



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-D-0140]

Draft Guidance for Industry on Notification to Food and Drug Administration of Issues That May Result in a Prescription Drug Shortage; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled “Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage.” This draft guidance relates to the Federal Food, Drug, and Cosmetic Act (FD&C Act), which requires sole manufacturers to notify FDA of a discontinuance of certain drug products and to the President’s Executive Order 13588 of October 31, 2011, directing FDA to use all available administrative tools to expand the Agency’s efforts to combat the problem of drug shortages. We are also requesting responsive comments from interested stakeholders on a specific question posed in this Federal Register document related to the draft guidance.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Submit either electronic or written comments concerning the proposed

collection of information by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002 or to the Office of Communication, Outreach and Development (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist the office in processing your request. The guidance may also be obtained by mail by calling CDER at 301-796-3400 or CBER at 1-800-835-4709 or 301-827-1800. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

Submit electronic comments to <http://www.regulations.gov>. Submit written comments on the draft guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background

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 no good therapeutic substitutes are available. The number of drug shortages has been rising steadily over the last 5 years, tripling from 61 in 2005 to 178 in 2010. In 2011, FDA tracked over 250 drug shortages. Some of these shortages delay or deny needed care for patients since they involve critical 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.

Under section 506C of the FD&C Act (21 U.S.C. 356c), 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 and that are approved under a new drug application (NDA) or abbreviated new drug application (ANDA). On October 31, 2011, FDA sent a letter to manufacturers reminding them of their mandatory reporting

requirements under section 506C of the FD&C Act and encouraging them to voluntarily notify the Agency of potential disruptions to supply of a prescription product that could lead to a product shortage, even beyond those instances that are required to be reported by statute. On the same day, the President issued Executive Order 13588 directing FDA to use all available administrative tools to expand its efforts to combat the problem of drug shortages.

FDA recognizes that some 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 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 product shortage. Notifying FDA in advance of incidents that may result in a shortage helps FDA work with manufacturers to take early action to prevent or alleviate shortages. For example, in 2011, early notification by manufacturers allowed FDA to help prevent shortages of 195 drugs, including 86 drugs produced by one company. However, as the President recognized in the Executive Order, FDA cannot begin to work with manufacturers or use 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 manufacturers, distributors, health care providers, and other stakeholders to identify the issues that can lead to shortages, to establish processes to avoid or mitigate critical shortages in the future, and to ensure continued patient access to vital safe and effective products. As part of this effort, we are issuing this guidance to help manufacturers better understand mandatory reporting obligations, to encourage voluntary reporting of additional issues that could lead to a shortage or disruption in supply of a drug or biological

product, and to address other issues, such as quality control and contingency planning related to product shortages or potential disruption in supply.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the Agency's current thinking on required and voluntary notifications to FDA of issues related to product shortages. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Request for Information

To assist us in finalizing guidance on drug shortages, FDA is seeking information and comments on the draft guidance from interested stakeholders. Although we welcome comment on any aspect of the draft guidance, we are particularly interested in obtaining information and comment regarding the appropriate scope of voluntary reporting of disruptions that may lead to a product shortage or potential disruption in supply. Specifically, please comment on whether manufacturers of all prescription drug and biological products should be encouraged to notify FDA of issues that may lead to a product shortage or potential disruption in supply. In your comments, please indicate whether the Agency should encourage voluntary reporting with regard to only a certain subset of prescription drug and biological products and, if so, please describe the products.

The comment period for the related interim final rule (IFR) on drug shortages published in the Federal Register of December 19, 2011 (76 FR 78530), and effective January 18, 2012, closed on February 17, 2012. Please do not submit comments on the IFR to the docket for the

draft guidance; we will not consider comments on the IFR submitted to the docket for the draft guidance.

III. Paperwork Reduction Act of 1995

Under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information that they conduct or sponsor. “Collection of information” is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA, 44 U.S.C. 3506(c)(2)(A), requires Federal Agencies to provide a 60-day notice in the Federal Register for each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing this notice of the proposed collection of information set forth in this document.

With respect to the collection of information associated with this draft guidance, FDA invites comments on the following topics: (1) Whether the proposed information collected is necessary for the proper performance of FDA’s functions, including whether the information will have practical utility; (2) the accuracy of FDA’s estimated burden of the proposed information collected, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information collected; and (4) ways to minimize the burden of information collected on the respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

The draft guidance provides information on the requirements for notification to FDA of a discontinuance of certain drug products under section 506C of the FD&C Act as implemented by 21 CFR 314.81(b)(3)(iii) and 314.91, and also reflects amendments to the implementing

regulations published in the Federal Register as an IFR on December 19, 2011 and effective January 18, 2012. The draft guidance also provides information to industry on voluntarily notifying FDA of other issues that may result in a shortage or disruption in supply of a prescription drug or biological product in the U.S. market. In addition, the draft guidance encourages manufacturers to make contingency plans for responding to situations that could lead to a drug or biological product shortage or potential disruption in supply. The draft guidance is intended for manufacturers of prescription drug and biological products regulated by CDER or CBER.

The burden analysis for the information collection resulting from the mandatory notification requirements under section 506C of the FD&C Act, as implemented by §§ 314.81(b)(3)(iii) and 314.91, and from the implementing regulations in the December 19, 2011, IFR, was submitted to OMB for emergency review under the PRA on December 21, 2011 (see “V. Paperwork Reduction Act of 1995” at 76 FR 78537). OMB has approved this information collection under OMB control number 0910-0699. A discussion of the scope and logistics of mandatory notification under section 506C of the FD&C Act and the IFR is found in section III of the draft guidance.

Under section IV of the draft guidance, manufacturers of all prescription drug and biological products are encouraged to voluntarily notify FDA of issues that may result in a shortage of a product in the U.S. market or a potential disruption in supply. Voluntary notification of issues that may lead to a potential shortage or disruption in supply includes reporting of circumstances beyond those instances that are required to be reported by section 506C, and includes the following:

- Product quality problems, such as the presence of particulates or impurities, microbial contamination, and stability concerns;
- Interruptions or other adjustments in manufacturing that may adversely affect market supply, such as routine maintenance, that may temporarily halt production or renovation of manufacturing facilities;
- Delays in acquiring critical raw materials or components, or loss of raw material or components supplier (e.g. vials, stoppers, bottles);
- 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 United States 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.

Based on the number of shortages we have seen during the past 12 months, we estimate that annually a total of approximately 480 manufacturers (“number of respondents” in table 1 of

this document) will voluntarily notify us of issues that may result in a shortage or potential disruption in supply of a drug or biological product, as described previously. We estimate that these manufacturers will submit annually a total of approximately 480 notifications (“total annual responses” in table 1 of this document). We also estimate that preparing and submitting this information to us will take approximately 2 hours per manufacturer (“hours per response” in table 1 of this document), including the time that some manufacturers may need to prepare information and take remedial steps in response to follow up questions and other action from FDA, as described in section V of the draft guidance. We base this estimate on our experience with the reporting of similar information to FDA, including mandatory reporting under section 506C of the FD&C Act of discontinuance of manufacturing of a sole source drug that is life-supporting, life-sustaining, or intended for use in the prevention of a serious disease or condition, and from the increase in voluntary notifications received since publication on October 31, 2011, of the letter to manufacturers requesting such reports.

Under section VI of the draft guidance, manufacturers are encouraged to engage in quality control, risk-management, and contingency planning for responding to situations that could lead to a drug or biological product shortage or potential disruption in supply. The draft guidance explains that contingency plans should cover additional manufacturing sites, production lines, and suppliers, such as building redundancy into manufacturing capabilities or providing for additional suppliers under the NDA, ANDA, and BLA processes. The plans may need to identify alternative API and component suppliers and/or have redundant manufacturing capacity registered and in compliance with current good manufacturing practices under 21 CFR parts 210 and 211.

In table 2 of this document, we estimate that a total of approximately 70 manufacturers (“number of recordkeepers” in table 2 of this document) will prepare contingency plans for responding to situations that could lead to a product shortage or potential disruption in supply, as described above. We estimate that these manufacturers will prepare a total of approximately 70 contingency plans (“total records” in table 2 of this document). We also estimate that preparing and maintaining each contingency plan will take approximately 500 hours per manufacturer (“average burden per recordkeeping” in table 2 of this document). We base this estimate on our experience with related contingency planning under the draft guidance for industry entitled: “Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products” (Absenteeism Draft Guidance) published in the Federal Register of January 8, 2010 (75 FR 1060), and October 18, 2010 (75 FR 63832), and the public comments we received on our burden estimate for that guidance. The Absenteeism Draft Guidance recommends that drug and biological product manufacturers develop written plans to maintain an adequate supply of medically necessary products during an emergency that results in high employee absenteeism. Although the draft guidance that is the subject of this Federal Register document is not related to employee absenteeism, the two guidance documents apply to a similar group of manufacturers and we believe the contingency plans recommended in both draft guidance documents will include similar elements. Accordingly, we believe the burden estimates from the Absenteeism Draft are relevant to this draft guidance. However, we specifically request comment on these contingency plan burden hour estimates.

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Reporting Burden¹

	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
Voluntary Reporting Under Section IV of the Draft Guidance	480	1	480	2	960
Total					960

¹ There are no capital costs or operating and maintenance costs associated with this information collection.

Table 2.--Estimated Recordkeeping Burden¹

	No. of Recordkeepers	No. of Records per Recordkeeper	Total Records	Average Burden per Recordkeeping (in Hours)	Total Hours
Voluntary Contingency Plans Under Section VI of the Draft Guidance	70	1	70	500	35,000
Total					35,000

¹ There are no capital costs or operating and maintenance costs associated with this information collection.

IV. Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) either written or electronic comments regarding this document. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

V. Electronic Access

Persons with access to the Internet may obtain the document at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.htm>, <http://www.fda.gov/cber/guidelines.htm>, or <http://www.regulations.gov>.

Dated: February 22, 2012.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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