers or use the tools at our disposal to avoid or mitigate a shortage until we know there is a potential problem.

There is no single, or simple, solution that can resolve the drug shortage problem, but we are committed to working with drug manufacturers and distributors, health care providers, and other stakeholders to identify the issues that can lead to drug shortages, to enhance processes to avoid or mitigate shortages in the future, and to ensure continued patient access to vital safe and effective drugs. As part of this effort, we are issuing this guidance to help manufacturers better understand mandatory reporting obligations and to encourage voluntary reporting of additional issues that could lead to a shortage of a prescription drug or biological product.

## **B. Overview of Current Drug Shortage Reporting**

The Agency has long recognized the significant public health impact drug shortages can have on patient care. Since 1997, section 506C has required manufacturers to notify the Agency of a discontinuance of certain drug products. Many discontinuances lead to drug shortages and can present public health concerns. Following enactment of section 506C, FDA promulgated regulations at 21 C.F.R. §§ 314.81(b)(3)(iii) and 314.91 to implement the statute. The Agency amended these regulations with the publication of the Interim Final Rule, *Applications for Food and Drug Administration Approval To Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance*<sup>8</sup> on December 19, 2011 (effective January 18, 2012) (referred to in this guidance as the IFR). CDER also published a Manual of Policy and Procedures on Drug Shortage Management (CDER MAPP) to provide internal guidance to Agency staff regarding drug shortages.<sup>9</sup>

Under section 506C, a manufacturer that is the sole manufacturer of a drug that is approved under section 505(b) or 505(j) of the FD&C Act (and that is not a product that was originally derived from human tissue and was replaced by a recombinant product) is required to notify

---

<sup>7</sup> A Review of FDA's Approach to Medical Product Shortages (Oct. 31, 2011), available at <http://www.fda.gov/DrugShortageReport>

<sup>8</sup> 76 FR 78530 (Dec. 19, 2011).

<sup>9</sup> CDER MAPP 6003.1, Drug Shortage Management (2006), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM079936.pdf>. FDA intends to revise and update this MAPP to incorporate issues addressed in the IFR and this guidance document.

***Draft – Not for Implementation  
Contains Nonbinding Recommendations***

FDA at least six months prior to discontinuing manufacture of the drug, if the drug is “life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition.” The FDA originally interpreted this requirement to apply only to permanent manufacturing discontinuances.

Mandatory notification under section 506C has been critical in enabling FDA to assist manufacturers in preventing or mitigating some drug shortages. For example, when notified of a discontinuance under section 506C, FDA has been able to expedite review of potential new products and suppliers and exercise regulatory flexibility for the product in shortage or an alternative product, where such action would not compromise patient safety.

However, while mandatory notification of permanent discontinuances is helpful in preventing or mitigating some drug shortages, this limited requirement is not sufficient to address the magnitude of the current drug shortage problem. In 2010, only 8% of drug shortages were due to permanent discontinuances of drug products; the majority of shortages were the result of problems at the manufacturing facility, delays in manufacturing or shipping, and API shortages.<sup>10</sup> Moreover, biological products licensed through a biologics license application (BLA) under section 351 the Public Health Service Act are also vulnerable to shortages, but are not subject to mandatory reporting under section 506C. Under current law, manufacturers are therefore not required to report to FDA the majority of situations that could lead to a drug shortage.

Consequently, in response to the Executive Order, FDA published the IFR, which expands the application of our authority under section 506C to require mandatory notifications in additional circumstances, and clarifies who is responsible for notifying the Agency of a discontinuance. Moreover, in addition to mandatory notification under section 506C, to effectively work with manufacturers to more fully combat the drug shortage crisis, FDA strongly encourages companies to voluntarily notify the Agency of any other issues that could lead to a shortage of any prescription drug or biological product supplied in the U.S.

### **III. SCOPE AND LOGISTICS OF MANDATORY NOTIFICATION**

As described in Section II.B. of this guidance, sole manufacturers are statutorily required to notify FDA of a discontinuance of manufacture of certain drug products. This section of the guidance is intended to clarify the scope and logistics of mandatory notification under section 506C and the IFR.

#### **A. Who is Required to Notify the Agency**

Under section 506C of the FD&C Act,

---

<sup>10</sup> A Review of FDA’s Approach to Medical Product Shortages (Oct. 31, 2011), p. 16, *available at* <http://www.fda.gov/DrugShortageReport>.

*Draft – Not for Implementation  
Contains Nonbinding Recommendations*

- if you are a sole manufacturer of a prescription drug product approved under section 505(b) or 505(j) of the FD&C Act (and that was not originally derived from human tissue and replaced by a recombinant product); and
- that product is “life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition”;

then you are required by statute to notify the Agency of a discontinuance of that drug product at least six months prior to discontinuing manufacture of the product.

*1. Sole Manufacturer*

In the IFR, we added 21 C.F.R. § 314.81(b)(3)(iii)(d) to define “sole manufacturer” to mean “an applicant that is the only entity currently manufacturing a drug product of a specific strength, dosage form, or route of administration for sale in the United States, whether the product is manufactured by the applicant or for the applicant under contract with one or more different entities.” The definition is intended to do three things.

First, it clarifies that “sole manufacturer” means the only applicant currently supplying the U.S. market with the drug product. It does not mean the sole holder of an approved new drug application (NDA) or abbreviated new drug application (ANDA). Accordingly, a manufacturer may not rely on the Orange Book (FDA’s publication on “Approved Drug Products with Therapeutic Equivalence Evaluations”) as the source for determining whether it is a sole manufacturer. Instead, the manufacturer should use commercial data or other methods to determine whether or not it is the only entity currently manufacturing for sale in the U.S. the product in question. We emphasize that it is the manufacturer’s responsibility to determine whether it is a sole manufacturer. Manufacturers who have questions about this determination may contact the drug shortages staff. Contact information for the CDER and CBER drug shortages programs is available on FDA’s drug shortage website at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>.

Second, the definition of sole manufacturer clarifies that the specific strength, dosage form, and route of administration of the product are critical in determining if a manufacturer is a sole manufacturer. The definition of sole manufacturer is linked to the specific strength, dosage form, and route of administration, because these characteristics may be critical for the targeted needs of particular patients. For example, a patient may be prescribed an injectable form of a particular drug product because the patient is not capable of swallowing an oral pill. If the injectable form is discontinued, the patient may be unable to continue life-saving treatment, even if the oral form is still available. Moreover, recent experience has shown that discontinuances of a specific strength, dosage form, or route of administration of a drug product may lead to a shortage of another strength, dosage form, or route of administration of the product, compounding patient difficulties in obtaining the drug product. For instance, in the previous example, if the oral form of the drug product is discontinued, providers may prescribe the injectable form to all patients. This increase in demand for the injectable form of the product may cause a shortage of the injectable form. If the FDA is notified in a timely manner of the



*Draft – Not for Implementation  
Contains Nonbinding Recommendations*

discontinuance of the oral form, we may be able to work with manufacturers and other stakeholders to avoid, or mitigate the impact of, a shortage of both formulations of the product. Accordingly, to enable the Agency to work most effectively with manufacturers and other stakeholders to prevent or mitigate potential shortages, discontinuances of a specific strength, dosage form, or route of administration of drug products subject to section 506C must be reported to us.<sup>11</sup>

Third, the IFR makes clear that it is the application holder of the drug product subject to section 506C who bears the responsibility for reporting a discontinuance to the Agency. For purposes of section 506C, an application holder will be considered a “manufacturer” even if the application holder contracts that function out to another entity. The application holder is responsible for establishing processes with contract manufacturers that ensure the application holder’s compliance with section 506C and the IFR. For example, Company X holds an NDA for a drug product subject to section 506C. Company X contracts with Company Y to manufacture the drug product for the purposes of marketing and selling the drug product in the United States. Company X would be considered the “sole manufacturer” and would be required to establish a process with Company Y that ensures Company X’s ability to report a discontinuance of the drug product to FDA.

The intention of section 506C is to alert FDA to possible disruptions in supply of certain drug products important to patient care to allow us to work with the manufacturer or others to minimize, to the extent possible, disruptions in patient access to those products. Considering this intention, we encourage manufacturers to be over-inclusive when determining whether they are a sole manufacturer. To best serve patients and protect the public health, the Agency should not be under-informed of information related to discontinuances. The Agency is better positioned to assist in preventing or mitigating a drug shortage that may be caused by a discontinuance if it is armed with all available information.

2. *“Life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition.”*

Section 506C of the FD&C Act requires reporting of discontinuances of drugs that are “life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition.” In 2007, the Agency interpreted “life-supporting or life-sustaining” to mean “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.” We have interpreted “debilitating disease or condition” to mean a “serious disease or condition.”<sup>12</sup> FDA should therefore be notified under section 506C if a drug product that is used to treat or prevent a serious disease or medical condition is discontinued.

Again, to enable FDA to be fully informed, we encourage manufacturers to be over-inclusive when determining whether a particular product is subject to mandatory notification under section 506C.

---

<sup>11</sup> 21 CFR 314.81(b)(3)(iii)(d), as amended by the IFR (76 FR 78530, 78540 (Dec. 19, 2011)).

<sup>12</sup> 72 FR 58993, 58994 (Oct. 18, 2007).

*Draft – Not for Implementation  
Contains Nonbinding Recommendations*

**B. What Information to Report to the Agency**

Under section 506C, sole manufacturers are required to notify FDA of a discontinuance of a drug product subject to section 506C. Previously, FDA indicated that a discontinuance did not include planned or unplanned temporary manufacturing cessations. Only manufacturers who intended to permanently discontinue manufacture and marketing of the drug were subject to the mandatory notification requirements.<sup>13</sup> In the IFR, however, we revise this policy position and define the term “discontinuance” to mean “any interruption of manufacturing of a drug product described in paragraph (b)(3)(iii)(a) for sale in the United States that could lead to a potential disruption in supply of the drug product, whether the interruption is intended to be temporary or permanent.”<sup>14</sup> Thus, the term “discontinuance” now includes both temporary and permanent interruptions in manufacturing, if the interruption could lead to a disruption in supply of the product.

Any permanent discontinuance of manufacturing by a sole manufacturer will lead, per se, to a disruption in supply of the product; thus, all permanent discontinuances must continue to be reported to FDA.<sup>15</sup> Temporary discontinuances must be reported to the Agency only if the discontinuance reasonably could be expected to lead to a disruption in supply of the product. For example, the following circumstances would trigger notification to the FDA of a discontinuance of a drug product subject to section 506C:

- A business decision to permanently discontinue manufacture of a drug product;
- A delay in acquiring API or inactive ingredients that leads to, or could lead to, a temporary interruption in manufacturing of a drug product while alternative suppliers are located;
- Equipment failure or contamination affecting the quality of a drug product that necessitates an interruption in manufacturing while the equipment is repaired or the contamination issue is addressed;
- Manufacturing shut-downs for maintenance or other routine matters, if the shut-down extends for longer than anticipated or otherwise could disrupt supply of a drug product.

Conversely, a manufacturer would not be required to notify FDA if a discontinuance is part of the normal manufacturing schedule and is not expected to lead to a disruption in supply of a drug product subject to section 506C. For example, FDA need not be notified in the following circumstances:

- The manufacturer uses the same manufacturing plant to manufacture two drug products, one of which (Product A) is subject to section 506C. From January to

---

<sup>13</sup> 72 FR 58993, 58995 (Oct. 18, 2007).

<sup>14</sup> 21 CFR § 314.81(b)(3)(iii)(d), as amended by the IFR (76 FR 78530, 78540 (Dec. 19, 2011)).

<sup>15</sup> Id.

*Draft – Not for Implementation  
Contains Nonbinding Recommendations*

June of each year the manufacturer uses the plant to produce Product A. From July to December of each year the manufacturer uses the plant to produce Product B. Although this could be considered a temporary discontinuance of Product A from July to December, because this is the usual manufacturing schedule and should not therefore result in a disruption in the supply of Product A, the manufacturer need not notify the Agency of the annual, temporary discontinuance of Product A.

- A manufacturer of a drug product implements a scheduled shutdown of its manufacturing facility each year for routine maintenance. The annual shutdown is anticipated and planned for in advance; therefore, it is not expected to disrupt supply of a drug product subject to section 506C. The shutdown does not need to be reported to the Agency under section 506C.
- A manufacturer of a drug product subject to section 506C experiences an unexpected power outage that results in an unscheduled interruption in manufacturing. The manufacturer expects to resume normal operations within a relatively short timeframe and does not expect a disruption in the supply of the drug product. The shutdown does not need to be reported to the Agency under section 506C.

If any of the circumstances described above do lead to a disruption in supply of the drug product, even if unanticipated, then it becomes a reportable discontinuance and the manufacturer would be required to notify FDA of a discontinuance of the product under section 506C. For example, if a scheduled or routine manufacturing shutdown continues for longer than expected, such that demand cannot be met with current inventory of the product, this would be a disruption in supply of the product and the shutdown would become a reportable discontinuance under section 506C.<sup>16</sup>

We revised our policy position to include temporary interruptions in manufacturing in the definition of discontinuance based on experience showing that even temporary discontinuances can have a significant impact on patient access to drug products. Moreover, this broader interpretation of the statutory language will expand FDA's ability to distribute information on the discontinuance of certain drugs to physician and patient organizations and better enable FDA to work with manufacturers and other stakeholders to respond to potential drug shortages.

Manufacturers are responsible for determining whether a particular situation falls within the mandatory reporting requirements of section 506C. If you are facing an actual or potential discontinuance and are unsure whether it must be reported under the regulation, you may contact the drug shortages staff in the relevant Center by e-mail or by phone at the contact information available on the Agency's drug shortages website. Again, we encourage over-inclusiveness

---

<sup>16</sup> 21 CFR 314.81(b)(iii)(3)(d), as amended by the IFR (76 FR 78530, 78540 (Dec. 19, 2011)). We understand that a manufacturer may be unable to report some temporary discontinuances six months in advance, as required by statute. The timing of reporting unplanned temporary discontinuances is discussed in Section III.C., below.

*Draft – Not for Implementation  
Contains Nonbinding Recommendations*

when determining whether a particular situation falls within the scope of mandatory reporting requirements.

**C. When and How to Notify the Agency**

*1. Six Month Notification Period & Certifications of “Good Cause”*

Section 506C requires manufacturers to notify the Agency at least six months prior to discontinuing manufacture of a drug product subject to section 506C. The six month period may be shortened if the FDA finds “good cause” exists for the reduction based on information submitted to the Agency by the manufacturer in a certified written request. We emphasize that the manufacturer must notify the Agency at least six months prior to the discontinuance unless: 1) the manufacturer has submitted a written certification of “good cause”; and 2) the Agency has affirmatively made a determination to allow a reduction in the notification period for one of the good cause reasons listed in 21 C.F.R. § 314.91(d), including if:

- (1) a public health problem may result from continuation of manufacturing for the 6-month period;
- (2) a biomaterials shortage prevents the continuation of the manufacturing for the 6-month period;
- (3) a liability problem may exist for the manufacturer if the manufacturing is continued for the 6 month period;
- (4) continuation of the manufacturing for the 6-month period may cause substantial economic hardship for the manufacturer;
- (5) the manufacturer has filed for bankruptcy under chapter 7 or 11 of title 11, United States Code (11 U.S.C. 701 *et seq.* and 1101 *et seq.*);
- (6) the manufacturer can continue distribution of the drug product to satisfy existing market need for 6 months; or
- (7) other good cause exists for the reduction.

The only exception to this requirement is if a manufacturer is unable to notify us of a temporary discontinuance six months prior to the discontinuance because it was an unforeseen occurrence (e.g., unexpected contamination). Under those circumstances, a manufacturer need not submit a written certification of good cause requesting a reduction in the notification period. Instead, the manufacturer must notify us as soon as possible after it knows that a discontinuance will occur.<sup>17</sup> In any other instance, a manufacturer seeking a reduction in the six-month notification period must submit a written certification of good cause and obtain affirmative Agency approval of the reduction in the notification period.<sup>18</sup>

*2. Procedures for Notifying the Agency of a Discontinuance and for Submitting a Certification of “Good Cause”*

Telephone calls or electronic communication are often the fastest and most efficient methods for conveying important information. The Agency already receives many reports of discontinuances

---

<sup>17</sup> 21 CFR 314.91.

<sup>18</sup> *Id.*

*Draft – Not for Implementation  
Contains Nonbinding Recommendations*

and potential drug shortages via phone and e-mail. To reflect this practice, the IFR requires manufacturers to report a notice of a discontinuance to FDA either electronically or by telephone according to instructions on the FDA's drug shortages website at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages>. As indicated on the website, products regulated by CDER should be reported to the CDER Drug Shortages Coordinator, and products regulated by CBER should be reported to the CBER Products Shortage Coordinator.

Certifications of good cause must continue to be submitted according to the procedure outlined in 21 C.F.R. § 314.91.

#### **IV. SCOPE AND LOGISTICS OF VOLUNTARY NOTIFICATION**

Given the magnitude of the drug shortage crisis in the U.S., and the limited scope of mandatory notification under section 506C, the FDA sent a letter to manufacturers of prescription products on October 31, 2011, encouraging them to voluntarily notify the Agency of any potential disruption to supply of a prescription product that could reasonably be expected to lead to a product shortage, beyond those circumstances required to be reported by statute. Unlike mandatory notification, voluntary notification includes prescription biological products licensed under a BLA. Voluntary notifications will improve FDA's knowledge of potential and existing drug and biological product shortages, allowing us to more effectively work with manufacturers to prevent or mitigate shortages. This section provides guidance on the scope and logistics of the voluntary notification process.

##### **A. Who Should Notify the Agency**

The Agency encourages manufacturers of all prescription drug or biological products to voluntarily notify the Agency of issues that may result in a shortage or potential disruption in supply of that product in the U.S. market. We encourage you to notify the FDA even if you are not a sole manufacturer of a drug or biological product, as described in relation to mandatory reporting under section 506C. Moreover, we encourage voluntary notification for all prescription drug and biological products.

##### **B. What Information to Report to the Agency**

Voluntary notification of issues that may lead to a potential shortage or disruption in supply includes reporting of circumstances beyond those instances (i.e., discontinuance) that are required to be reported by section 506C. Shortages and disruptions in supply may arise from a wide range of factors other than a manufacturer's decision to discontinue a product. FDA encourages manufacturers to notify the Agency's drug shortages staff of the following issues if they reasonably could be expected to lead to a potential shortage or disruption in supply of a prescription drug or biological product:

- product quality problems, such as the presence of particulates or impurities, microbial contamination, and stability concerns;

*Draft – Not for Implementation  
Contains Nonbinding Recommendations*

- interruptions or other adjustments in manufacturing that temporarily halt production and that may adversely affect market supply, such as renovation of manufacturing facilities;
- delays in acquiring critical raw materials or components, or loss of raw material or components (e.g., vials, stoppers, bottles) suppliers;
- transfer of manufacturing to an alternate facility (e.g., due to loss of an existing manufacturing site or to add additional capacity);
- loss of a production line or production capacity (e.g., machinery failure or malfunction or quality issues related to a cell line);
- any production problems that occur during or after manufacturing that could result in supply disruptions (e.g., out of specification test results, stability problems, or labeling and packaging defects);
- import delays (e.g., shipments detained upon entry to the U.S. for any reason that may delay delivery to the manufacturing firm);
- unexpected increases in demand (e.g., due to a shortage of an alternative product); and
- product discontinuances (e.g., a business decision to stop manufacturing or marketing the product or a temporary product hold while investigating issues that may result in a recall), even if you are not a sole manufacturer or the product in question is not subject to section 506C.

This is not an exhaustive list of circumstances that may result in a shortage or potential disruption in supply of a prescription drug or biological product and does not change manufacturers' responsibility to report issues to the Agency under other applicable regulations. We reiterate that FDA encourages manufacturers to be over-inclusive and to report any issue that reasonably could be expected to have an impact on the manufacturer's ability to supply the market and/or could lead to a product shortage.

**C. When and How to Notify the Agency**

Early notification is critical to the Agency's ability to respond effectively to potential shortage situations. Manufacturers should notify the Agency as soon as the manufacturer becomes aware of an issue that may result in a product shortage. The sooner FDA is notified, the better the chance of averting shortages of important products and minimizing disruptions in patient access to the product.

Manufacturers should notify FDA either electronically or by telephone according to instructions on the FDA's drug shortages website at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages>. As

*Draft – Not for Implementation  
Contains Nonbinding Recommendations*

noted on the website, products regulated by CDER should be reported to the CDER Drug Shortages Coordinator, and products regulated by CBER should be reported to the CBER Products Shortage Coordinator.

## **V. WHAT FDA DOES WITH INFORMATION REPORTED**

Communication and cooperation between the Agency and industry is vital to successfully combating the drug shortage crisis. The best way for FDA to become aware of potential drug or biological product shortages is for industry to notify us of potential problems as soon as possible. Once FDA is notified of any incident that could result in a product shortage, whether a required notification of a discontinuance under section 506C or a voluntary notification, the Agency will work closely with the manufacturer to help prevent a shortage. FDA may undertake a variety of actions to help prevent or mitigate a product shortage, including the following:

- Expedite review of submissions from manufacturers. These submissions may support a marketing application for a new product (an NDA, ANDA, or BLA), may support a manufacturing change that will allow a product to be available (for example, a chemistry supplement for a new manufacturing site), or may involve other issues (for example, toxicity data for an impurity identified in a product). FDA makes every effort to prioritize review and inspections needed for any change that will help mitigate a product shortage. FDA also communicates with foreign regulators as appropriate.
- Identify additional sources of supply or alternate manufacturers that can initiate or ramp-up production. For example, if the manufacturer has data to support extension of the expiration dating for certain inventory, FDA may review the data and consider appropriate action, such as exercising regulatory discretion for use of a product beyond its labeled expiration date. In addition, if another safe and effective product is available, FDA may work with other manufacturers to supply that product to patients during a shortage.
- Find new/additional sources of raw material. If the shortage is due to an inadequate supply of API or other raw materials, FDA can work with the manufacturer, as appropriate, to identify and approve new API suppliers or alternative suppliers of other raw materials.
- Consult with and advise sponsors on resolution of manufacturing or quality issues. FDA can work with the manufacturer to address issues as quickly and safely as possible.
- Exercise regulatory discretion for the temporary importation of a non-U.S. product, in rare instances. Temporary importation of foreign drugs is considered in rare cases when there is a shortage of an approved U.S. drug that is important to patients and the shortage cannot be resolved by manufacturers of the approved U.S. drug in the immediate future. In these cases, FDA searches for companies that manufacture drugs for foreign markets to determine whether such sources may help meet critical patient needs in the U.S. When a firm is located that is willing and able to import a foreign drug, FDA evaluates

*Draft – Not for Implementation  
Contains Nonbinding Recommendations*

the overseas drug to ensure that it is of adequate quality and that the drug does not pose significant risks for U.S. patients. The information about the imported product and how patients can access supplies is posted on the FDA Drug Shortage website along with the Dear Healthcare Professional letter from the company that is importing the product.

Using these strategies, FDA is able to help prevent many drug shortages each year. We recognize, however, that not all drug shortages can be prevented. For example, some shortages involve unanticipated problems such as a manufacturing line breakdown that will take some time to resolve; if other manufacturers are unable to make up a production shortfall, an unavoidable shortage may occur. Similarly, some problems such as bacterial contamination or dangerous particulates in injectable products may involve risks that are too significant and would cause patient harm. In cases where a shortage cannot be avoided entirely, FDA's goals are to minimize the effect on patients of the shortage by getting product back to the market as quickly and safely as possible.

FDA also communicates information to the public about shortages based on information provided by manufacturers. FDA posts information about all actual shortages on the FDA drug shortages website. When manufacturers of products in shortage report updates to the Agency, FDA posts information on shortages on the FDA drug shortages website. FDA also responds to consumer inquiries through the e-mail account [drugshortages@fda.hhs.gov](mailto:drugshortages@fda.hhs.gov) to keep the health care community up to date on shortage situations. However, FDA does not post on its website information regarding potential shortages, because we are sensitive to the possibility that this could lead to increased stockpiling of a product facing a potential shortage, possibly worsening the situation. Potential shortages may never progress to actual shortages if the efforts that manufacturers and FDA undertake to help prevent the shortage are successful. In addition, when communicating with healthcare providers, patients, and other third parties, FDA does not disclose trade secret or confidential commercial information that we receive from manufacturers in connection with a drug shortage unless authorized by law.<sup>19</sup>

More information about FDA's response to actual and potential shortages is available on the FDA drug shortages website at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages>.

## **VI. ADDITIONAL CONSIDERATIONS FOR MANUFACTURERS**

Manufacturers play a primary role in preventing or responding to drug or biological product shortages, because they make the products needed by doctors and patients. In addition to early notification to the FDA of issues that may result in a shortage or potential disruption in supply, manufacturers can engage in other actions that may help prevent some shortages.

For example, many drug shortages arise from quality or other issues experienced during the manufacturing process. It is a primary responsibility of manufacturers to maintain their compliance with current good manufacturing practice (CGMP) requirements and to ensure that their suppliers of ingredients, components, and substances used in the manufacture of their

---

<sup>19</sup> See, e.g., 18 USC 1905; 21 USC 301(j); 21 CFR Part 20.



***Draft – Not for Implementation  
Contains Nonbinding Recommendations***

products meet standards of safety and quality sufficient to ensure that the final drug or biological product is safe and effective. Adequate attention to this responsibility, including by implementation of well-defined risk management systems at all layers of the supply chain, and through continuous evaluation and investment in manufacturing operations will help avoid many manufacturing problems that lead to product shortages.

Contingency planning by manufacturers may also help prevent some shortages. Analysis of 127 drug shortages between January 1, 2010 and August 26, 2011 showed that approximately 60% of the shortages were caused by circumstances that may have been avoided or mitigated if the manufacturer had undertaken enhanced redundancy or contingency planning.<sup>20</sup> We encourage manufacturers to make contingency plans for responding to situations that could lead to a shortage. This could include building redundancy into manufacturing capabilities, establishing relationships with and adequate controls over contract manufacturers, and/or identifying and seeking approval for alternative API and component suppliers. FDA is available to discuss with industry contingency plans for additional manufacturing sites, production lines, and suppliers to help prevent shortages. When contemplating such contingency plans, the sponsor should contact the FDA Office and specific review division with regulatory responsibility for the product in question. When contacting any of these offices, we recommend that the sponsor make clear its intention to build additional capacity or develop other contingency plans to be better prepared to prevent potential product shortages.

---

<sup>20</sup> A Review of FDA's Approach to Medical Product Shortages (Oct. 31, 2011), p. 16, *available at* <http://www.fda.gov/DrugShortageReport>.