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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 314

[Docket No. FDA-2011-N-0898]

Applications for Food and Drug Administration Approval To Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance

AGENCY: Food and Drug Administration, HHS.

ACTION: Interim final rule; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is issuing an interim final rule amending its postmarketing reporting regulations implementing certain provisions of the Federal Food, Drug and Cosmetic Act. The provisions of the Federal Food, Drug and Cosmetic Act require manufacturers who are the sole manufacturers of certain drug products to notify FDA at least 6 months before discontinuance of manufacture of the products. This interim final rule modifies the term “discontinuance” and clarifies the term “sole manufacturer” with respect to notification of discontinuance requirements. The broader reporting resulting from these changes will enable FDA to improve its collection and distribution of drug shortage information to physician and patient organizations and to work with manufacturers and other stakeholders to respond to potential drug shortages.

DATES: This interim final rule is effective January 18, 2012. Submit either electronic or written comments on the provisions of this interim final rule by February 17, 2012. Submit comments on the information collection requirements under the Paperwork Reduction Act of 1995 by January 3, 2012 (see the “Paperwork Reduction Act of 1995” section of this document).

ADDRESSES: You may submit comments, identified by Docket No. FDA-2011-N-0898 by any of the following methods, except that comments on information collection issues under the Paperwork Reduction Act of 1995 must be

submitted to the Office of Regulatory Affairs, Office of Management and Budget (OMB) (see the “Paperwork Reduction Act of 1995” section of this document).

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- *Fax:* (301) 827-6870.
- *Mail/Hand delivery/Courier (for paper, disk, or CD-ROM submissions):* Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2011-N-0898 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the “Comments” heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Kalah Auchincloss, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, (301) 796-0659, or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, (301) 827-6210.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of October 18, 2007 (72 FR 58993), we (FDA) issued a final rule to revise our postmarketing reporting requirements to implement section 506C of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356c). Section 506C of the Federal Food, Drug, and Cosmetic Act (section 506C) requires manufacturers who are the sole manufacturers of certain drug products

to notify us at least 6 months before discontinuance of manufacture of the products. Section 506C applies to sole manufacturers of products that meet the following three criteria:

1. The products are life supporting, life sustaining, or intended for use in the prevention of a debilitating disease or condition;
2. The products are approved under section 505(b) or (j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b) or (j)); and
3. The products are not originally derived from human tissue and replaced by a recombinant product.

These three criteria are statutory requirements. FDA assesses whether a drug is “life supporting, life sustaining, or intended for use in the prevention of a debilitating disease or condition” on a case-by-case basis, but intends to provide further guidance on this issue in the near future.

Section 506C also requires us to distribute certain information about covered discontinuances to appropriate physician and patient organizations. Under section 506C, FDA may reduce the 6-month notification period if we find good cause exists for the reduction.

Recent experience with drug shortages in the United States has shown the serious and immediate impacts they can have on patients and healthcare providers, particularly those shortages involving drugs that are manufactured by a small number of firms and for which there are no good therapeutic substitutes available. The number of drug shortages annually has tripled from 61 in 2005 to 178 in 2010. Some shortages delay or deny needed care for patients, because they involve critical drugs used to treat cancer, to provide required parenteral nutrition, or to address other serious medical conditions. Other shortages can result in providers prescribing second-line alternatives, which may be less effective and higher risk than first-line therapies. A survey of 1,800 health practitioners conducted by the Institute for Safe Medication Practices (ISMP) concluded that drug shortages could lead to medication errors and poor patient outcomes because shortages can result in the use of secondary alternative therapies (Ref. 1).

In light of increasing concerns about the impact of drug shortages on health care in the United States, on October 31, 2011, the President issued Executive Order 13588 directing the FDA to “take steps that will help to prevent and reduce current and future disruptions in the supply of lifesaving medicines” and noting that “one important step is ensuring that the FDA and the public

receive adequate advance notice of shortages whenever possible” (Ref. 2). In response to the Executive Order’s directive to address the growing drug shortage problem, this rule modifies the regulation at § 314.81(b)(3)(iii) (21 CFR 314.81(b)(3)(iii)), which, in addition to § 314.91 (21 CFR 314.91), implements section 506C of the Federal Food, Drug, and Cosmetic Act.

II. Overview of the Interim Final Rule

This interim final rule adds two definitions to § 314.81(b)(3)(iii)—a definition of “discontinuance” and a definition of “sole manufacturer.” Although these terms were discussed in the preamble to the final rule issuing § 314.81(b)(3)(iii) published on October 18, 2007 (72 FR 58993) (2007 Preamble), and have been used in various documents informally expressing the Agency’s interpretation of section 506C and its implementing regulations (see, for example, the Center for Drug Evaluation and Research (CDER) Manual of Policies and Procedures 6003.1, Drug Shortage Management (Ref. 3)), these terms were not defined in the regulation. Given the serious and growing threat to public health due to drug shortages, the Agency believes it is appropriate at this time to codify definitions of these terms. This modification and clarification of our existing regulations will further the public health objective of the Federal Food, Drug, and Cosmetic Act as a whole, and section 506C specifically by increasing the scope of information that FDA receives regarding discontinuances. This will enable the Agency to: (1) Expand collection and distribution of information on the discontinuance of certain drugs to appropriate physician and patient organizations as required by section 506C(c); and (2) work with manufacturers and other stakeholders to implement appropriate strategies to reduce, to the greatest extent possible, the public health impact of discontinuances of products that can lead to drug shortages. We believe that clarification of terminology will also improve statutory compliance.

A. Discontinuance

The Agency is revising an earlier policy position and defining the term “discontinuance” in the regulation to include both permanent and temporary interruptions in the manufacturing of a drug product, if the interruption could lead to a disruption in supply of the product. This interpretation of the statutory language best achieves the public health purpose of section 506C

and the Federal Food, Drug, and Cosmetic Act as a whole.

Under section 506C, sole manufacturers are required to notify FDA of a “discontinuance” of a drug product subject to section 506C. In the 2007 Preamble, in response to a comment on the meaning of the term discontinuance, we indicated that a discontinuance did not include planned or unplanned temporary manufacturing cessations (72 FR 58993 at 58995, response to comment 4). At that time, we stated that only manufacturers who intended to permanently discontinue manufacture and marketing of the drug product were subject to mandatory reporting requirements under section 506C. In our response to the comment in the 2007 Preamble, however, we did request that manufacturers who experience an unplanned temporary manufacturing cessation keep the Agency informed of the status of the shutdown because “the duration of an unplanned shutdown may be unpredictable and could affect the availability of needed therapy for patients.”

FDA no longer believes that this narrow policy position regarding the term “discontinuance” serves the public health need that the Federal Food, Drug, and Cosmetic Act was intended to address. In 2007, the Agency believed that the supply of drug product available to patients during a temporary manufacturing cessation, particularly one that was planned, would not be greatly affected during the interruption in manufacturing. However, subsequent experience has shown that even temporary discontinuances of manufacturing can have a significant impact on patient access to drug products. For example, if an equipment failure necessitates an unexpected temporary interruption in manufacturing of a drug product subject to section 506C, this discontinuance could have serious implications for patient access to the product. Notification to FDA of such discontinuances will expand FDA’s ability to distribute information on the discontinuance of certain drugs to physician and patient organizations and enable FDA to work with manufacturers and other stakeholders to respond to potential drug shortages.

The interim final rule therefore adds § 314.81(b)(3)(iii)(d) to provide that “discontinuance” means “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.” 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. This interpretation of “discontinuance” is consistent with Webster’s Third New International Dictionary, which defines the term to mean “cessation, shutdown, closure; interruption” (Ref. 4). The dictionary definition indicates that a discontinuance can be interpreted to include both situations that are permanent (cessation, shutdown, closure) and those that are temporary (interruption).

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. Temporary discontinuances must be reported to the Agency under this interim final rule only if the discontinuance could lead to a disruption in supply of the product.

We understand that a manufacturer may be unable to report some temporary discontinuances 6 months before the discontinuance, as required by statute. When notification at least 6 months prior to the discontinuance is impossible because it was unforeseen, the manufacturer must notify the Agency as soon as possible after it knows that a discontinuance will occur. For example, if a contamination problem requires immediate shut down of a manufacturing plant for a drug product subject to section 506C, the manufacturer will not be able to provide the FDA with 6 months prior notification, but would be required to notify FDA as soon as the manufacturer becomes aware that the contamination necessitates a temporary discontinuance of manufacture of the product.

Other circumstances that would trigger notification to the FDA of a discontinuance of a drug product subject to section 506C include:

- A business decision to permanently discontinue manufacture of a drug product;
- A delay in acquiring active pharmaceutical ingredients 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 is not 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 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 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 506C. The shutdown does not need to be reported to the Agency under section 506C.

- A manufacturer of a drug product subject to 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 under this rule and the manufacturer would be required to notify FDA of a discontinuance of the product.

In addition to revising the definition of “discontinuance,” this interim final rule makes a minor conforming change by striking the phrase “discontinuing manufacture” in the first sentence of § 314.81(b)(3)(iii)(a) and replacing it with the phrase “discontinuance of manufacture.” This change ensures that the regulations contain an appropriate cross-reference to the revised definition of discontinuance.

The interim final rule also makes a minor change to the procedures in § 314.81(b)(3)(iii)(b) for reporting notices of discontinuances to the Agency. The interim final rule 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 Web site at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages>. Products regulated by CDER must be reported to the CDER Drug Shortages Coordinator. Products regulated by the Center for Biologics Evaluation and Research (CBER) must be reported to the CBER Products Shortage Coordinator. This change ensures that the appropriate offices are timely notified of all relevant discontinuances. It also reflects existing practice for submitting notices of discontinuance, and reduces the burden on industry to submit multiple copies of the notification.

B. Sole Manufacturer

To best achieve the public health purposes of the Federal Food, Drug, and Cosmetic Act, and section 506C, the Agency is clarifying the term sole manufacturer to ensure that we receive timely reports of all discontinuances of drug products subject to section 506C, including where other strengths, dosage forms, or routes of administration of the same drug product are marketed. The clarification is intended to improve statutory compliance and to minimize instances where manufacturers fail to make reports to the Agency as required by section 506C. This clarification of the statutory language best achieves the purpose of section 506C and the Federal Food, Drug, and Cosmetic Act as a whole.

Section 314.81(b)(3)(iii) currently does not include a definition of the term “sole manufacturer.” In the 2007 Preamble, we rejected a suggestion to rely on the “Orange Book” (FDA’s publication on “Approved Drug Products with Therapeutic Equivalence Evaluations”) as the source for determining whether an entity is a sole manufacturer (72 FR 58993 at 58995, comment 3). The comment to the proposed rule had expressed concern that, although the Orange Book lists all drug products with approved new drug applications (NDA) and abbreviated new drug applications (ANDA), it is not possible to determine whether the listed approved products are, in fact, being manufactured. The comment requested that we define sole manufacturer as “an applicant listed in the Orange Book who is the holder of the only listed approved application under section 505(b) or (j) of

the [FD&C] Act.” We declined to accept this definition of sole manufacturer, and reliance on the Orange Book, to determine whether an applicant was a sole manufacturer for several reasons in 2007, including the following: (1) There may be delays in updating the Orange Book, rendering it temporarily inaccurate; (2) the suggested definition could create potential confusion because some drugs are approved but not marketed and are therefore placed in the “discontinued” section of the Orange Book; and (3) there are other generally reliable sources for obtaining commercial manufacturing information to assist in determining whether an applicant is a sole manufacturer.

We continue to believe that reference to the Orange Book is not the appropriate way to identify a “sole manufacturer” for purposes of implementing section 506C. In addition, we believe there has been some confusion as to the scope of the term. Accordingly, the interim final rule adds § 314.81(b)(3)(iii)(d) to define “sole manufacturer” in the regulation 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 in this interim final rule is intended to clarify that a sole manufacturer means the only applicant currently supplying the U.S. market with the drug product. It does not mean sole NDA or ANDA holder. A manufacturer is considered a sole manufacturer even if other manufacturers hold an approved NDA or ANDA for the same product, if the other applicants are no longer manufacturing (or have never manufactured) the product for sale in the United States. For example, Company A holds an NDA for a drug product subject to section 506C and manufactures and sells that product in the United States. Company B holds an ANDA for the drug product, but does not manufacture or sell the product in the United States. Company A would be considered a sole manufacturer of the drug product for purposes of reporting a discontinuance of the drug product under section 506C. If Company B began manufacturing and selling the drug product in the United States, then Company A would no longer be considered a sole manufacturer. A manufacturer is responsible for determining if it is a sole manufacturer under this regulation. There is commercial information available to

help with this determination. If an applicant is unsure if it is a sole manufacturer of a drug product subject to section 506C, FDA's drugs shortages staff may be able to work with it to help it determine whether it is or is not the sole manufacturer of the drug.

The interim final rule also 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. For example, if a company manufactures for sale in the United States an injectable dosage form of a drug product subject to section 506C, that company is considered a sole manufacturer of that drug product, even if a second company manufactures and sells in the United States an oral dosage form of the same drug product for the same indication. In this example, if the second company was the only applicant manufacturing and selling the oral dosage form in the United States, both companies would be considered sole manufacturers for purposes of section 506C.

It is important that an entity currently manufacturing a drug product of a specific strength, dosage form, or route of administration for sale in the United States report a discontinuance to FDA because that specific strength, dosage form, or route of administration may be critical for the targeted needs of particular patients. To enable the Agency to fully distribute information under section 506C(c), and to work most effectively with manufacturers and other stakeholders to implement appropriate strategies to reduce, to the greatest extent possible, the public health impact of drug shortages, discontinuances of a specific strength, dosage form, or route of administration of drug products subject to section 506C must be reported to us. 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.

Finally, the new definition in the interim final rule clarifies who bears the responsibility for reporting to FDA a discontinuance of a drug product subject to section 506C. The inclusion of "whether the product is manufactured by the applicant or for the applicant under contract with one or more different entities" in the definition makes clear that the application holder must report a discontinuance to FDA. 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 a process with any relevant contract manufacturer that ensures the application holder's compliance with this rule. This could include contractual terms between the application holder and the contract manufacturer, as well as monitoring. 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" in the above situation, and is required to establish a process with Company Y that ensures Company X's ability to report a discontinuance of the drug product to FDA.

III. Legal Authority

FDA is amending its postmarketing reporting regulations implementing section 506C of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356c). Section 506C requires manufacturers who are the sole manufacturers of certain drug products to notify us at least 6 months before discontinuance of manufacture of the drug products. This interim final rule modifies the term "discontinuance" and clarifies the term "sole manufacturer" with respect to section 506C notification requirements. FDA's authority for this rule also derives from section 701(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 371(a)).

The Administrative Procedure Act permits an agency to promulgate a rule without notice and comment procedures when an agency for "good cause finds (and incorporates the finding and a brief statement of reasons therefor in the rules issued) that notice and public procedure thereon are impracticable, unnecessary, or contrary to the public interest" (5 U.S.C. 553(b); 21 CFR 10.40(e)). FDA has determined that good cause exists for this interim final rule and that notice and comment procedures are contrary to the public interest given the serious and growing threat to public health due to drug shortages.

Recent experience with drug shortages in the United States has shown serious and immediate impacts on patients and healthcare providers, particularly those shortages involving drugs that are manufactured by a small number of firms and for which there are no good therapeutic substitutes available. Some shortages delay or deny needed care for patients, because they involve critical drugs used to treat

cancer, to provide required parenteral nutrition, or to address other serious medical conditions. Other shortages can result in providers prescribing second-line alternatives, which may be less effective and higher risk than first-line therapies. The number of drug shortages annually has tripled from 61 in 2005 to 178 in 2010. New shortages are occurring at the present time.

The scope of information FDA receives under the current regulations has not adequately enabled the Agency to distribute information on the discontinuance of certain drugs to physician and patient organizations as required by section 506C(c) and to work with manufacturers and other stakeholders to respond to potential drug shortages. There are significant non-quantifiable benefits of reporting information about discontinuances to FDA, including better enabling the Agency, manufacturers, healthcare providers, and patients to monitor and evaluate these discontinuances to mitigate or prevent potential drug shortages that can arise as a result of these discontinuances and that could otherwise lead to serious and widespread adverse health consequences. Any delay in the implementation of this rule would limit the ability of healthcare providers to respond to potential and actual shortages, and would reduce the ability of FDA to work with manufacturers and other stakeholders to prevent and mitigate drug shortages. In this instance, FDA has determined that an interim final rule is legally permissible and in the public's interest.

IV. Analysis of Impacts

A. Introduction and Summary

1. Introduction

FDA has examined the impacts of the interim final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). This interim final rule is a significant regulatory action as defined by Executive Order 12866 and accordingly has been reviewed by the Office of Management and Budget.

The Regulatory Flexibility Act requires agencies to analyze regulatory

options that would minimize any significant impact of a rule on small entities. The Agency projects that the interim final rule will not likely have a significant economic impact on a substantial number of small entities, but seeks comments on its analysis below.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$136 million, using the most current (2010) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this interim final rule to result in any 1-year expenditure that would meet or exceed this amount.

2. Summary

The interim final rule modifies the term “discontinuance” and clarifies the term “sole manufacturer” with respect to notifications of discontinuance of products that are life supporting, life sustaining, or intended for use in the prevention of a debilitating disease or condition. The interim final rule will impose annual reporting costs of up to

\$15,064 in total. Non-quantifiable benefits include the value of the reported information about discontinuances in helping FDA, manufacturers, healthcare providers, and patients to monitor and evaluate these discontinuances to mitigate or prevent potential drug shortages that can arise as a result of these discontinuances and that could otherwise lead to serious and widespread adverse health consequences.

B. Objective of and Need for the Interim Final Rule

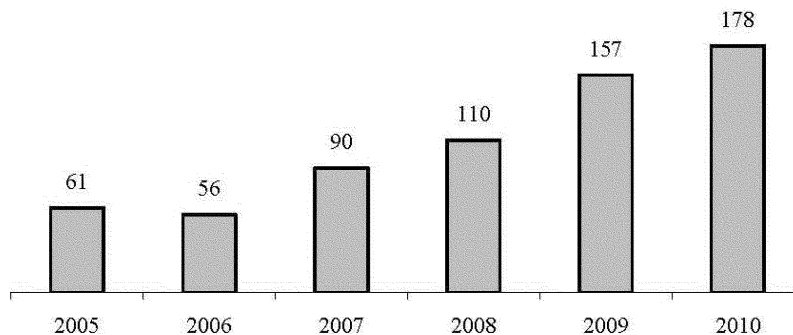
Current regulations require that a sole manufacturer of a drug product that is: (1) Life supporting, life sustaining, or intended for use in the prevention of a debilitating disease or condition; (2) approved under section 505(b) or 505(j) of the Federal Food, Drug, and Cosmetic Act; and (3) not a product that was originally derived from human tissue and was replaced by a recombinant product report permanent discontinuances to FDA at least 6 months prior to the discontinuance. FDA can reduce the 6-month notification period if the applicant submits a certification of good cause, and the Agency finds good cause.

The purpose of the interim final rule is to define the terms “discontinuance” and “sole manufacturer.” In the interim final rule, “discontinuance” is defined

as “any interruption in 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.” “Sole manufacturer” is defined as “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.” These definitions will require additional manufacturers to report to FDA a wider range of discontinuances that could potentially lead to a drug shortage than under the current, existing regulations.

While existing regulations require that only permanent discontinuances be reported to FDA, in practice, some manufacturers voluntarily notify FDA about temporary discontinuances. In the past 2 years, such notifications have enabled FDA to prevent 233 drug shortages by expediting review of new manufacturing sites, new suppliers, and specification changes. Nonetheless, recent data from FDA’s Drug Shortages Program (DSP) indicate that the number of drug shortages has tripled from 2005 to 2010 (see figure 1 below, Ref. 5).

Figure 1.
Number of Drug Shortages



A survey conducted by the American Hospital Association (AHA) concluded that drug shortages are experienced by hospitals. For example, almost 100 percent of the 820 hospitals surveyed had experienced at least one drug shortage in the 6 months preceding the survey (Ref. 6). Another survey of 1,800 health practitioners conducted by the ISMP suggested that because drug shortages often result in the need for physicians to prescribe alternative

therapies which may be less effective and higher risk than first-line treatments, drug shortages can lead to the potential for medication errors and poor patient outcomes as well as higher costs (Refs. 1 and 7).

The interim final rule is intended to increase the scope of information that FDA receives, enabling the Agency to: (1) Expand distribution of information on the discontinuance of certain drugs to appropriate physician and patient

organizations as required by section 506C(c); and (2) work with manufacturers and other stakeholders to implement appropriate strategies to reduce, to the greatest extent possible, the public health impact of discontinuances of products that can lead to drug shortages. The public health purpose of section 506C and the Federal Food, Drug, and Cosmetic Act as a whole are best achieved with this modification to our existing regulations.

Currently it appears that some manufacturers may lack sufficient incentives to either take steps to prevent certain shortages or to notify FDA early enough for the Agency to act (Ref. 7). By providing clear definitions, the interim final rule will address this concern and require all applicants to report appropriate information to the Agency in a timely manner.

C. Benefits

The interim final rule modifies the term “discontinuance” and clarifies the term “sole manufacturer” with respect to postmarketing reporting requirements of products subject to section 506C. The clarification in terminology captures additional manufacturers as “sole manufacturers” by explicitly linking the definition of sole manufacturer to a specific strength, dosage form, or route of administration of a drug product. Requiring notification of temporary discontinuances and clarifying the term sole manufacturer will result in FDA receiving better and more timely information on a wider range of discontinuances. This increased reporting will enable FDA to distribute information on discontinuances to appropriate physician and patient organizations and to work with manufactures and other stakeholders to try to prevent a discontinuance from leading to a drug shortage, or to mitigate the impacts of an unavoidable drug shortage on patients and healthcare providers.

There is evidence that the negative impact of drug shortages could be significant. For instance, the American Society of Health System Pharmacists (ASHP) reported that annual labor costs to manage drug shortages are approximately \$216 million in the United States (Ref. 7). Moreover, drugs in several major therapeutic classes are

in shortage, including oncology products, antibiotics, and electrolyte/nutrition products. For example, statistics indicate that cancer alone affects more than 11 million people in the United States (Ref. 8). Therefore, the potential benefits of the interim final rule as a result of prevention or mitigation of these drug shortages could be substantial from both an economic and public health viewpoint. Because the shortage of even one critical drug can impact a large number of patients and healthcare providers, the potential benefits could be substantial even if the interim final rule only results in a small number of additional notifications of discontinuances to the Agency.

D. Costs

Currently, FDA receives one mandatory notification that meets the statutory and regulatory criteria of a section 506C discontinuance per year and zero certifications of good cause. In addition, there are several dozen voluntary submissions of information to FDA that are related to section 506C discontinuances but do not meet the applicable statutory criteria, as implemented by the current regulation. We note that as a result of FDA’s letter to industry (Ref. 10), FDA has experienced a significant increase in the number of notifications. We estimate that the total number of manufacturers who would be required to notify us of a discontinuance under the interim final rule would be 80 per year.¹ However, the impact of the interim final rule represents the incremental impact, which is the difference between the total number of reports required by the interim final rule and the baseline, *i.e.*, the estimated number of reports that we would receive without the interim final rule. We estimate that as a result of the interim final rule, we will receive an

additional 9 to 24 notifications of section 506C discontinuances (both temporary and permanent discontinuances) and 2 to 5 associated certifications of good cause. In the 2007 Preamble, we estimated that it would take two hours to prepare a notification of discontinuance and 16 hours to prepare a certification of good cause (72 FR 58993 at 58999). Since neither the format nor the content of these submissions will change as a result of the interim final rule, we continue to estimate that it will take two hours to prepare a notification of discontinuance and 16 hours to prepare a certification of good cause. We estimate that it will take longer to prepare a certification of good cause than a notification of discontinuance because preparing a certification of good cause requires a detailed narrative justifying a reduction in the notification period, which is more labor intensive than the simpler notification of discontinuance.

Notifications are generally prepared and submitted by a regulatory affairs manager. Thus, labor hours are valued using the median hourly wage for Management Occupations (occupation code 11–0000) in Pharmaceutical and Medicine Manufacturing (North American Industry Notification, NAICS, code 325400) as reported by the Bureau of Labor Statistics 2010 Employment Occupational Statistics (Ref. 9). The median hourly wage is \$117, which is adjusted for benefits and overhead.

The estimated cost is \$234 ($\117×2 hours) per notification of discontinuance, and \$1,872 ($\117×16 hours) per certification of good cause. In table 1 below we present the estimated costs. The estimated annual cost of the interim final rule is between \$5,850 and \$15,064.

TABLE 1—ESTIMATED ADDITIONAL ANNUAL REPORTING COSTS OF THE INTERIM FINAL RULE

| Type of response | Number of additional responses | Hours per response | Cost per response | Total estimated cost |
|--|--------------------------------|--------------------|-------------------|-------------------------|
| Notification of Discontinuance (§ 314.81(b)(3)(iii)) | 9–24 | 2 | \$234 | \$2,106–\$5,704 |
| Certification of Good Cause (§ 314.91) | 2–5 | 16 | \$1,872 | \$3,744–9,360 |
| Total | | | | \$5,850–\$15,064 |

E. Analysis of Regulatory Alternatives

The interim final rule will result in the submission of additional notifications to FDA of a discontinuance of a drug product subject to section

506C. As noted in FDA’s recent report on medical product shortages (Ref. 5), any system that increases reporting must ensure that, in the pursuit of more “signal,” FDA is not overwhelmed with

“noise.” We welcome comments on how the notifications can be designed in line with this principle. Such an approach is consistent with Section 4 of Executive Order 13563, which calls

¹ The total is estimated based on 220 shortages tracked by FDA’s CDER Drug Shortages Coordinator from January through October of 2011, of which we

estimate 30 percent would relate to discontinuances subject to mandatory reporting under section 506C and this interim final rule. The estimated number

of discontinuances subject to mandatory reporting (220 × 30 percent) is then adjusted to include two additional months of reporting.

upon agencies “to identify and consider regulatory approaches that reduce burdens and maintain flexibility and freedom of choice for the public.” FDA identified the following alternatives to the interim final rule: (1) No change in regulation; and (2) publish guidance that encourages sole manufacturers (including manufacturers of specific strengths, dosage forms, and routes of administration) to notify FDA about temporary discontinuances of drug products subject to the rule, and (3) provide incentives for voluntary reporting.

1. Alternative 1: No Change in Regulation

A simple alternative would be to leave the current regulation unchanged. While this alternative may not impose additional costs on sole manufacturers of drug products subject to section 506C, the benefits of this option would be uncertain and would not provide any additional tools to reduce the number of product shortages.

2. Alternative 2: Publish Guidance

FDA could draft additional guidance to encourage voluntary notification of upcoming discontinuances. A recent example is a FDA’s letter to industry (Ref. 10). However, such communications and guidance cannot impose new regulatory requirements. Without this regulation defining which manufacturers are required to notify FDA about both temporary and

permanent discontinuances of drug products subject to section 506C, FDA may not have adequate information to distribute to physician and patient organizations and to work effectively with manufacturers and other stakeholders to better prevent and mitigate drug shortages.

3. Alternative 3: Provide Incentives for Voluntary Reporting

It may be possible to develop a system of incentives to encourage increased reporting on a voluntary basis. FDA welcomes comments from the public on how such a system could be implemented, including the types of incentives that would advance the FDA’s mission to protect the public health while encouraging additional reporting.

F. Regulatory Flexibility Analysis

FDA has examined the economic implications of the interim final rule as required by the Regulatory Flexibility Act. The Agency projects that the interim final rule will not likely have a significant economic impact on a substantial number of small entities, but seeks comment on its analysis below.

1. Economic Effect on Small Entities

The Small Business Administration (SBA) uses different definitions of what a small entity is for different industries. Using SBA standard size definitions, a firm categorized in NAICS code 315412 (Pharmaceutical Preparations) or NAICS

code 325414 (Biological Products) is considered small if it employs fewer than 750 or 500 people, respectively (Ref. 11). The most currently available data from the 2007 Economic Census (Ref. 12) show that at least 92 percent of these establishments would be considered small by SBA standards.² We note that using data at the establishment level implicitly assumes that the typical manufacturing establishment is roughly equivalent to the typical small manufacturing firm.

We estimate that the cost per response as a percent of average sales for manufacturers in NAICS code 325412 could represent up to 0.002 percent of sales. The greatest impact is on establishments hiring fewer than 10 employees, where the cost per response as a percent of average sales ranges from 0.029 percent to 0.235 percent. The analysis of the effect on small versus large entities for NAICS 312314 is limited by data restrictions imposed to safeguard the confidentiality of some establishments. Consequently, for NAICS code 312314 the average value of shipments is only presented for all establishments. We estimate that the cost per response as a percent of average sales in this industry is between 0.001 percent and 0.004 percent (see table 2). Therefore, the Agency concludes that this rule will not likely have a significant impact on a substantial number of small entities, but we request comments on our analysis.

TABLE 2—ESTIMATED ECONOMIC IMPACT OF INTERIM FINAL RULE ON SMALL ENTITIES

| Number of employees | Number of establishments | Total value of shipments (\$000) | Average value of shipments (\$1,000) | Cost per response as a percent of average sales | |
|---------------------|--------------------------|----------------------------------|--------------------------------------|---|--|
| | | | | (\$234 per response—notification of discontinuance) (%) | (\$1,872 per response—certification of good cause) (%) |
| NAICS Code 325412: | | | | | |
| 0–9 | 408 | 324,604 | 796 | 0.029 | 0.235 |
| 10–19 | 77 | 317,551 | 4,124 | 0.006 | 0.045 |
| 20–99 | 249 | 8,377,347 | 33,644 | 0.001 | 0.006 |
| 100–499 | 182 | 32,516,961 | 178,665 | 0.000 | 0.001 |
| 500 and over | 75 | 68,162,155 | 908,829 | 0.000 | 0.000 |
| All | 991 | 109,698,618 | 110,695 | 0.000 | 0.002 |
| NAICS Code 325414: | | | | | |
| All | 350 | 16,112,435 | 46,036 | 0.001 | 0.004 |

2. Additional Flexibility Identified

In this section, we identify alternatives that would present reductions in costs to small entities.

Alternative 1: Exempt Small-sized Entities: Exempting small-sized businesses from the interim final rule would reduce the economic impact to

small businesses by up to 0.235 percent of average sales. However, not imposing these notification requirements on drug products subject to section 506C could

² For NAICS code 325412, total value of shipments data are not available for establishments employing fewer than 750 employees. The

estimated percent of small establishments (92 percent) is based on the total number of establishments with fewer than 500 employees. For

NAICS code 324514 the percent of establishments with fewer than 750 employees is 96 percent.

exacerbate the increasing trend in drug shortages that affect a substantial number of patients and healthcare providers. Moreover, these reporting requirements enable FDA to distribute information to physician and patient organizations, to assess potential drug shortages, and to evaluate mitigation strategies. Thus, exempting small business entities may in the long-term lead to high social costs associated with outcomes such as worsening of conditions for patients for whom these products are necessary.

Alternative 2: Extend the Compliance Period for Small Businesses: An alternative to reduce costs would be to extend the compliance period for small-sized entities. While a longer compliance period may enable small businesses to reduce labor costs, it would delay FDA's receipt of notices of discontinuance and limit the Agency's ability to distribute information to physician and patient organizations as required by section 506C(c), to assess potential drug shortages, and to work with manufacturers and other stakeholders to prevent or mitigate shortages.

V. Paperwork Reduction Act of 1995

This interim final rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520) (the PRA). The title, description, and respondent description of these provisions are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on: (1) Whether the proposed collections of information are necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collections of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility and clarity of the information to be collected; and (4) ways to minimize the burden of the collections of information on respondents, including through the use of automated collection techniques, when appropriate, or other forms of information technology.

Title: Applications for Food and Drug Administration Approval to Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance.

Description: Sections 314.81(b)(3)(iii) and 314.91 of FDA's regulations ("§ 314.81(b)(3)(iii)" and "§ 314.91", respectively) implement section 506C. Section 314.81(b)(3)(iii) requires entities who are the sole manufacturers of certain drug products to notify us at least 6 months before discontinuance of manufacture of the product. For the regulations to apply, a product must meet the following three criteria:

1. The product must be life supporting, life sustaining, or intended for use in the prevention of a debilitating disease or condition;
2. The product must have been approved by FDA under section 505(b) or 505(j) of the Federal Food, Drug, and Cosmetic Act; and
3. The product must not have been originally derived from human tissue and replaced by a recombinant product.

Under § 314.81(b)(3)(iii)(c), we will publicly disclose information about drug products subject to section 506C that are to be discontinued. Section 314.91 allows us to reduce the 6-month notification period if we find that good cause exists for the reduction. A manufacturer may request that we reduce the notification period by certifying that good cause for the reduction exists.

In the October 18, 2007 final rule (72 FR 58993), we added §§ 314.81(b)(3)(iii) and 314.91 to our regulations. Sections 314.81(b)(3)(iii) and 314.91 require two new reporting requirements to FDA that are subject to OMB approval under the PRA: Notification of Discontinuance and Certification of Good Cause. The interim final rule adds two new definitions to § 314.81(b)(3)(iii): "discontinuance" and "sole manufacturer." The interim final rule clarifies the scope of manufacturers required to report and expands the range of circumstances required to be reported to the Agency under § 314.81(b)(3)(iii), but does not change the substantive content of the reports required to be submitted to the Agency. This PRA analysis covers the information collection resulting from the October 18, 2007 final rule and also includes our estimates of how the number of Notifications of Discontinuance and Certifications of Good Cause may increase as a result of this interim final rule. Accordingly, the estimates included in the Analysis of Impacts will not directly match the estimates in the PRA analysis because the PRA analysis represents an estimate of the total reporting burden under §§ 314.81(b)(3)(iii) and 314.91, while the Analysis of Impacts examines only the increased costs and benefits as a result of the interim final rule.

A. Notification of Discontinuance

Under § 314.81(b)(3)(iii), at least 6 months before a sole manufacturer intends to discontinue manufacture of a drug product subject to section 506C, the manufacturer must send us notification of the discontinuance. The notification of discontinuance generally contains the name of the manufacturer, the name of the product to be discontinued, the reason for the discontinuance, and the date of discontinuance. We will work with relevant manufacturers during the 6-month notification period to help minimize the effect of the discontinuance on patients and health care providers, and to distribute appropriate information about the discontinuance to physician and patient organizations. The interim final rule adds definitions of "discontinuance" and "sole manufacturer" to § 314.81(b)(3)(iii). The inclusion of these definitions expands notification requirements under § 314.81(b)(3)(iii) to additional discontinuance circumstances and clarifies the scope of manufacturers who must report discontinuances. The interim final rule also requires that notifications of discontinuance be submitted either electronically or by telephone according to instructions on FDA's Drug Shortage Web site at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages>. This change ensures that the appropriate offices are timely notified of all relevant discontinuances. It also reflects existing practice for submitting notices of discontinuance, and reduces the burden on industry to submit multiple copies of the notification.

B. Certification of Good Cause

We may reduce the 6-month notification period if we find good cause for the reduction. As described in § 314.91, a manufacturer can request a reduction in the notification period by submitting written certification that good cause exists to the following designated offices: (1) The CDER Drug Shortage Coordinator at the address of the Director of CDER; (2) the CDER Drug Registration and Listing Team, Division of Compliance Risk Management and Surveillance in CDER; and (3) the director of either the CDER division or the CBER office that is responsible for reviewing the application. The following circumstances may establish good cause:

- A public health problem may result from continuation of manufacturing for the 6-month period (§ 314.91(d)(1));

- A biomaterials shortage prevents the continuation of manufacturing for the 6-month period (§ 314.91(d)(2));
- A liability problem may exist for the manufacturer if the manufacturing is continued for the 6-month period (§ 314.91(d)(3));
- Continuation of the manufacturing for the 6-month period may cause substantial economic hardship for the manufacturer (§ 314.91(d)(4));
- The manufacturer has filed for bankruptcy under chapter 7 or 11 of title 11, United States Code (§ 314.91(d)(5));
- The manufacturer can stop making the product but still distribute it to satisfy existing market need for 6 months (§ 314.91(d)(6)); or
- Other good cause exists for a reduction in the notification period (§ 314.91(d)(7)).

With each certification described previously, the manufacturer must describe in detail the basis for its conclusion that such circumstances exist. We require that the written certification that good cause exists be submitted to the offices identified previously to ensure that our efforts to address the discontinuance take place in a timely manner. The interim final rule makes no changes to the requirements or process for certification of good cause.

Description of Respondents: An applicant that is the sole manufacturer and who is discontinuing manufacture of a drug product that meets the following criteria: (1) Is life supporting, life sustaining, or intended for use in the prevention of a debilitating disease or condition; (2) was approved by FDA under section 505(b) or (j) of the Federal Food, Drug, and Cosmetic Act; and (3) was not originally derived from human tissue and replaced by a recombinant product.

Burden Estimate: Table 3 of this document provides an estimate of the annual reporting burden for notification of a product discontinuance and certification of good cause under §§ 314.81(b)(3)(iii) and 314.91, as amended by this interim final rule.

Notification of Discontinuance: Based on data collected from the CDER Drug Shortage Coordinator since December 17, 2007, when §§ 314.81(b)(3)(iii) and 314.91 went into effect, one manufacturer during each year reported to FDA a discontinuance of one drug product meeting the criteria of section 506C and its implementing regulations (*i.e.*, the drug product was approved under section 505(b) or (j) of the Federal Food, Drug, and Cosmetic Act, the drug product was “life-supporting, life-sustaining or intended for use in the prevention of a debilitating disease or condition,” the drug product was produced by a sole manufacturer, and the drug product was permanently discontinued). CDER’s Drug Shortages Coordinator tracked 220 drug shortages between January and October of 2011. The Agency estimates that 30 percent (66) of these shortages would relate to discontinuances subject to mandatory reporting under section 506C as a result of the interim final rule. Adjusting to include an additional two months of reporting (November and December), we estimate that FDA will receive a total of 80 notifications of a discontinuance per year under section 506C, as amended by the interim final rule. Based on experience, a manufacturer submits only one notification of a discontinuance per year, thus the total number of manufacturers who would be required to notify us of a discontinuance would be 80. Therefore, the number of respondents is estimated to be 80. The hours per response is the estimated number of hours that a respondent would spend preparing the information to be submitted with a notification of product discontinuance, including the time it takes to gather and copy the statement. Based on experience in working with manufacturers to submit notifications under § 314.81(b)(3)(iii), we estimate that approximately 2 hours on average are needed per response. We do not expect the changes in the interim final rule to affect the number of hours per response. Therefore, we estimate

that respondents will spend 160 hours per year notifying us of a product discontinuance under these regulations.

Certification of Good Cause: Based on data collected from the CDER drug shortage coordinator since 2007, one manufacturer each year reported a discontinuance of one drug product under section 506C and its implementing regulations. Each manufacturer has the opportunity under § 314.91 to request a reduction in the 6-month notification period by certifying to us that good cause exists for the reduction. The Agency has received no certifications of good cause since 2007. Although we expect we will receive an increase in the number of reports of discontinuances as a result of the changes in the interim final rule, because of the limited circumstances under which good cause can be requested or would be appropriately granted, we do not expect a correspondingly large increase in the number of manufacturers requesting a certification of good cause. We estimate that only 5 manufacturers will request a certification of good cause each year. Therefore, the number of respondents is estimated to be 5. The total annual responses are the total number of certifications of good cause that are expected to be submitted to us in a year. We estimate that the total annual responses will remain small, averaging one response per respondent. The hours per response is the estimated number of hours that a respondent spends preparing the detailed information certifying that good cause exists for a reduction in the notification period, including the time it takes to gather and copy the documents. We estimate that approximately 16 hours on average are needed per response. Therefore, we estimate that 80 hours will be spent per year by respondents certifying that good cause exists for a reduction in the 6-month notification period under § 314.91.

TABLE 3—ESTIMATED ANNUAL REPORTING BURDEN ¹

| 21 CFR Section | Number of respondents | Number of responses per respondent | Total annual responses | Hours per response | Total hours |
|--|-----------------------|------------------------------------|------------------------|--------------------|-------------|
| Notification of Discontinuance (314.81(b)(3)(iii)) | 80 | 1 | 80 | 2 | 160 |
| Certification of Good Cause (314.91) | 5 | 1 | 5 | 16 | 80 |
| Total | 240 | | | | |

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

The information collection provisions for this interim final rule have been submitted to OMB for emergency review under the Paperwork Reduction Act of 1995. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Interested persons are requested to fax comments regarding the information collection to the Office of Information and Regulatory Affairs, OMB. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: (202) 395-5806, or emailed to OIRA_submission@omb.eop.gov. All comments should be identified with the title, "Applications for Food and Drug Administration Approval to Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance."

VI. Federalism

FDA has analyzed this interim final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VII. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) either electronic or written comments regarding this document. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed 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.

IX. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified all Web site addresses, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**).

1. Institute for Safe Medication Practices. Drug Shortages: National Survey Reveals High Level of Frustration, Low Level of Safety. ISMP Medication Safety Alert. Sept 23, 2010, available at <http://www.ismp.org/newsletters/acutecare/articles/20100923.asp>, accessed December 2011.

2. Executive Order 13588, Reducing Prescription Drug Shortages, October 31, 2011, available at <http://www.gpo.gov/fdsys/pkg/FR-2011-11-03/pdf/2011-28728.pdf> accessed December 2011.

3. Center for Drug Evaluation and Research, Manual of Policies and Procedures 6003.1, Drug Shortage Management, September 26, 2006, available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079936.pdf>, accessed December 2011.

4. Webster's Third New International Dictionary of the English Language Unabridged, 2002, defining "discontinuance."

5. Food and Drug Administration. A Review of FDA's Approach to Medical Product Shortage, October 31, 2011, available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm275051.htm>, accessed December 2011.

6. American Hospital Association. AHA Survey on Drug Shortages, available at <http://www.aha.org/aha/content/2011/pdf/drugshortagesurvey.pdf>, accessed December 2011.

7. Department of Health and Human Services. Assistant Secretary for Planning and Evaluation. Economic Analysis of the Causes of Drug Shortages, October 2011, available at <http://aspe.hhs.gov/sp/reports/2011/DrugShortages/ib.shtml>, accessed December 2011.

8. American Cancer Society. Cancer Facts & Figures 2011. Atlanta: American Cancer Society; 2011, available at <http://www.cancer.org/acs/groups/content/epidemiologysurveillance/documents/document/acspc-029771.pdf>, accessed December 2011.

9. Bureau of Labor Statistics. National Occupational Employment and Wage Estimates. Occupational Employment Statistics, May 2010, available at http://www.bls.gov/oes/current/oes_nat.htm, accessed December 2011.

10. Food and Drug Administration. Letter to Industry, October 31, 2011, available at <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm277675.htm>, accessed December 2011.

11. Small Business Administration. Table of Small Business Size Standards Matched to North American Industry Classification System Codes. November 2010, available at http://www.sba.gov/sites/default/files/Size_Standards_Table.pdf, accessed December 2011.

12. United States Census Bureau. 2007 Economic Census. Sector 31: Manufacturing: General Summary: Industry Statistics for Subsectors and Industries by Employment Size: 2007, available at http://factfinder.census.gov/servlet/IBQTable?_bm=y&-geo_id=&-fds_name=EC0700A1&-ds_name=EC0731SG3&-lang=en, accessed December 2011.

List of Subjects in 21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 314 is amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

■ 1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 356a, 356b, 356c, 371, 374, 379e.

■ 2. In § 314.81, paragraph (b)(3)(iii)(a) is amended by removing the phrase "discontinuing manufacture" and adding in its place the phrase "discontinuance of manufacture"; by revising paragraph (b)(3)(iii)(b); and by adding new paragraph (b)(3)(iii)(d) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(3) * * *

(iii) * * *

(b) Notifications required by paragraph (b)(3)(iii)(a) of this section must be submitted to FDA either electronically or by phone according to instructions on FDA's Drug Shortages Web site at: <http://www.fda.gov/Drugs/DrugSafety/DrugShortages>.

* * * * *

(d) For purposes of this section and § 314.91, the terms "discontinuance" and "sole manufacturer" are defined as follows:

Discontinuance means any interruption in manufacturing of a drug product described in paragraph (b)(3)(iii)(a) of this section 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.

Sole manufacturer means 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.

* * * * *

Dated: December 13, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011-32354 Filed 12-15-11; 8:45 am]

BILLING CODE 4160-01-P

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[TD 9565]

RIN 1545-BG15

Corporate Reorganizations; Guidance on the Measurement of Continuity of Interest

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Final regulations and removal of temporary regulations.

SUMMARY: This document contains final regulations that provide guidance regarding the continuity of interest requirement for corporate reorganizations. The guidance is necessary to establish the date upon which continuity of interest is measured. These regulations affect corporations and their shareholders.

DATES: *Effective Date:* These regulations are effective on December 19, 2011.

Applicability Date: For dates of applicability, see § 1.368-1(e)(9)(ii).

FOR FURTHER INFORMATION CONTACT: Richard Starke at (202) 622-7790 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Background

The Internal Revenue Code of 1986 (Code) provides for general non-recognition treatment for reorganizations described in section 368 of the Code. In addition to satisfying the statutory requirements of a reorganization, a transaction also must satisfy certain non-statutory requirements, such as continuity of interest (COI). COI requires that, in substance, a substantial part of the value of the proprietary interests in the target

corporation be preserved in the reorganization. A proprietary interest in the target corporation is preserved if, in a potential reorganization, it is exchanged for a proprietary interest in the issuing corporation, it is exchanged by the acquiring corporation for a direct interest in the target corporation enterprise, or it otherwise continues as a proprietary interest in the target corporation. See § 1.368-1(e)(1)(i).

On August 10, 2004, the IRS and the Treasury Department published a notice of proposed rulemaking (REG-129706-04, 2004-2 CB 479) in the **Federal Register** (69 FR 48429) (2004 proposed regulations) identifying certain circumstances in which the determination of whether a proprietary interest in the target corporation is preserved would be made by reference to the value of the issuing corporation's stock on the day before there is an agreement to effect the potential reorganization. Specifically, the 2004 proposed regulations provided that, in determining whether a proprietary interest in the target corporation is preserved, the consideration to be exchanged for the proprietary interests in the target corporation pursuant to a contract to effect the potential reorganization is valued on the last business day before the first date such contract is a binding contract (the Pre-Signing Date), if such consideration was fixed at the signing date (the signing date rule). On September 16, 2005, the IRS and the Treasury Department published final regulations (TD 9225, 2005-2 CB 716) in the **Federal Register** (70 FR 54631) (2005 final regulations) that retained the general framework of the 2004 proposed regulations but made several modifications in response to comments received regarding the proposed regulations. After consideration of comments relating to the 2005 final regulations, the IRS and the Treasury Department published temporary (TD 9316, 2007-1 CB 962) and proposed (REG-146247-06, 2007-1 CB 977) regulations in the **Federal Register** (72 FR 12974 and 72 FR 13058 respectively) (the 2007 temporary regulations generally narrowed the definition of fixed consideration, and accordingly, limited the application of the signing date rule. The preamble explained that the signing date rule is based on the principle that, where a binding contract provides for fixed consideration, the target corporation shareholders can generally be viewed as being subject to the economic fortunes of the issuing corporation as of the signing date. However, if the contract

does not provide for fixed consideration, the signing date value of the issuing corporation stock is not relevant for purposes of determining the extent to which a proprietary interest in the target corporation is preserved.

On March 17, 2010, the IRS released Notice 2010-25 (the Notice), 2010-1 CB 527. Notice 2010-25 acknowledged that the 2007 temporary regulations would, as required by sunset provisions of section 7805(e)(2), expire on March 19, 2010. It also noted that proposed regulations (REG-146247-06, 2007-1 CB 977) previously published in the **Federal Register** (72 FR 13058) had the same text as the expiring temporary regulations and would remain outstanding after that expiration. The Notice provided that, until the issuance of new regulations, taxpayers could choose, as long as a specified condition of consistency among parties was satisfied, to apply the rules in the proposed regulations. The ability of taxpayers to elect to apply the rules of the proposed regulations, as provided in the Notice, is incorporated into § 1.368-1(e)(9)(ii), the effective/applicability date of these final regulations. See § 601.601(d)(2)(ii)(b).

Explanation of Revisions

These final regulations adopt the 2007 temporary regulations with only minor changes. First, questions were raised concerning whether a contract can provide for fixed consideration under the general definition of fixed consideration if the contract provides for a shareholder election. These final regulations clarify that a shareholder election does not prevent a contract from satisfying the general definition of fixed consideration if that requirement is otherwise met. Second, *Example 9* is modified to address a more typical fact pattern.

In response to comments regarding the application of the signing date rule and after further consideration of the purpose and operation of that rule, the IRS and the Treasury Department have proposed a regulation, published elsewhere in this issue of the **Federal Register**, under which application of the signing date principles would be expanded. That notice of proposed rulemaking (REG-124627-11) also requests comments regarding the propriety of applying signing date principles more generally to transactions in which the target corporation shareholders, pursuant to a binding contract to effect a potential reorganization, become subject to the economic fortunes of issuing corporation consideration between the signing date and the closing date. In