

session). To be considered, oral comments must be presented during the transcribed portions of the public meetings. The NRC staff will also accept written comments at any time during the public meetings.

Persons interested in presenting oral comments at the December 2, December 4, or December 9 public meetings are encouraged to pre-register. Persons may pre-register to present oral comments at either meeting by calling 301-287-9392 or by emailing WCRegistration@nrc.gov no later than 3 days prior to the meeting. Members of the public may also register in-person to provide oral comments at each meeting. Individual oral comments may be limited by the time available, depending on the number of persons who register.

If special equipment or accommodations are needed to attend or to present information at either public meeting, then the need should be brought to the NRC's attention no later than 10 days prior to the meeting to provide the NRC staff adequate notice to determine whether the request can be accommodated. The meeting agenda and participation details for each meeting will be available on the NRC's Public Meeting Schedule Web site at <http://www.nrc.gov/public-involve/public-meetings/index.cfm> no later than 10 days prior to each meeting.

Dated at Rockville, Maryland, this 29th day of October 2013.

For the Nuclear Regulatory Commission.

Carrie M. Safford,

Deputy Director, Waste Confidence Directorate, Office of Nuclear Material Safety and Safeguards.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 20, 310, 314, and 600

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

RIN 0910-AG88

Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is proposing to amend its regulations to implement certain drug shortages

provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA). The proposed rule would require all applicants of covered approved drugs or biological products—including certain applicants of blood or blood components for transfusion and all manufacturers of covered drugs marketed without an approved application—to notify FDA electronically of a permanent discontinuance or an interruption in manufacturing of the product that is likely to lead to a meaningful disruption in supply (or a significant disruption in supply for blood or blood components) of the product in the United States.

DATES: Submit either electronic or written comments on the provisions of this proposed rule by January 3, 2014. Submit comments on the information collection requirements under the Paperwork Reduction Act of 1995 (the PRA) by December 4, 2013 (see the “Paperwork Reduction Act of 1995” section).

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 PRA must be submitted to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB) (see the “Paperwork Reduction Act of 1995” section).

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:

- Mail/Hand delivery/Courier (for paper 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. 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., Bldg. 51, Rm. 6208, 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.

Table of Contents

I. Executive Summary	
A. Purpose of the Proposed Rule	
B. Summary of the Major Provisions of the Proposed Rule	
C. Summary of the Costs and Benefits of the Proposed Rule	
II. Introduction	
III. Description of the Proposed Rule	
A. Persons Subject to the Proposed Rule	
B. Products Subject to the Proposed Rule	
C. Notification of a Permanent Discontinuance or an Interruption in Manufacturing	
IV. Legal Authority	
V. Analysis of Impacts	
A. Introduction	
B. Summary	
VI. Paperwork Reduction Act of 1995	
VII. Federalism	
VIII. Environmental Impact	
IX. Comments	
X. References	

SUPPLEMENTARY INFORMATION:

I. Executive Summary

A. Purpose of the Proposed Rule

FDASIA (Pub. L. 112-144) significantly amended provisions in the FD&C Act related to drug shortages. Among other things, FDASIA amended section 506C of the FD&C Act (21 U.S.C. 356c) to require all manufacturers of certain drugs to notify FDA of a permanent discontinuance or an interruption in manufacturing of these drugs 6 months in advance of the permanent discontinuance or interruption in manufacturing, or as soon practicable. FDASIA also added section 506E to the FD&C Act (21 U.S.C. 356e) requiring FDA to maintain a current list of drugs that are determined by FDA to be in shortage in the United States, and to include on that public list certain information about those shortages. Finally, FDASIA permits FDA to apply section 506C to biological products by regulation, and requires FDA to issue a final rule implementing

certain drug shortages provisions in FDASIA by January 9, 2014.

In accordance with FDASIA, FDA is issuing this proposed rule, which we believe will improve FDA's ability to identify potential drug shortages and to prevent or mitigate the impact of these shortages.

B. Summary of the Major Provisions of the Proposed Rule

The proposed rule would modify FDA's regulations to implement sections 506C and 506E of the FD&C Act as amended by FDASIA.

Proposed §§ 310.306, 314.81(b)(3)(iii) (21 CFR 314.81(b)(3)(iii)), and 600.82 would require all applicants of certain approved drugs or biological products,¹ including applicants of blood or blood components for transfusion ("blood or blood components") that manufacture a significant percentage of the U.S. blood supply, and all manufacturers of certain drugs marketed without an approved application ("unapproved drug manufacturers"), to notify FDA electronically of a permanent discontinuance or an interruption in manufacturing of the product that is likely to lead to a meaningful disruption in supply (for drugs and biological products other than blood or blood components) or a significant disruption in supply (for blood or blood components) of the product in the United States. Applicants² would be required to notify FDA of a permanent discontinuance or an interruption in supply if the drug or biological product is a prescription product that is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery, and excluding radiopharmaceutical products (referred to in this document as "covered" drugs or biological products). The proposed rule would require notification to FDA at least 6 months prior to date of the permanent discontinuance or

interruption in manufacturing, or, if 6 months' advance notice is not possible, as soon as practicable thereafter, but in no case later than 5 business days after the permanent discontinuance or interruption in manufacturing occurs.

The proposed rule would also require FDA to issue a public noncompliance letter to an applicant for failure to notify FDA under the proposed rule; specify minimum information that must be included in the notification; codify FDA's current practice of publicly disseminating information on shortages and maintaining public lists of drugs and biological products in shortage (subject to certain confidentiality protections); and define the terms, "drug shortage," "biological product shortage," "meaningful disruption," "significant disruption," "life supporting or life sustaining," and "intended for use in the prevention or treatment of a debilitating disease or condition."

Finally, the proposed rule would include a technical revision to § 20.100 (21 CFR 20.100) (public disclosure regulations) to include a cross-reference to the disclosure provisions in §§ 310.306, 314.81, and 600.82; and would remove § 314.91 (21 CFR 314.91) related to reducing the 6-month notification period for "good cause," since it is no longer applicable under the FDASIA-revised section 506C.

C. Summary of the Costs and Benefits of the Proposed Rule

The proposed rule would impose annual reporting costs of up to \$16,576 on those applicants affected by the rule, and up to \$441,000 on FDA in review costs. Undertaking mitigation strategies, as measured by labor resources, is estimated to cost FDA between \$2.44 and \$7.84 million, and industry between \$3.86 and \$12.43 million. We also estimate annual costs for industry between \$8.54 and \$26.89 million associated with increasing production. Estimated total annual costs of the interactions between industry and FDA range between \$14.99 and \$47.62 million. Discounting over 20 years, annual quantified benefits from avoiding the purchase of alternative products, managing product shortages, and life-years gained, would range from \$27.56 million to \$86.77 million using a 3 percent discount rate, and from \$27.50 million to \$86.61 million using a 7 percent discount rate. The public health benefits, mostly nonquantified, include the value of information that would assist FDA, manufacturers, health care providers, and patients in evaluating, mitigating, and preventing shortages of drugs and biological

products that could otherwise result in delayed patient treatment or interruption in clinical trial development.

II. Introduction

Recent experience with shortages of drugs and biological products in the United States has shown the serious and immediate effects they can have on patients and health care providers. According to information from FDA's drug and biological product shortages databases, the number of drug and biological product shortages quadrupled from approximately 61 in 2005 to more than 250 shortages in 2011. Although the number of drug shortages significantly decreased in 2012 to 117 shortages, drug and biological product shortages still represent an ongoing challenge to public health.³ Shortages can involve critical drugs used to treat cancer, to provide required parenteral nutrition, or to address other serious medical conditions and can delay or deny needed care for patients. Shortages can also result in providers prescribing second-line alternatives, which may be less effective or higher risk than first-line therapies.

Preventing drug and biological product shortages is a top priority for FDA. Working closely with manufacturers and other stakeholders, FDA was able to help prevent just under 200 drug and biological product shortages in 2011 and more than 280 such shortages in 2012, using tools such as:

- Working with manufacturers to resolve manufacturing and quality issues contributing to short supply.
- Expediting FDA inspections and reviews of submissions from manufacturers to prevent and/or alleviate shortages.
- Identifying and working with manufacturers willing to initiate or increase production to cover expected gaps in supply.
- Exercising enforcement discretion in appropriate circumstances, if this would not cause undue risk to patients.

In response to the increasing concerns about the impact of shortages on health care in the United States, on October 31, 2011, President Obama issued Executive Order 13588 directing 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

³ Information on drug shortages can be found at <http://www.fda.gov/drugs/drugsafety/drugshortages/default.htm> (drug shortages) and <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm> (biological product shortages).

¹ As used throughout this preamble, the term "biological product" refers to a biological product licensed under section 351 of the Public Health Service Act, other than a biological product that also meets the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

² In this document, for the sake of convenience, we collectively refer to applicants holding an abbreviated new drug application (ANDA), new drug application (NDA), or biologics license application (BLA) and unapproved drug manufacturers subject to this proposed rule as the "applicant" (although we recognize that an unapproved drug manufacturer is not an applicant). We may also individually refer to the ANDA, NDA, and BLA applicant or unapproved drug manufacturer as needed, if the context requires distinguishing between these entities.

ensuring that FDA and the public receive adequate advance notice of shortages whenever possible” (Ref. 1 of this proposed rule). In response to the Executive Order’s directive to address the growing problem of drug shortages, FDA published an interim final rule (IFR) on December 19, 2011 (effective January 18, 2012), modifying the regulation at § 314.81 related to drug shortages (76 FR 78530). As a result of the Executive Order and IFR, early notifications to FDA of potential shortages increased from an average of 10 a month before the Executive Order to approximately 60 a month in the months after the IFR. This dramatic increase in early notifications enabled FDA to work with manufacturers to successfully prevent numerous shortages. As we stated above, FDA was able to prevent just under 200 drug and biological product shortages in 2011 and more than 280 such shortages in 2012. Moreover, the number of new drug shortages decreased from more than 250 in 2011 to 117 in 2012—a 50 percent reduction.

In July 2012, FDASIA amended the FD&C Act to modify existing drug shortages requirements and to add new drug shortages provisions. This rule proposes to implement the drug shortages provisions of FDASIA, and, when final, will supersede the IFR. Although many of the issues raised by the 11 comments we received on the IFR are no longer directly applicable to this rulemaking given the changes to the underlying statute made by FDASIA, when drafting this proposed rule we considered these comments to the extent that they were applicable.⁴ Where appropriate, we have summarized and responded to the IFR comments in this preamble.

III. Description of the Proposed Rule

Section 1001 of FDASIA made substantial changes to section 506C of the FD&C Act related to reporting and addressing “permanent discontinuances” or “interruptions in manufacturing” of certain drug products. Most significantly for purposes of this proposed rule, section 506C of the FD&C Act as amended:

- Requires all manufacturers of a prescription drug that is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery, and excluding radiopharmaceutical products, to notify FDA of a permanent discontinuance in the manufacture of the drug or an interruption in the manufacturing of the drug that is likely to lead to a meaningful disruption in the supply of that drug in the United States at least 6 months prior to the date of the permanent discontinuance or interruption in manufacturing, or, if that is not possible, as soon as practicable.
- Requires the manufacturer to include in the notification the reason for the permanent discontinuance or interruption in manufacturing.
- Requires FDA to issue a letter to a “person” who fails to comply with the notification requirements in section 506C.
- Defines the terms “drug,” “drug shortage,” and “meaningful disruption,” and requires FDA to define the terms “life supporting,” “life sustaining,” and “intended for use in the prevention or treatment of a debilitating disease or condition.”
- Permits FDA to apply section 506C to biological products, including vaccines and plasma-derived products

and their recombinant analogs, if FDA determines the inclusion would benefit public health, taking into account existing supply reporting programs and aiming to reduce duplicative notifications.

- Requires FDA to distribute information on drug shortages to the public, to the maximum extent possible, subject to certain confidentiality protections.

In addition to modifying section 506C, FDASIA added several new drug shortage-related sections to the FD&C Act, including section 506E. Section 506E of the FD&C Act requires FDA to maintain an up-to-date list of drugs that are determined by FDA to be in shortage, including the names and the National Drug Codes (NDCs) of such drugs in shortage, the name of each manufacturer of the drug, the reason for each shortage as determined by FDA (choosing from a list of reasons enumerated in the statute), and the estimated duration of each shortage. Section 506E of the FD&C Act also includes confidentiality provisions.

This rule proposes to implement sections 506C and 506E of the FD&C Act by amending § 314.81(b)(3)(iii) (permanent discontinuance or interruption in manufacturing of approved prescription drugs) and § 20.100 (cross-reference to disclosure provisions); adding new § 310.306 (permanent discontinuance or interruption in manufacturing of marketed prescription unapproved new drugs) and § 600.82 (permanent discontinuance or interruption in manufacturing of prescription biological products); and removing § 314.91 (reduction in the discontinuance notification period). Table 1 compares the proposed rule to the current regulation (IFR).

TABLE 1—CURRENT REGULATION (IFR) COMPARED WITH PROPOSED RULE

Requirement	Current regulation (IFR)	Proposed rule
Scope of products subject to notification requirements.	<p>§ 314.81(b)(3)(iii)(a)</p> <p>A drug product approved under an NDA or ANDA that is:</p> <ul style="list-style-type: none"> • Life supporting, life sustaining or intended for use in the prevention of a serious disease or condition; and • Not originally derived from human tissue and replaced by a recombinant product. 	<p>§ 310.306.</p> <p>§ 314.81(b)(3)(iii)(a) and (f).</p> <p>§ 600.82(a) and (f).</p> <p>All prescription drugs and biological products, including marketed unapproved prescription drugs, that are:</p> <ul style="list-style-type: none"> • Life supporting, life sustaining or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery; and • That are not radiopharmaceutical products.⁵

⁴ The IFR comments are available electronically at <http://www.regulations.gov>, Docket No. FDA-2011-N-0898, or can be obtained in person at the

Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

⁵ With respect to blood and blood components for transfusion, the reporting requirement applies only to an applicant that manufactures a significant percentage of the U.S. blood supply.

TABLE 1—CURRENT REGULATION (IFR) COMPARED WITH PROPOSED RULE—Continued

Requirement	Current regulation (IFR)	Proposed rule
What triggers notification	<p>§ 314.81(b)(3)(iii)(a) and (d)</p> <p>A “discontinuance,” defined as “any interruption in manufacturing . . . that could lead to a potential disruption in supply of the drug product [in the United States], whether the interruption is intended to be temporary or permanent”.</p>	<p>The terms “life supporting or life sustaining” and “intended for use in the prevention or treatment of a debilitating disease or condition” are defined in the proposed rule.</p> <p>§ 314.81(b)(3)(iii)(a) and (f). § 600.82(a)(1) and (f).</p> <p>For products other than blood or blood components, a “permanent discontinuance” or an “interruption in manufacturing that is likely to lead to a meaningful disruption in supply of the product in the United States”; “meaningful disruption” is defined in the statute and the proposed rule.</p> <p>§ 600.82(a)(2) and (f).</p> <p>For blood or blood components, a “permanent discontinuance” or an “interruption in manufacturing that is likely to lead to a significant disruption in supply of the product in the United States”; “significant disruption” is defined in the proposed rule.</p>
Who must notify FDA	<p>§ 314.81(b)(3)(iii)(a) and (d)</p> <p>Applicants who are sole manufacturers of covered drugs; sole manufacturer is defined in the regulation.</p>	<p>§ 314.81(b)(3)(iii)(a). § 600.82(a).</p> <p>All applicants for covered, approved drugs and biological products (other than blood or blood components), all applicants for blood or blood components that manufacture a significant percentage of the U.S. blood supply, and all manufacturers of covered drugs marketed without an approved application.</p>
When to notify FDA	<p>§ 314.81(b)(3)(iii)(a)</p> <p>At least 6 months prior to the discontinuance. § 314.91</p> <p>Applicants may seek, and FDA may grant, a reduction in the 6-month notification period for “good cause.”</p>	<p>§ 314.81(b)(3)(iii)(b). § 600.82(b).</p> <ul style="list-style-type: none"> • At least 6 months prior to the permanent discontinuance or interruption in manufacturing; or • If notification at least 6 months prior is impossible, “as soon as practicable,” which is further described in the proposed rule. • Deletes § 314.91 in its entirety, because it is no longer applicable under section 506C of the FD&C Act as amended by FDASIA.
How to notify FDA	<p>§ 314.81(b)(3)(iii)(b)</p> <p>Electronically or by phone, according to instructions on FDA’s drug shortages Web page.</p>	<p>§ 314.81(b)(3)(iii)(b). § 600.82(b).</p> <p>Electronically in a format FDA can process, review, and archive.</p>
What to include in the notification.	<p>Not specified</p>	<p>§ 314.81(b)(3)(iii)(c). § 600.82(c).</p> <ul style="list-style-type: none"> • Name, NDC (or, for certain biological products, an alternative, as applicable), and applicant of the product; • Whether the notification is a permanent discontinuance or an interruption in manufacturing; • A description of the reason for the permanent discontinuance or interruption in manufacturing; and Estimated duration of the interruption in manufacturing.
Dissemination of information	<p>§ 314.81(b)(3)(iii)(c)</p> <p>FDA will publicly disclose a list of all drug products discontinued under § 314.81(b)(3)(iii)(a).</p>	<p>§ 310.306(c). § 314.81(b)(3)(iii)(c). § 600.82(c).</p> <p>FDA will maintain public lists of drugs and biological products determined by FDA to be in shortage, including the names, NDCs (or, for certain biological products, an alternative, as applicable), and each applicant of the product (or, for marketed unapproved prescription drugs, each manufacturer of the product); the reason for the shortage; and the estimated duration of the shortage.</p>
Confidentiality	<p>Not specified in regulation, but information submitted to FDA under the regulation is subject to protections for trade secrets and confidential commercial and financial information where applicable.</p>	<p>§ 314.81(b)(3)(iii)(d) § 600.82(d)</p> <p>Includes specific reference to protection of trade secrets and confidential commercial information submitted to FDA under the proposed rule and allows FDA to choose not to make certain other information public if it determines that would adversely affect the public health.</p>
	<p>No equivalent provision</p>	<p>§ 20.100(c)(45).</p>

TABLE 1—CURRENT REGULATION (IFR) COMPARED WITH PROPOSED RULE—Continued

Requirement	Current regulation (IFR)	Proposed rule
Noncompliance	No equivalent provision	Cross-reference to disclosure provisions in §§ 310.306, 314.81, and 600.82. § 310.306(b). § 314.81(b)(3)(iii)(e). § 600.82(e). If an applicant of a covered drug or biological product, or manufacturer of a covered, marketed unapproved prescription drug, fails to submit a notification required under the proposed rule within the required timeframe, FDA will issue a publicly available non-compliance letter to the applicant or unapproved drug manufacturer.

A. Persons Subject to the Proposed Rule

Proposed §§ 310.306, 314.81(b)(3)(iii), and 600.82 would require notification to FDA of a permanent discontinuance or an interruption in manufacturing of a covered drug or biological product. Under the proposed rule, the following persons would be subject to these notification requirements:

- All applicants with an approved NDA or ANDA for a covered drug product (proposed § 314.81(b)(3)(iii)).
- All applicants with an approved BLA for a covered biological product, other than blood or blood components (proposed § 600.82(a)(1)).
- Applicants with an approved BLA for blood or blood components, if the applicant is a manufacturer of a significant percentage of the U.S. blood supply (proposed § 600.82(a)(2)).
- All manufacturers of a covered drug product marketed without an approved NDA or ANDA (proposed § 310.306, which applies § 314.81(b)(3)(iii) in its entirety to covered drug products marketed without an approved NDA or ANDA).

Section 506C of the FD&C Act as amended by FDASIA requires a “manufacturer” to notify FDA of a permanent discontinuance or an interruption in manufacturing. The proposed rule would require the ANDA, NDA, or BLA applicant (for approved drugs or biological products) or the unapproved drug manufacturer (for marketed, unapproved drugs) to notify FDA of a permanent discontinuance or an interruption in manufacturing.

For purposes of section 506C of the FD&C Act, under the proposed rule an ANDA, NDA, or BLA applicant would be considered the manufacturer of an approved, covered product, even if the ANDA, NDA, or BLA applicant contracts that function out to another entity. In other words, the proposed rule makes clear that for approved, covered drugs and biological products, the ANDA, NDA, or BLA applicant bears

the responsibility for reporting to FDA a permanent discontinuance or an interruption in manufacturing, whether the product is manufactured by the applicant itself or for the applicant under contract with one or more different entities.

As such, the ANDA, NDA, or BLA applicant should establish a process with any relevant contract manufacturer, active pharmaceutical ingredient (API) supplier, or other nonapplicant that ensures the applicant’s compliance with this proposed rule. For example, assume that Applicant X holds an ANDA, NDA, or BLA for a covered drug or biological product and contracts with a third party to manufacture the drug or biological product for the purposes of marketing and selling the drug or biological product in the United States. If the third party contract manufacturer experiences a manufacturing issue that results in a permanent discontinuance or an interruption in manufacturing of Applicant X’s product that would be reportable under proposed § 314.81(b)(3)(iii) or § 600.82, Applicant X, not the contract manufacturer, must notify FDA of this permanent discontinuance or interruption in manufacturing. Therefore, Applicant X should establish a process with the contract manufacturer that ensures Applicant X’s ability to timely report to FDA the permanent discontinuance or interruption in manufacturing.

Section 506C(j)(3) of the FD&C Act, as amended by FDASIA, directs FDA to “take into account any supply reporting programs [for biological products] and . . . aim to reduce duplicative notification” in applying section 506C to biological products by regulation. Accordingly, with respect to blood or blood components, we are proposing to limit this rule only to applicants that are manufacturers of a “significant percentage of the United States blood supply.” As described more fully in

sections II.B.2.c and II.C.1.b.ii, FDA believes that this approach with respect to blood or blood components will ensure that the Agency receives information that is essential to preventing shortages of these products, without being unnecessarily duplicative of existing systems or unduly burdensome to industry. For purposes of this proposed rule, FDA intends to consider an applicant that holds a BLA for blood or blood components to be a manufacturer of a “significant percentage” of the U.S. blood supply if the applicant manufactures 10 percent or more of the U.S. blood supply (e.g., greater than 1.5 million units of whole blood annually or approximately 125,000 units per month).

B. Products Subject to the Proposed Rule

1. Prescription Drug and Biological Products That Are Life Supporting, Life Sustaining, or Intended for Use in the Prevention or Treatment of a Debilitating Disease or Condition

The proposed rule would apply to all prescription drug products approved under an NDA or ANDA (proposed § 314.81(b)(3)(iii)), all marketed unapproved prescription drug products (proposed § 310.306), and all prescription biological products approved under a BLA (proposed § 600.82) that are:

- Life supporting; life sustaining; or intended for use in the prevention or treatment of a debilitating disease or condition, including any such product used in emergency medical care or during surgery; and
 - not radiopharmaceutical products.⁶
- FDASIA does not define the terms “life supporting,” “life sustaining,” or “intended for use in the prevention or treatment of a debilitating disease or

⁶ With respect to blood and blood components for transfusion, the reporting requirement applies only to an applicant that manufactures a significant percentage of the U.S. blood supply.

condition,” but instead requires FDA to define them. Proposed §§ 314.81(b)(3)(iii)(f) and 600.82(f) would define a “life supporting or life sustaining” drug product as one that is “essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.” This definition of “life supporting” or “life sustaining” is consistent with language used to describe this term in the preamble to the final rule implementing the pre-FDASIA section 506C (72 FR 58993 at 58994 (October 18, 2007)), and in medical device regulations (see 21 CFR 821.3(g)).

Under the proposed rule, “intended for use in the prevention or treatment of a debilitating disease or condition” would refer to “a drug product intended for use in the prevention or treatment of a disease or condition associated with mortality or morbidity that has a substantial impact on day-to-day functioning” (proposed §§ 314.81(b)(3)(iii)(f) and 600.82(f)). We have equated “debilitating disease or condition” with “serious disease or condition” under this proposed definition and defined it according to the definition of “serious” found in 21 CFR 312.300. This definition of “intended for use in the prevention or treatment of a debilitating disease or condition” is also consistent with our discussion of the term in the preamble to the proposed rule implementing the pre-FDASIA section 506C (65 FR 66665 at 66666 (November 7, 2000)).

When defining these terms, we also took into account comments we received on the IFR, including: A request for additional clarity on how these terms relate to FDA’s use of the term “medically necessary” with respect to drug and biological product shortages; comments recommending that FDA interpret this terminology to require notification for “medicines at risk of being in shortage”; and a related comment suggesting that once FDA identifies “medicines at risk of being in shortage,” the Agency should establish a mechanism for the purchase and storage of advance supplies of drugs on the list. According to this comment, this “government stockpile” could prevent shortages from occurring or mitigate the impact of an unavoidable shortage.

In response to the first comment, the proposed definitions of “life supporting or life sustaining” and “intended for use in the prevention or treatment of a debilitating disease or condition” are, in important respects, different than FDA’s definition of “medically necessary” as used in the context of the existing Center for Drug Evaluation and Research

(CDER) Manual of Policies and Procedures (MAPP) on drug shortages (CDER MAPP 6003.1) (Ref. 2 of this proposed rule). FDA considers a product to be medically necessary under this internal MAPP if “there is no other adequately available drug product that is judged by medical staff to be an appropriate substitute” (Ref. 2 of this proposed rule). Under this proposed rule, the applicant would be required to notify FDA of a permanent discontinuance or an interruption in manufacturing of a drug or biological product that is life supporting, life sustaining, or intended for use in the prevention or treatment of debilitating disease or condition, whether or not the product is considered medically necessary under the MAPP. Under the MAPP, FDA uses the definition of medically necessary to prioritize the Agency’s response to specific shortages or potential shortages and to allocate resources appropriately.

In response to the second group of comments, the proposed rule does not define either “life supporting or life sustaining” or “intended for use in the prevention or treatment of debilitating disease or condition” to mean “medicines at risk of being in shortage,” because shortages are often triggered by factors related to manufacturing and product quality that cannot be anticipated in advance, making it difficult, if not impossible, to accurately predict drugs or biological products that are vulnerable to shortage. This suggested interpretation of these terms would also be inconsistent with the statutory text, which defines drugs subject to the notification provisions by their uses, and contains separate language to explain when risks to supply require a notification.

Finally, in response to the suggestion to create a national stockpile of drugs and biological products vulnerable to shortage, FDA concludes that this is beyond the scope of the current proposal, which is to implement amended sections 506C and 506E of the FD&C Act.

We are interested in comments on the definitions of “life supporting or life-sustaining” and “intended for use in the prevention or treatment of a debilitating disease or condition.” FDA believes these definitions are consistent with the industry’s (and Agency’s) current understanding of the terms, and that more information rather than less is essential for resolving drug shortages. However, we are specifically interested in comments on whether these definitions might unintentionally broaden the scope of reporting to such an extent that the Agency is “over-

notified,” particularly in the context of the requirement for applicants to notify FDA of a meaningful disruption in *the manufacturer’s* supply, without regard to the market as a whole (see section III.C.1. for further discussion on meaningful disruption in supply).

2. Biological Products

Section 506C of the FD&C Act, as amended, states that for purposes of this section the term “drug” does not include biological products as defined in section 351(i) of the Public Health Service Act, unless the Secretary of Health and Human Services (the Secretary) applies section 506C to such products by regulation. Section 506C(i)(3) of the FD&C Act provides that FDA may, by regulation, apply section 506C to biological products, “including plasma products derived from human plasma protein and their recombinant analogs” if “the Secretary determines that such inclusion would benefit the public health,” taking into account “any [existing] supply reporting programs” and aiming to reduce “duplicative notification.” Additionally, FDA may apply section 506C of the FD&C Act to vaccines, but the Secretary must determine whether notification of a vaccine shortage to the Centers for Disease Control and Prevention (CDC) under its “vaccine shortage notification program” could satisfy a vaccine manufacturer’s obligation to notify FDA of a permanent discontinuance or an interruption in manufacturing under section 506C.

We are proposing to apply section 506C of the FD&C Act to all biological products, including recombinant therapeutic proteins, monoclonal antibody products, vaccines, allergenic products, plasma-derived products and their recombinant analogs, blood or blood components, and cellular and gene therapy products. Like drug shortages, shortages of biological products can have serious negative consequences for patients who rely on these products for their treatment. For example, recent shortages of biological products such as agalsidase beta (Fabrazyme), peginterferon alfa-2a (Pegasys), and BCG⁷ Live (Intravesical) (TheraCys) have adversely affected patient care. Fabrazyme is indicated for the treatment of Fabry’s disease, a life shortening, inherited disease caused by a deficiency of alpha-galactosidase A, an enzyme needed to metabolize lipids. The Fabrazyme shortage resulted from contamination at the manufacturing

⁷ BCG is an attenuated live culture preparation of the *Bacillus* of Calmette and Guerin (BCG) strain of *Mycobacterium bovis*.

plant and led to rationing of the product at one-third the recommended dose for current patients using the drug. As a result of the reduced doses, some patients reported a progression of Fabry's disease, including serious adverse events affecting the heart, central nervous system, and kidneys. Similarly, shortages of the antiviral drug Pegasys and the bladder cancer biological drug TheraCys threatened the timely treatment of patients with debilitating diseases, interrupting the continuity (and potentially undercutting the effectiveness) of treatment for patients prescribed these medications as well as preventing new patients from obtaining these medications.

Early notification of a permanent discontinuance or an interruption in the manufacturing of biological products would allow FDA to address, prevent, or mitigate a shortage of these products, greatly benefiting the public health. In addition, for the reasons described in this document, we have determined that requiring manufacturers of biological products to notify FDA under this proposed rule would not duplicate the existing reporting programs of which we are aware.

a. Plasma-derived products and their recombinant analogs. As stated previously, we are proposing to apply section 506C of the FD&C Act to all biological products, including plasma products derived from human plasma protein and their recombinant analogs (referred to in this document as plasma-derived products and their recombinant analogs). With respect to plasma-derived products and their recombinant analogs, FDA recognizes that the Plasma Protein Therapeutics Association (PPTA) has developed a voluntary data system that captures the distribution and supply of five plasma product groups in the United States: Plasma-Derived Factor VIII, Recombinant Factor VIII, Immune Globulin (Ig), Albumin 5%, and Albumin 25%. The PPTA, in consultation with a third party, voluntarily submits a monthly report to FDA of aggregate distribution data for these five product groups. This information provides a picture of the total supply and distribution of these five products in any given month as compared to the last 12 months (see, e.g., <http://www.pptaglobal.org/UserFiles/file/Sept2012PDFviii.pdf>). (FDA has verified the Web sites in this document but is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

FDA recognizes and greatly appreciates the efforts by PPTA to provide plasma product supply

information to FDA and the public. However, in addition to the PPTA system, for several reasons we believe that it would benefit the public health for the Agency to receive direct notification under this proposed rule from all manufacturers of these products. First, the PPTA system does not include all plasma-derived products and their recombinant analogs. FDA has approved many plasma-derived products (and their recombinant analogs) that are not included in the PPTA monthly report, but that would be subject to this proposed rule, such as Rho(D) Immune Globulin and Hepatitis B Immune Globulin; Coagulation Factor VIIa (Recombinant); and Coagulation Factor IX.

Second, the product distribution data is submitted to PPTA (and subsequently to FDA) on a voluntary basis; reporting under this proposed rule would be mandatory. Finally, the PPTA data is aggregate distribution data derived from historical supply and demand. Unlike the notifications proposed under this rule, it is not real-time data, nor does it capture the types of circumstances that would be considered a "permanent discontinuance" or an "interruption in manufacturing" under this proposed rule. Rather, as described previously, the PPTA data provides a snapshot of current aggregate supply as compared to historical supply. It is not intended to identify circumstances that could lead to a future permanent discontinuance or an interruption in manufacturing of all plasma-derived products and their recombinant analogs.

Because the PPTA program, although helpful, does not serve the same purpose as notification under this proposed rule, including plasma-derived products and their recombinant analogs in this rulemaking will not duplicate the PPTA system. FDA believes that including these products within the scope of the proposed rule is essential to FDA's efforts to identify permanent discontinuances and interruptions in manufacturing of these products, and consequently, essential to our efforts to address, prevent, or mitigate shortages of these products.

b. Vaccines. We are proposing to apply section 506C of the FD&C Act to all biological products, including vaccines. Under section 506C(i)(3)(B) of the FD&C Act, if FDA applies section 506C to vaccines, the Secretary must specifically consider whether the notification requirement may be satisfied by submitting a notification to CDC under CDC's "vaccine shortage notification program."

CDC contracts with vaccine manufacturers as part of the Vaccines

for Children (VFC) program.⁸ FDA recognizes that CDC includes language in its contracts with vaccine manufacturers requiring the manufacturer to notify CDC of vaccine supply issues that could affect the manufacturer's ability to fulfill its contract with CDC.⁹

Only certain vaccines are included under the existing CDC program, and thus, only manufacturers of certain vaccines are obligated to provide notification of supply issues to CDC. Based on information from CDC, FDA estimates that approximately 30 percent of vaccines licensed in the United States are not subject to CDC notification, including vaccines for rabies, yellow fever, and typhoid.

Moreover, even for the vaccines that are subject to CDC notification, the information collected is not adequate for purposes of this rule, because the existing CDC program does not require vaccine manufacturers to provide notice 6 months in advance of a permanent discontinuance or interruption in manufacturing. Early notice of permanent discontinuances and interruptions is critically important to the prevention of drug shortages. Although FDA and its HHS partners work together closely on vaccine supply issues, and the current framework for CDC notification is useful for contractual purposes, FDA believes including vaccines within the scope of this rulemaking is necessary to fully support FDA's efforts to identify, address, prevent, or mitigate a vaccine shortage and would not be duplicative of existing notification systems.

c. Blood or blood components for transfusion. We are proposing to apply section 506C of the FD&C Act to blood

⁸ The VFC program is a federally funded program that provides vaccines at no cost to children and adults who might not otherwise be vaccinated because of inability to pay. VFC was created by the Omnibus Budget Reconciliation Act of 1993 as a new entitlement program to be a required part of each state's Medicaid plan. CDC buys vaccines at a discount from the manufacturers and distributes them to awardees—i.e., State health departments and certain local and territorial public health Agencies—who in turn distribute them at no charge to those private physicians' offices and public health clinics registered as VFC providers. (See <http://www.cdc.gov/vaccines/programs/vfc/index.html>.)

⁹ The Biomedical Advanced Research and Development Authority (BARDA), which is responsible for the procurement of certain vaccines related to medical countermeasures, also includes similar language in its procurement contracts. Contracts for the procurement of medical countermeasures against chemical, biological, nuclear, and radiological threat agents (e.g. smallpox and anthrax vaccines) are administered by BARDA, part of the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services (HHS). (See <http://www.hhs.gov/aspr/>.)

or blood components, but in a more limited manner than for other biological products. The proposed rule would require blood or blood component applicants (i.e., blood collection establishments subject to licensure) that manufacture a significant percentage of the U.S. blood supply to notify FDA of a permanent discontinuance or an interruption in manufacturing that is likely to lead to a “significant disruption” in the applicant’s supply of blood or blood components. As described more fully in sections II.A and II.C.1.b.ii, the proposed rule is intended to require reporting of large-scale, permanent discontinuances, or interruptions in manufacturing of blood or blood components.

The proposed rule would ensure that FDA receives information essential to the Agency in preventing, mitigating, or addressing shortages of blood or blood components, while avoiding duplication with existing programs that monitor local and regional supplies of blood or blood components by ABO blood group. We are aware of two significant efforts to monitor local and regional supplies of blood or blood components.

i. America’s Blood Centers and the Blood Availability and Safety Information System. America’s Blood Centers (ABC) is a network of nonprofit community blood centers in North America. ABC members operate more than 600 blood collection sites in 45 states and provide blood or blood components to more than 3,500 hospitals and health care facilities. ABC also maintains a voluntary supply monitoring program for blood and blood components. Information on local and regional blood supply is provided weekly to ABC members nationwide through a newsletter, and online (see <http://www.americasblood.org/stopligh.aspx>). In addition, ABC and certain other large licensed blood establishments provide voluntary, daily blood supply reports to HHS, which maintains a system called the Blood Availability and Safety Information System (BASIS) (see <https://www.usbloodreport.net/About.aspx>). Certain sentinel hospitals also voluntarily provide inventory reports to the BASIS system, and these data are compiled into a weekly status report on blood supplies, stratified by ABO blood group. Upon request, FDA receives BASIS reports from HHS.

The ABC and BASIS systems monitor the supply and demand of blood or blood components on a daily and weekly basis, and in the event of a national disaster. In other words, ABC and BASIS are tools for local blood centers and hospitals to track their day-

to-day inventory of blood or blood components. Unlike the notifications required under this proposed rule, ABC and BASIS are not designed to predict large-scale or nationwide disruptions in the supply of blood or blood components. Moreover, ABC and BASIS are voluntary systems; the proposed rule would require mandatory reporting.

ii. Task Force. Also critical to the management of the national blood supply is the coordinating function of the Interorganizational Task Force on Domestic Disasters and Acts of Terrorism (Task Force), which is managed by the AABB (formerly the American Association of Blood Banks). The Task Force was formed in January 2002 to help make certain that blood collection efforts resulting from domestic disasters and acts of terrorism are managed properly, and to deliver clear and consistent messages to the public regarding the status of the U.S. blood supply. The Task Force is comprised of representatives from blood establishments, trade associations, commercial entities, and liaisons from governmental Agencies (including FDA), who work together to ensure that adequate blood inventories are in place at all times. In addition, the Task Force operates a system for assessing the need for collections and transportation of blood components, should a disaster or act of terrorism occur.

Again, the Task Force efforts, although critical to public health, are focused on inventory management and are not intended to predict large-scale disruptions in the supply of blood or blood components. The Task Force coordinates the movement of blood throughout the United States and appeals to the public for blood donations, but it is not sufficient for FDA in the context of predicting a permanent discontinuance or an interruption in manufacturing of these products that would have a large-scale impact.

In short, although the information already available to FDA from the ABC, BASIS, and Task Force programs is useful, the existing frameworks are voluntary, do not result in a direct notification from an applicant to FDA, and, as explained previously, only capture short-term, day-to-day supply and distribution information. In addition, in contrast to this proposed rule, the existing systems are not equipped to predict large-scale, significant disruptions of blood or blood components. Accordingly, FDA has determined that including blood or blood components within the scope of this rule would benefit the public health, providing information that is

essential to FDA’s efforts to address shortages of these products.

However, recognizing that the existing ABC, BASIS, and Task Force programs do provide certain information concerning the supply of blood or blood components, we have limited the proposed reporting requirements to apply only to applicants of blood or blood components that manufacture a significant percentage of the U.S. blood supply, and only to a permanent discontinuance of manufacture or an interruption in manufacturing that is likely to lead to a “significant disruption” in supply of that blood or blood component, as further described in sections II.A and II.C.1.

d. Distribution reports (for all biological products). Under § 600.81 (21 CFR 600.81), applicants are required to submit to the Center for Biologics Evaluation and Research (CBER) or CDER, information about the quantity of product distributed under the biologics license, including the quantity distributed to distributors. As part of this safety reporting requirement, manufacturers provide distribution data to FDA every 6 months or at other intervals as may be required by FDA. Although distribution reports submitted by applicants are helpful in the analysis of safety reporting data, particularly for newly approved products, these reports do not include information about a permanent discontinuance or an interruption of the manufacture of a biological product that is likely to lead to a meaningful disruption in the supply of that product. Furthermore, the production cycles of biological products vary widely (e.g., some are manufactured once a year, some are manufactured every other year, and some are manufactured more or less frequently), such that any distribution data received from the manufacturer at 6-month intervals for such products will not be current. Therefore, FDA has determined that the reporting requirements under § 600.81 do not constitute a duplicate supply reporting program.

In summary, we are proposing to apply section 506C of the FD&C Act to all biological products. For the reasons discussed in this document, FDA finds that this inclusion would benefit the public health by facilitating prompt FDA action to address, prevent, or mitigate drug shortages, without duplicating existing reporting programs or creating redundant reporting. With respect to vaccines, for the reasons already described, we have determined that notification to CDC is not sufficient for purposes of reporting to FDA under

section 506C of the FD&C Act and may not replace section 506C notifications.

3. Scope of the Term “Product”

For purposes of this proposed rule, “product” refers to a specific strength, dosage form, or route of administration of a drug or biological product. For example, if Applicant X experiences an interruption in manufacturing of the 50-milligram (mg) strength of a drug product that would be subject to proposed § 314.81(b)(3)(iii), but the 100 mg strength continues to be manufactured without delay, under the proposed rule, Applicant X must notify FDA of the interruption in manufacturing of the 50 mg strength if the interruption is likely to lead to a meaningful disruption in the applicant’s supply of the 50 mg strength. Recent experience has shown that the permanent discontinuance or interruption in manufacturing of a specific strength, dosage form, or route of administration of a drug or biological product can have a significant impact on the targeted needs of particular patients (e.g., although the 100 mg tablet from Applicant X is available, it may not be split in half easily for a patient that is prescribed the 50 mg strength).

Moreover, shortages of a specific strength, dosage form, or route of administration may lead to a shortage of another strength, dosage form, or route of administration of the product, exacerbating patient difficulties in acquiring the product. Obtaining this information is consistent with the emphasis in the IFR on the importance of notifying FDA of permanent or temporary interruptions in supply of a specific strength, dosage form, or route of administration of covered products (76 FR 78530 at 78533), and with the general support for this approach we received in comments on the IFR.

C. Notification of a Permanent Discontinuance or an Interruption in Manufacturing

1. Notification

a. Permanent discontinuance. Section 506C of the FD&C Act requires manufacturers to notify FDA of a permanent discontinuance of manufacture of a covered drug. Proposed §§ 314.81(b)(3)(iii) and 600.82 would require the applicant to report all permanent discontinuances of covered drugs and biological products to FDA. For purposes of this rule, we are interpreting a permanent discontinuance to be a decision by the applicant for business or other reasons to cease manufacturing and distributing the product indefinitely.

b. Interruption in manufacturing. In addition to permanent discontinuances, section 506C of the FD&C Act requires manufacturers to notify FDA of an interruption in manufacturing of a covered drug that is likely to lead to a meaningful disruption in supply of that drug in the United States. The statute defines “meaningful disruption” to mean “a change in production that is reasonably likely to lead to a reduction in the supply of a drug by a manufacturer that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for its product; and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time” (emphasis added).

i. Drugs and biological products other than blood or blood components. Proposed §§ 314.81(b)(3)(iii)(a) and 600.82(a)(1) would require the applicant for a product other than blood or blood components to report to FDA an interruption in manufacturing of the drug or biological product that is likely to lead to a meaningful disruption in supply of that drug or biological product in the United States. Proposed §§ 314.81(b)(3)(iii)(f) and 600.82(f) would adopt the statutory definition of meaningful disruption in supply.

Consistent with the statutory definition of meaningful disruption, the proposed rule would require an applicant to report an interruption in manufacturing likely to lead to a meaningful disruption in its *own supply* of a covered drug or biological product. In other words, when evaluating whether an interruption in manufacturing is reportable to FDA under this proposed rule, rather than considering the potential impact of the interruption on the market as a whole, the relevant question (regardless of how large or small the applicant’s market share may be) is whether the interruption is likely to lead to a reduction in the applicant’s supply of a covered drug or biological product that is more than negligible, and affects the ability of the applicant to fill its own orders or meet the expected demand of its clients for the covered product. Consistent with the statute, the proposed rule would not require an applicant to predict the market-wide impact of its own interruption in manufacturing, which can be difficult to accurately assess and could lead to inconsistent interpretation of the regulation, less accurate predictions,

and under- or reporting, as suggested by multiple comments on the IFR.

Under the proposed rule, reportable discontinuances or interruptions in manufacturing of a covered drug or biological product would include:

- A business decision to permanently discontinue manufacture of a covered drug or biological product.
 - A delay in acquiring APIs or inactive ingredients that is likely to lead to a meaningful disruption in the applicant’s supply of a covered drug or biological product while alternative API suppliers are located.
 - Equipment failure or contamination affecting the quality of a covered drug or biological product that necessitates an interruption in manufacturing while the equipment is repaired or the contamination issue is addressed and that is likely to lead to a meaningful disruption in the applicant’s supply of the product.
 - Manufacturing shutdowns for maintenance or other routine matters, if the shutdown extends for longer than anticipated or otherwise is likely to lead to a meaningful disruption in the applicant’s supply of a covered drug or biological product.
 - A merger of firms or transfer of an application for a covered drug or biological product to a new firm, if the merger or transfer is likely to lead to a meaningful disruption in the applicant’s supply of the product.
 - An interruption in manufacturing (e.g., contamination of a manufacturing line) that in the applicant’s view may not meaningfully disrupt the market-wide supply of the covered drug or biological product (for example, because the applicant holds only a small share of the market for the product), but that the applicant determines is likely to lead to a meaningful disruption in its own supply of the covered product.
- Conversely, an applicant would not be required under the proposed rule to notify FDA if an interruption in manufacturing is not likely to lead to a meaningful disruption in the applicant’s supply of the drug or biological product. For example, FDA would not need to be notified in the following circumstances:
- A scheduled shutdown of an applicant’s manufacturing facility for routine maintenance, if the shutdown is anticipated and planned for in advance; and therefore, is not expected to lead to a meaningful disruption in the applicant’s supply of a covered drug or biological product.
 - An unexpected power outage that results in an unscheduled interruption in manufacturing of a covered drug or biological product, if the applicant expects to resume normal operations

within a relatively short timeframe and does not expect to experience a meaningful disruption in its supply of the covered drug or biological product.

In either of these circumstances, if the interruption in manufacturing subsequently appears likely to lead to a meaningful disruption in the applicant's supply of the covered drug or biological product, then it would become a reportable interruption in manufacturing under this proposed rule and the applicant would be required to notify FDA.

The list of examples described in this document is intended to assist industry in understanding what would (or would not) be required to be reported under amended section 506C of the FD&C Act, but it is not exhaustive. The proposed rule would require *any* permanent discontinuance or *any* interruption in manufacturing that is likely to lead to a meaningful disruption in the applicant's supply of a covered drug or biological product to be reported to FDA, even if not specifically described in this preamble.

ii. Blood or blood components for transfusion. Proposed § 600.82(a)(2) would require an applicant that manufactures a significant percentage of the U.S. blood supply to report to FDA an interruption in manufacturing of a blood or blood component that is likely to lead to a "significant disruption" in supply of that product in the United States. As we discussed in section II.A, an applicant that manufactures 10 percent or more of the U.S. blood supply (e.g., greater than 1.5 million units of whole blood annually or approximately 125,000 units per month), would be considered to manufacture a significant percentage of the U.S. blood supply for purposes of this proposed rule. Proposed § 600.82(f) defines "significant disruption" to mean "a change in production that is reasonably likely to lead to a reduction in the supply of blood or blood components by a manufacturer that substantially affects the ability of the manufacturer to fill orders or meet expected demand for its product; and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time." This definition of significant disruption closely follows, but is not identical to, the statutory and regulatory definition of meaningful disruption.

For purposes of the proposed rule, FDA intends to consider an interruption in manufacturing that leads to a reduction of 20 percent or more of an

applicant's own supply of blood or blood components over a one-month period to "substantially affect" the ability of the applicant to fill orders or meet expected demand; accordingly, such an interruption would be considered a "significant disruption" in supply. Again, when determining when an interruption in manufacturing is likely to lead to a significant disruption in supply, the blood or blood component applicant should not consider the market as a whole, but rather, should consider only its own supply of product.

The proposed definition of "significant disruption" (interpreted to mean affecting 20 percent or more of an individual applicant's supply over a one-month period) as applied to blood or blood components, in combination with the limitation of the proposed rule only to applicants of blood or blood components that manufacture a significant percentage (10 percent or more) of the nation's blood supply, is intended to avoid duplication with existing programs to monitor the daily and weekly distribution of blood or blood components described in section II.B.2.c. As described in that section, in general, existing programs maintained by ABC, BASIS, and the Task Force monitor and resolve temporary, local shortfalls of a particular ABO blood group or a particular blood component. Accordingly, the definition of "significant disruption" is intended to capture events that are likely to precipitate large-scale disruptions in an applicant's blood supply, and that are unlikely to be identified and corrected by the existing ABC, BASIS, and Task Force programs. The additional limitation of the proposed rule to applicants that manufacture a significant percentage of the nation's blood supply further ensures that reporting to FDA will not unnecessarily duplicate reporting to the ABC, BASIS, and Task Force systems, but still allows FDA to receive information that is essential to the Agency in preventing large-scale shortages of these products.

Under the proposed rule, circumstances that would trigger notification to FDA of a permanent discontinuance or an interruption in manufacturing of blood or blood components would include the following examples. We recognize that, with the exception of the first example of a permanent discontinuance, the following interruptions are unlikely to be reasonably anticipated 6 months in advance. In that case they would be reportable as soon as practicable, but in no case later than 5 business days after

the interruption in manufacturing occurs:

- A business decision by an applicant that manufactures 10 percent or more of the nation's blood supply to permanently discontinue manufacture of blood or blood components;
- A computer system failure that causes an applicant of a blood establishment that collects 10 percent or more of the nation's blood supply to be unable to label blood for 2 weeks, resulting in a 20 percent monthly shortfall of blood for that applicant;
- An issue with blood collection bags, such that they are unavailable, causing an applicant that manufactures 10 percent or more of the nation's blood supply to experience a 20 percent monthly shortfall in normal production for that applicant;
- An issue with apheresis collection devices that causes an applicant of a blood establishment that collects 10 percent or more of the nation's blood supply to be unable to collect platelets by apheresis, resulting in a 20 percent monthly shortfall in platelet supply for that applicant;
- An explosion or fire that damages a large testing laboratory that performs blood testing for an applicant that manufactures 10 percent or more of the nation's blood supply, resulting in a 20 percent monthly shortfall of blood or blood components for that applicant.

Conversely, a covered blood or blood component applicant would not be required under the proposed rule to notify FDA if an interruption in manufacturing is not likely to lead to a significant disruption in the applicant's supply of blood or blood components. For example, FDA would not need to be notified if a covered blood or blood component applicant experiences a temporary drop in blood donations at one of its local blood donation centers, such that it is unable to fully supply its hospital customers with blood for several days, provided the donation center quickly returns to its normal donation and supply levels and the dip in blood donations is not likely to lead to a 20 percent decrease in the applicant's overall supply of blood over a one-month period. We expect that this type of situation would be identified and resolved through the ABC, BASIS, and Task Force systems (e.g., these systems would identify the issue and locate temporary, alternative blood supplies for the applicant's customers). If such an event does lead to a significant disruption in a covered applicant's supply of blood or blood components, it would need to be reported to FDA under the proposed rule.

Again, the list of examples described in this document is intended to assist industry in understanding what must be reported under amended section 506C of the FD&C Act, but the list is not exhaustive. The proposed rule would require *any* permanent discontinuance or *any* interruption in manufacturing that is likely to lead to a significant disruption (as defined by the proposed rule) in a covered applicant's supply of blood or blood components to be reported to FDA, even if not specifically discussed in this preamble.

c. Consideration of comments to the IFR. Several comments on the IFR suggested alternative ways of defining circumstances that must be reported to FDA under pre-FDASIA section 506C of the FD&C Act. We have considered whether these may be relevant to amended section 506C of the FD&C Act. For example, one comment suggested that historical supply and demand should be considered when determining whether to notify FDA under section 506C of the FD&C Act. Specifically, the comment suggested that notification should only be required if an interruption in manufacturing is expected to affect the supply of the product based on "historical inventory levels and other factors." Another comment suggested that an applicant should be required to report to FDA only after the disruption in supply occurs, for example when it is "unable to ship 90 percent or more of its full quantity of [covered] product as reasonably ordered by its customers for more than 4 weeks." In other words, the applicant should report to FDA if it experiences a 10 percent reduction in supply for a 4-week period. A third comment suggested that notification should be required when an event causes an applicant to predict that patients will be unable to obtain a covered product for a certain, extended period of time (e.g., at the point when an applicant projects that it will be unable to ship the drug or biological product to customers for 8 weeks).

Although we agree that it could be appropriate to consider historical supply and demand or shipping schedules in deciding whether a notification would be required under this proposed rule, we decline to limit the term "interruption in manufacturing that is likely to lead to a meaningful disruption in supply" to consideration only of such factors, and we decline to define the requirement by codifying a preset, numerical threshold. The purpose of FDASIA, and this proposed rule, is to improve FDA's ability to prevent or mitigate the impact of drug and biological product shortages by

broadening the scope of information that the Agency receives regarding permanent discontinuances and interruptions in manufacturing. If reportable circumstances are limited to situations in which a manufacturer is unable to ship a certain percentage of historic demand for a certain period time, or unable to ship at all for a certain period of time, some circumstances that could lead to a shortage may not be reported to FDA, putting the Agency at a disadvantage in addressing those situations.

For example, if notification under this proposed rule is triggered only by the inability of an applicant to ship at least 90 percent of its full quantity of a particular drug product as reasonably ordered by its customers for more than 4 weeks (10 percent reduction in supply), if an applicant were able to ship 92 percent of its supply (i.e., it experiences an 8 percent reduction in supply), the interruption would not be reportable to FDA. Yet this interruption in manufacturing may still have an impact on a patient's ability to obtain the product and could still lead to a product shortage that is "more than negligible."

Instead, this proposed rule defines "meaningful disruption in supply" consistent with the statutory text, and this preamble provides examples of reportable interruptions in manufacturing as illustrations for industry. An applicant may, at its discretion, analyze historical supply and demand and estimate shipping schedules to help determine whether an interruption in manufacturing is likely to lead to a meaningful disruption in supply, but the applicant should not substitute a rigid calculation for a full consideration of all circumstances applicable to determining whether the change in production is reasonably likely to lead to a reduction in supply that is more than negligible and that affects the manufacturer's ability to fill orders or meet expected demand for its product.

2. Timing and Submission of Notification

a. Timing of notification. Section 506C of the FD&C Act requires notification to FDA "(1) at least 6 months prior to the date of the permanent discontinuance or interruption [in manufacturing]; or (2) if compliance with paragraph (1) is not possible, as soon as practicable." Consistent with the statute, proposed §§ 314.81(b)(3)(iii)(b) and 600.82(b) would require an applicant to notify FDA of a permanent discontinuance or an interruption in manufacturing at

least 6 months in advance of the date of the permanent discontinuance or interruption in manufacturing; or, if 6 months' advance notice is not possible, as soon as practicable thereafter, but in no case later than 5 business days after the permanent discontinuance or interruption in manufacturing occurs.

The Agency's most powerful tool for addressing drug and biological product shortages is early notification, which provides lead time for FDA to work with manufacturers and other stakeholders to prevent a shortage or to mitigate the impact of an unavoidable shortage. As such, we expect that applicants would provide 6 months' advance notice whenever possible. In particular, FDA believes that an applicant will generally know of a permanent discontinuance at least 6 months in advance, and in that case the applicant would be required to provide notification of a permanent discontinuance to FDA at least 6 months in advance. We understand that an applicant may not reasonably be able to anticipate certain interruptions in manufacturing that are likely to lead to a meaningful disruption in supply 6 months in advance. For example, if an applicant discovers fungal contamination that requires an immediate, temporary shutdown of its manufacturing plant for a covered product, the applicant will not be able to provide FDA with 6 months' advance notice of the interruption in manufacturing. Instead, the proposed rule would require the applicant to notify FDA "as soon as practicable," but in no case more than 5 business days after the interruption in manufacturing occurs. In this example, the applicant would need to notify FDA as soon as it reasonably anticipates that an interruption in manufacturing caused by fungal contamination is *likely* to result in a meaningful disruption in supply of the applicant's product. The applicant should not wait until it or its manufacturer begins rejecting or delaying fulfillment of orders for the product from available inventory (i.e., the applicant should not wait until the interruption in manufacturing actually begins to disrupt supply and affect patient access to the product).

In our experience, even if it is not possible for an applicant to notify the Agency before a permanent discontinuance or an interruption in manufacturing occurs, it should generally be possible for the applicant to provide notice within a day or two, and it should *always* be possible for the applicant to notify the Agency no later than 5 days after the permanent discontinuance or interruption occurs, even in the event of a natural disaster

or some other catastrophic incident. Accordingly, the 5-day provision in our proposal represents a date certain after which FDA would be able to take action under section 506C(f) of the FD&C Act against an applicant for failure to comply with the notification requirements (see section II.C.5 of this document for further discussion of the consequences of failure to notify FDA). Additionally, an applicant that could have notified the Agency before five days had passed, but waited until the end of the 5-day period would be in violation of the proposed regulation. Consistent with the statutory intent, whenever possible, applicants would be required to provide us with advance notice, whether 6 months' advance notice, or "as soon as practicable" thereafter (e.g., 3 months' advance notice).

b. Submission of notification.

Proposed §§ 314.81(b)(3)(iii)(b) and 600.82(b) would require an applicant to notify FDA of a permanent discontinuance or an interruption in manufacturing electronically in a format FDA can process, review, and archive. Applicants must email notifications to drugshortages@fda.hhs.gov (for products regulated by CDER) or cbershorage@fda.hhs.gov (for products regulated by CBER). In the future, the Agency may consider creating an electronic notification portal linked to the Agency's internal drug shortages database to facilitate submission of these notifications. Unless and until this portal is created, however, email notifications will be used.

c. Reduction in notification period for "good cause". Under the pre-FDASIA section 506C(b), a manufacturer could seek, and FDA could grant, a reduction in the required 6-month advance notification period for "good cause." The statute listed several reasons that would constitute "good cause," including when continuing to manufacture the product for the full 6-month notification period could cause a public health problem or result in substantial economic or legal hardship for the manufacturer. The regulation at § 314.91 implemented the pre-FDASIA section 506C(b). Because section 506C of the FD&C Act as amended by FDASIA does not include an option for formally seeking a reduction in the 6-month advance notification period based on "good cause," this rule proposes to eliminate § 314.91 in its entirety.

3. Contents of the Notification

Proposed §§ 314.81(b)(3)(iii)(c) and 600.82(c) would require an applicant to include the following items in

notifications submitted under section 506C(a) of the FD&C Act:

- The name of the drug or biological product subject to the notification, including the NDC for the drug or biological product (or, for a biological product that does not have an NDC, an alternative standard for identification and labeling that has been recognized as acceptable by the Center Director);
- The name of the applicant of the drug or biological product;
- Whether the notification relates to a permanent discontinuance of the drug or biological product or an interruption in manufacturing of the drug or biological product;
- A description of the reason for the permanent discontinuance or interruption in manufacturing; and
- The estimated duration of the interruption in manufacturing.

FDA is proposing to require applicants to include the minimum information listed in this document in the initial notification to assist the Agency in complying with section 506E of the FD&C Act, which requires FDA to maintain a publicly available list of drugs in shortage, as described in section II.C.4 of this document. We recognize that the duration of an interruption in manufacturing can be difficult to accurately predict. The applicant should provide FDA with its best estimate of the expected duration of the interruption in manufacturing. If, after the initial notification is submitted, the estimated duration changes, the applicant should notify FDA of the new expected duration of the interruption in manufacturing so that FDA can respond appropriately. In addition, the applicant should include a detailed, factual description of the reason for the shortage in the notification to assist FDA in responding to the notification.

In addition to the proposed required elements of the notification, applicants are encouraged to include any other information in the notification that may be helpful to the Agency in working with the applicant to resolve the permanent discontinuance or interruption in manufacturing. Such information could include the applicant's market share, inventory on hand or in distribution channels, allocation procedures and/or plans for releasing available product, copies of communications to patients and providers regarding the shortage (e.g., Dear Healthcare Professional letters), or initial proposals to prevent or mitigate the shortage. As appropriate, the Agency will also follow up with the applicant after the notification is submitted to obtain additional information and to work with the applicant to facilitate

resolution of any shortage or potential shortage.

4. Public Lists of Products in Shortage

Section 506E of the FD&C Act requires FDA to maintain a publicly available list of drugs (and biological products, if FDA applies section 506C to biological products by regulation) that are determined by FDA to be in shortage, including providing the names and NDCs of the drugs, the name of each manufacturer of the drug, the reason(s) for the shortage, and the estimated duration of the shortage. Section 506C(h)(2) of the FD&C Act defines "drug shortage" to mean "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug." For purposes of section 506E of the FD&C Act, under the proposed rule, the ANDA, NDA, or BLA applicant would be considered the manufacturer of an approved drug or biological product, even if the ANDA, NDA, or BLA applicant contracts that function out to another entity.

Section 506E of the FD&C Act further requires FDA to include on the drug shortages list the reason for the shortage, choosing from the following statutory list of categories:

- Requirements relating to complying with current good manufacturing practices (CGMPs);
- Regulatory delay;
- Shortage of an active ingredient;
- Shortage of an inactive ingredient component;
- Discontinuation of the manufacture of the drug;
- Delay in shipping of the drug; and
- Demand increase in the drug.

Consistent with the statute, and with FDA's current practice, under proposed §§ 310.306(b), 314.81(b)(3)(iii)(d), and 600.82(d), FDA would maintain publicly available lists of drugs and biological products that are determined by FDA to be in shortage, whether or not FDA has received a notification under this proposed rule concerning the product in shortage. Proposed §§ 314.81(b)(3)(iii)(f) and 600.82(f) adopt the statutory definition of drug shortage (substituting "biological product shortage" for "drug shortage" in § 600.82(f)). Under the proposed rule, the shortages lists would include the following required statutory elements for drugs or biological products in shortage: Names and NDCs (or the alternative standard for certain biological products) of the drugs or biological products, names of each applicant, reason for each shortage, and estimated duration of each shortage.

If FDA has received a notification under the proposed rule for the drug or biological product, FDA would consider the reason for the shortage supplied by the applicant in its notification, and, where applicable, other relevant information before the Agency, in determining how to categorize the reason for the shortage under the proposed rule. Consistent with the statute, the Agency, not the applicant, would be responsible for determining which categorical reason best fits a particular situation. FDA would generally choose the categorical reason that best fits the applicant's supplied description. To facilitate FDA's determination of the categorical reason for the shortage, under the proposed rule we would expect applicants to supply as many details and facts as possible concerning the reason for the permanent discontinuance or interruption in manufacturing when submitting a 506C notification. This information would also assist FDA in responding quickly to the notification. FDA works proactively with applicants and others experiencing issues that could lead to a product shortage. We are committed to working with industry to address any underlying quality or manufacturing issues, and we seek to avoid shutdowns and long-term interruptions in supply whenever possible to ensure continued patient access to vital safe and effective drugs and biological products.

If FDA has not received a notification under the proposed rule, but becomes aware of a shortage through other means, FDA would consider information before the Agency when determining and choosing the reason for the shortage to be included on the public list.

In addition to the list of statutory reasons for the shortage that FDA may choose from, we are also proposing to add an eighth category, entitled "Other reason." We are proposing to add this category because the Agency believes that some quality or manufacturing problems that result in a shortage may not fit into any of the listed categories in the statute (e.g., not all quality concerns are the result of noncompliance with CGMPs). The Agency would only choose "Other reason" if none of the other listed reasons is applicable. For example, an interruption in manufacturing as a result of a natural disaster or other catastrophic loss would fall into the "Other reason" category. Moreover, as described in this document, although FDA may choose the "Other reason" category, the public shortages list would also include a brief summary of the

reason for the shortage submitted by the applicant, thus providing additional information to the public on the cause of the shortage.

As noted previously, the proposed rule would codify, consistent with FDASIA, FDA's current practice of maintaining public lists of drugs and biological products in shortage, available on FDA's Web site at <http://www.fda.gov/drugs/drugsafety/drugshortages/default.htm> (drug shortages) and <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm> (biological product shortages).

FDA's current drug shortages list was reorganized after the enactment of FDASIA to begin implementing revised section 506E of the FD&C Act. The drug shortages list now includes six categories of information about each drug product on the list: Company (manufacturer of product and contact information); Product (name, strength, formulation, dosage, and NDC); Availability and Estimated Shortage Duration; Related Information (includes applicant's submitted description of reason for shortage); Shortage Reason (FDA-determined reason for the shortage, chosen from the list in proposed §§ 314.81(b)(3)(iii)(d)); and Date Updated (last date FDA updated the information for that particular product). The biological product shortage list includes similar information in fields for Product Name, Reason for Shortage, and Status.

In reformatting and revising the drug shortages list and drafting this proposed rule, we considered several comments on the IFR and other suggestions from stakeholders to improve the Agency's public communication about shortages. We agree that communication between FDA and interested stakeholders, including industry, providers (such as physicians, pharmacists, and nurses), and patients, is an essential component of preventing and mitigating both drug and biological product shortages. FDA updates the drug and biological product shortages lists regularly, and strives to communicate in "real-time" so that patients and providers have the most current data available for planning purposes.

Moreover, consistent with section 506D(d) of the FD&C Act, FDA is encouraging patients, providers, pharmacists, and other nonapplicants to communicate with the Agency about potential shortages or disruptions in supply via one of the following email addresses: drugshortages@fda.hhs.gov or cbershortage@fda.hhs.gov. FDA is already in frequent contact with third

parties to collect and disseminate shortage-related information, and we hope the availability of these dedicated email addresses will further facilitate communication. We are continuing to work diligently to improve our drug and biological product shortages Web sites and to consider new methods for communicating with all stakeholders about shortages. We appreciate suggestions on how to do this more effectively.

5. Confidentiality and Disclosure

In general, as required by section 506C(c) and 506E of the FD&C Act, and as described in this document, FDA will publicly disclose, to the maximum extent possible, information on drug shortages, including information provided by applicants in a notification of a permanent discontinuance or an interruption in manufacturing.

Proposed §§ 314.81(b)(3)(iii)(d) and 600.82(d) contain an exception to these provisions, stating that FDA may choose not to make information collected under the authority of this proposed rule available to the public on the drug or biological product shortages lists or under its general obligation to disseminate drug shortage information under section 506C(c) of the FD&C Act if the Agency determines that disclosure of such information would adversely affect the public health (such as by increasing the possibility of hoarding or other disruption of the availability of the drug or biological product to patients). These proposed provisions closely track the statutory language in sections 506C(c)(3) and 506E(c)(3) of the FD&C Act.

In addition, proposed §§ 310.306(c), 314.81(b)(3)(iii)(d), and 600.82(d) state that FDA will not provide on the public drug or biological product shortages lists or under section 506C(c) of the FD&C Act, information that is protected by 18 U.S.C. 1905 or 5 U.S.C. 552(b)(4), including trade secrets and commercial or financial information that is considered confidential or privileged under 21 CFR 20.61. These proposed provisions would ensure appropriate protection for commercial and trade secret information protected by other Federal law and are consistent with the statutory language in sections 506C(d) and 506E(c)(2) of the FD&C Act, which clarify that the information provisions in sections 506C and 506E do not alter or amend 18 U.S.C. 1905 or 5 U.S.C. 552(b)(4). Additionally, by reference to section 506E of the FD&C Act, the Agency's obligation to disseminate to the public, to the maximum extent possible, drug shortage information under section 506C(c) does not alter or

amend the protections afforded by 18 U.S.C. 1905 or 5 U.S.C. 552(b)(4). FDA is also proposing a technical amendment to § 20.100 to include a cross-reference to §§ 310.306, 314.81, and 600.82. Proposed § 20.100 describes, by cross-reference to other regulations, the rules on public availability of certain specific categories of information.

One comment on the IFR expressed concern that FDA had not discussed how the Agency would preserve the confidentiality of proprietary information reported to FDA in the context of (pre-FDASIA) section 506C notifications. The comment was specifically concerned that as FDA attempts to mitigate a potential drug shortage by contacting manufacturers to increase production, it might reveal confidential information, even if the interruption in manufacturing by the original manufacturer is only temporary. Proposed §§ 314.81(b)(3)(iii)(d) and 600.82(d) are intended to make clear that FDA will adhere to applicable laws to protect trade secrets and confidential commercial information as it works to mitigate or prevent a shortage.

6. Failure To Notify

Proposed §§ 310.306(b), 314.81(b)(iii)(3)(e), and 600.82(e) would require FDA to issue a noncompliance letter to an applicant (or, for a covered, unapproved drug, to a manufacturer) who fails to submit a section 506C notification as required under proposed §§ 314.81(b)(iii)(3)(a) and 600.82(a) within the timeframe stated in proposed §§ 314.81(b)(iii)(3)(b) and 600.82(b). Consistent with the statute, as proposed in this rule, failure to notify FDA would include failure to *timely* notify FDA. For example, if FDA discovers that an applicant did not notify FDA of the permanent discontinuance of a covered drug or biological product 6 months in advance, even though the applicant anticipated the permanent discontinuance 6 months in advance, FDA would issue a noncompliance letter under this proposed rule. Similarly, if FDA determines that an applicant experienced a reportable interruption in manufacturing that it could not reasonably anticipate 6 months in advance, but the applicant failed to notify FDA “as soon as practicable,” the proposed rule would require FDA to issue a noncompliance letter. Refer to section II.C.2.a of this document for a discussion of the required timing for section 506C notifications.

As required by statute, the proposed rule would provide the applicant with 30 days from the date of issuance of the

noncompliance letter to respond to the letter. The applicant’s response must set forth the basis for noncompliance and provide the required notification with the required information. Under the proposed rule, not later than 45 days after the date of issuance of the letter, FDA would make the letter and the applicant’s response public, after appropriate redaction to protect any trade secret or confidential commercial information. FDA would not make the letter and the applicant’s response public if FDA determines, based on the applicant’s response, that the applicant had a reasonable basis for not notifying FDA as required.

IV. Legal Authority

FDA is amending its regulations to implement sections 506C and 506E of the FD&C Act (21 U.S.C. 356c and 356e) as amended by FDASIA. FDA’s authority for this rule also derives from section 701(a) of the FD&C Act (21 U.S.C. 371(a)).

V. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the proposed 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). OMB has determined that this proposed rule may be an economically significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The estimated per notification cost for small business entities, \$224, represents a small percentage of average annual sales (up to 0.10 percent), for all entities covered by the proposed rule. Although the final rule does not require specific mitigation strategies, for firms that choose to implement mitigation or prevention strategies, there could be additional costs of \$112,000 associated with labor resources. For pharmaceutical companies with fewer than 20 workers, these could be 2 to 7.8 percent of average annual sales. In FDA’s experience, 4–5 small business

entities per year have been affected by a shortage. For these companies, the average annual sales was \$17.54 million, and the estimated costs of implementing mitigation or prevention strategies would represent less than 0.64 percent of their average annual sales. The Agency anticipates that the proposed rule will not have a significant economic impact on a substantial number of small entities, and seeks comments on its Initial Regulatory Flexibility Analysis.

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 \$141 million, using the most current (2012) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

B. Summary

The proposed rule would amend FDA’s regulations to implement sections 506C and 506E of the FD&C Act, as amended by FDASIA. The proposed rule would require all applicants of covered, approved drugs or biological products other than blood or blood components, all applicants of blood or blood components that manufacture a significant percentage of the U.S. blood supply, and all manufacturers of covered drugs marketed without an approved application, to notify FDA electronically of a permanent discontinuance or an interruption in manufacturing of the product that is likely to lead to a meaningful disruption in supply (or a significant disruption for blood or blood components) of the product in the United States. Notification would be required 6 months in advance of the permanent discontinuance or interruption in manufacturing, or, if that is not possible, as soon as practicable. The proposed rule also describes how to submit such a notification, the information required to be included in such a notification, the consequences for failure to submit a required notification, the disclosure of shortage-related information, and the meaning of certain terms.

The proposed rule would impose annual costs of up to \$39.34 million on those applicants or entities affected by

the rule, and up to \$8.29 million on FDA associated with reporting and undertaking mitigation strategies. Estimated total annual costs of the interactions between industry and FDA range between \$14.99 million and \$47.62 million. Discounting over 20 years, annual quantified benefits from avoiding the purchase of alternative products, managing product shortages, and life-years gained, would range from \$27.56 million to \$86.77 million using a 3 percent discount rate, and from \$27.50 million to \$86.61 million using a 7 percent discount rate. Annualized over 20 years, net benefits range from

\$12.57 million to \$39.15 million using a 3 percent discount rate, and from \$12.51 million to \$38.99 million using a 7 percent discount rate. The public health benefits, mostly nonquantified, include the value of information that would assist FDA, manufacturers, health care providers, and patients in evaluating, mitigating, and preventing shortages of drugs and biological products that could otherwise result in non-fatal adverse events, errors, delayed patient treatment, or interruption in clinical trial development. The costs and benefits are summarized in table 2. Under the current environment all

notifications provide meaningful information to identify a shortage or to prevent one, but there is uncertainty as to whether the scope of the proposed rule could result in notifications that do not provide information about any shortage and lead to additional costs. FDA seeks comments on this issue.

The full discussion of economic impacts is available in docket FDA-2011-N-0898 and at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm> (Ref. 3 of this proposed rule).

TABLE 2—SUMMARY OF BENEFITS, COSTS AND DISTRIBUTIONAL EFFECTS OF PROPOSED RULE

Category	Primary estimate	Low estimate	High estimate	Year dollars	Discount rate	Period covered	Notes
Benefits							
Annualized Monetized (millions \$/year).	\$57.165 \$57.055	\$27.556 \$27.501	\$86.773 \$86.609	2012 2012	3% 7%	2014–33 2014–33	There is uncertainty surrounding these estimates since some underlying estimates came from non-representative studies. 20–63 preventable shortages per year.
Annualized Quantified	3% 7%	2014–33 2014–33	
Qualitative	Reduction in errors and non-fatal adverse events associated with shortages. Uninterrupted patient access to drugs and biological products necessary for treatment; continued access to drugs used in clinical trial development.						
Costs							
Annualized Monetized (millions \$/year).	\$31.306 \$31.306	\$14.990 \$14.990	\$47.621 \$47.621	2012 2012	3% 7%	2014–33 2014–33	There is uncertainty about potential noise from notifications that might not provide meaningful information, but which could result in additional review costs. In addition, these estimates assume that applicants will participate in mitigation or preventive strategies.
Annualized Quantified	None estimated.						
Qualitative	None estimated.						
Transfers							
Federal Annualized Monetized (millions \$/year).	None estimated.						
Other Annualized Monetized (millions \$/year).	None estimated.						
Effects							
State, Local or Tribal Gov't.	None.						
Small Business	FDA anticipates that when finalized, small business entities covered by the proposed rule will incur small costs, \$224 per notification or up to 0.10 percent of their average annual sales. Although the proposed rule would not require it, some firms may choose to incur additional costs associated with mitigation or prevention strategies.						
Wages	No estimated effect.						
Growth	No estimated effect.						

VI. Paperwork Reduction Act of 1995

This proposed rule contains collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520) (the PRA). A description of these provisions is given below with an 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 the collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for 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 collection 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 collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products; Proposed Rule

Description: Under the proposed rule, applicants with an approved NDA or ANDA for a covered drug product, manufacturers of a covered drug product marketed without an approved application, and applicants with an approved BLA for a covered biological product (including certain applications of blood or blood components) would be required to notify FDA in writing of a permanent discontinuance of the manufacture of the drug or biological product or an interruption in manufacturing of the drug or biological product that is likely to lead to a meaningful disruption in the applicant's supply (or a significant disruption for blood or blood components) of that product. The notification would be required if the drug or biological product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including use in emergency medical care or during surgery, and if the drug or biological product is not a radiopharmaceutical drug product.

The proposed rule would require the notification to include the following information: (1) The name of the drug or

biological product subject to the notification, including the NDC (or, for a biological product that does not have an NDC, an alternative standard for identification and labeling that has been recognized as acceptable by the Center Director); (2) the name of each applicant of the drug or biological product; (3) whether the notification relates to a permanent discontinuance of the drug or biological product or an interruption in manufacturing of the product; (4) a description of the reason for the permanent discontinuance or interruption in manufacturing; and (5) the estimated duration of the interruption in manufacturing.

Under the proposed rule, the notification would be required to be submitted to FDA electronically at least 6 months prior to the date of the permanent discontinuance or interruption in manufacturing. If 6 months' advance notice is not possible because the permanent discontinuance or interruption in manufacturing was unanticipated 6 months in advance, the applicant would be required to notify FDA as soon as practicable, but in no case later than 5 business days after the permanent discontinuance or interruption in manufacturing occurs.

If an applicant fails to submit the required notification, the proposed rule would require FDA to issue a letter informing the applicant or manufacturer of its noncompliance. The applicant would be required to submit to FDA, not later than 30 calendar days after FDA issues the letter, a written response setting forth the basis for noncompliance and providing the required notification.

Description of Respondents: Applicants of prescription drugs and biological products subject to an approved NDA, ANDA, or BLA, and manufacturers of prescription drug products marketed without an approved ANDA or NDA, if the product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including use in emergency medical care or during surgery, and is not a radiopharmaceutical product. If the BLA applicant is a manufacturer of blood or blood components, it is only subject to this rule if it manufactures a significant percentage of the nation's blood supply.

Burden Estimates: Based on the number of drug and biological product shortage related notifications we have seen during the past 12 months, we estimate that annually a total of approximately 75 respondents ("number of respondents" in table 3) would notify us of a permanent discontinuance of the manufacture of a drug or biological

product or an interruption in manufacturing of a drug or biological product that is likely to lead to a meaningful disruption in the respondent's supply of that product under the proposed rule. We estimate that these respondents would submit annually a total of approximately 305 notifications as required under proposed §§ 310.306, 314.81(b)(3)(iii), and 600.82. Approximately 80 of these notifications are notifications that we currently receive under OMB control number 0910–0699 for the IFR, thus we expect to receive approximately 225 new notifications under the proposed rule ("total annual responses" in table 3).¹⁰ We estimate three notifications per respondent, because a respondent may experience multiple discontinuances or interruptions in manufacturing in a year that require notification ("no. of responses per respondent" in table 3). We also estimate that preparing and submitting these notifications to FDA would take approximately 2 hours per respondent ("hours per response" in table 3).

We base these estimates on our experience with the reporting of similar information to FDA since the issuance of the President's Executive Order 13588 of October 31, 2011 (Ref. 1 of this proposed rule), and under the interim final rule entitled "Applications for Food and Drug Administration Approval To Market a New Drug; Revision of Postmarketing Reporting Requirements—Permanent" (76 FR 78530; December 19, 2011), and the draft guidance entitled "Draft Guidance for Industry on Notification to Food and Drug Administration of Issues That May Result in a Prescription Drug Shortage" (77 FR 11550; February 27, 2012).

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

¹⁰This estimate is based on the number of new notifications we would receive under the proposed rule as compared to notifications we currently receive under the IFR. The IFR is our baseline for comparison for purposes of estimating the burden under the PRA, because additional notifications that we may currently receive, but that are not required under the IFR (e.g., as requested in the draft guidance for industry on Notification to the Food and Drug Administration of Issues That May Result in a Prescription Drug Shortage) are not covered under any existing OMB control number, and thus must be captured in this PRA estimate. In contrast, the preliminary analysis of impacts of the proposed rule estimates the costs and benefits of the proposed rule as compared to current practice. As a result of the use of different baselines for comparison, the estimate of new notifications under the PRA does not match the estimate of new notifications included in the preliminary analysis of impacts (see Table 2B of Ref. 3, which estimates the number of new notifications we would receive under the proposed rule, as compared to the number of notifications the Agency receives currently, including all voluntary notifications not specifically required by the IFR).

TABLE 3—ESTIMATED REPORTING BURDEN ¹

	Number of respondents	Number of responses per respondent	Total annual responses	Hours per response	Total hours
Notifications required under proposed §§310.306 (unapproved drugs), 314.81(b)(3)(iii) (products approved under an NDA or ANDA), and 600.82 (products approved under a BLA)	75	3	225	2	450

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

The information collection provisions of this proposed rule have been submitted to OMB for review. Interested persons are requested to fax comments regarding the information collection by December 4, 2013, 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: 202-395-7245, or emailed to oir_submission@omb.eop.gov. All comments should be identified with the title of this information collection and should include the FDA docket number found in brackets in the heading of this document.

VII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized, 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 tentatively concludes that the proposed 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.

VIII. 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.

IX. Comments

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see ADDRESSES). 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, and will be posted to the docket at <http://www.regulations.gov>.

X. References

The following references have been placed 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, and are available electronically at <http://www.regulations.gov>. (FDA has verified all the Web site addresses in this reference section, but we are not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**).

1. 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 November 2012.
2. 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 November 2012.
3. Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis for Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products; Proposed Rule, available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

List of Subjects

21 CFR Part 20

Confidential business information, Courts, Freedom of information, Government employees.

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical

devices, Reporting and recordkeeping requirements.

21 CFR Part 314

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

21 CFR Part 600

Biologics, 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, it is proposed that 21 CFR parts 20, 310, 314, and 600 be amended as follows:

PART 20—PUBLIC INFORMATION

■ 1. The authority citation for 21 CFR part 20 continues to read as follows:

Authority: 5 U.S.C. 552; 18 U.S.C. 1905; 19 U.S.C. 2531–2582; 21 U.S.C. 321–393; 1401–1403; 42 U.S.C. 241, 242, 242a, 242l, 242n, 243, 262, 263, 263b–263n, 264, 265, 300u–300u–5, 300aa–1.

■ 2. Revise § 20.100 by adding paragraph (c)(45) to read as follows:

§ 20.100 Applicability; cross-reference to other regulations.

* * * * *

(c) * * *

(45) Postmarket notifications of a permanent discontinuance or an interruption in manufacturing of certain drugs or biological products, in §§ 310.306, 314.81(b)(3)(iii), and 600.82 of this chapter.

PART 310—NEW DRUGS

■ 3. The authority citation for 21 CFR part 310 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356c, 356e, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

■ 4. Add § 310.306 to subpart D to read as follows:

§ 310.306 Notification of a permanent discontinuance or an interruption in manufacturing of marketed prescription drugs for human use without approved new drug applications.

(a) *Applicability.* Marketed prescription drug products that are not the subject of an approved new drug or abbreviated new drug application are subject to this section.

(b) *Notification of a permanent discontinuance or an interruption in manufacturing.* The manufacturer of each product subject to this section must make the notifications required under § 314.81(b)(3)(iii) of this chapter and otherwise comply with § 314.81(b)(3)(iii) of this chapter. If the manufacturer of a product subject to this section fails to provide notification as required under § 314.81(b)(3)(iii), FDA will send a letter to the manufacturer and otherwise follow the procedures set forth under § 314.81(b)(3)(iii)(e).

(c) *Drug Shortages List.* FDA will include on the drug shortages list required by § 314.81(b)(3)(iii)(d) drug products that are subject to this section that it determines to be in shortage. For such drug products, FDA will provide the names of each manufacturer rather than the names of each applicant. With respect to information collected under this paragraph FDA will observe the confidentiality and disclosure provisions set forth in § 314.81(b)(3)(iii)(d)(2).

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

■ 5. The authority citation for 21 CFR part 314 is revised to read as follows:

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

■ 6. Revise § 314.81 paragraph (b)(3)(iii) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(3) * * *

(iii) *Notification of a permanent discontinuance or an interruption in manufacturing.*

(a) An applicant of a prescription drug product must notify FDA in writing of a permanent discontinuance of manufacture of the drug product or an interruption in manufacturing of the drug product that is likely to lead to a meaningful disruption in supply of that drug in the United States if:

(1) The drug product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in

emergency medical care or during surgery; and

(2) The drug product is not a radiopharmaceutical drug product.

(b) Notifications required by paragraph (b)(3)(iii)(a) of this section must be submitted to FDA electronically in a format that FDA can process, review, and archive:

(1) At least 6 months prior to the date of the permanent discontinuance or interruption in manufacturing; or

(2) If 6 months' advance notice is not possible because the permanent discontinuance or interruption in manufacturing was not reasonably anticipated 6 months in advance, as soon as practicable thereafter, but in no case later than 5 business days after the permanent discontinuance or interruption in manufacturing occurs.

(c) Notifications required by paragraph (b)(3)(iii)(a) of this section must include the following information:

(1) The name of the drug subject to the notification, including the NDC for such drug;

(2) The name of the applicant;

(3) Whether the notification relates to a permanent discontinuance of the drug or an interruption in manufacturing of the drug;

(4) A description of the reason for the permanent discontinuance or interruption in manufacturing; and

(5) The estimated duration of the interruption in manufacturing.

(d)(1) FDA will maintain a publicly available list of drugs that are determined by FDA to be in shortage. This drug shortages list will include the following information:

(i) The names and NDC(s) for such drugs;

(ii) The name of each applicant for such drugs;

(iii) The reason for the shortage, as determined by FDA from the following categories: Requirements related to complying with good manufacturing practices; regulatory delay; shortage of an active ingredient; shortage of an inactive ingredient component; discontinuation of the manufacture of the drug; delay in shipping of the drug; demand increase for the drug; or other reason; and

(iv) The estimated duration of the shortage.

(2) FDA may choose not to make information collected to implement this paragraph available on the drug shortages list or available under section 506C(c) of the FD&C Act if FDA determines that disclosure of such information would adversely affect the public health (such as by increasing the possibility of hoarding or other disruption of the availability of drug to

patients). FDA will also not provide information on the public drug shortages list or under section 506C(c) of the FD&C Act that is protected by 18 U.S.C. 1905 or 5 U.S.C. 552(b)(4), including trade secrets and commercial or financial information that is considered confidential or privileged under § 20.61.

(e) If an applicant fails to submit a notification as required under paragraph (b)(3)(iii)(a) of this section and in accordance with paragraph (b)(3)(iii)(b) of this section, FDA will issue a letter to the applicant informing it of such failure.

(1) Not later than 30 calendar days after the issuance of such a letter, the applicant must submit to FDA a written response setting forth the basis for noncompliance and providing the required notification under paragraph (b)(3)(iii)(a) of this section and including the information required under paragraph (b)(3)(iii)(c) of this section; and

(2) Not later than 45 calendar days after the issuance of a letter under paragraph (b)(3)(iii)(e) of this section, FDA will make the letter and the applicant's response to the letter public, unless, after review of the applicant's response, FDA determines that the applicant had a reasonable basis for not notifying FDA as required under paragraph (b)(3)(iii)(a) of this section.

(f) The following definitions of terms apply to paragraph (b)(3)(iii) of this section:

Drug shortage or *shortage* means a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug.

Intended for use in the prevention or treatment of a debilitating disease or condition means a drug product intended for use in the prevention or treatment of a disease or condition associated with mortality or morbidity that has a substantial impact on day-to-day functioning.

Life supporting or life sustaining means a drug product that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.

Meaningful disruption means a change in production that is reasonably likely to lead to a reduction in the supply of a drug by a manufacturer that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for its product, and does not include interruptions in manufacturing due to matters such as routine maintenance or

insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time.

* * * * *

§ 314.91 [Removed]

■ 7. Remove § 314.91.

PART 600—BIOLOGICAL PRODUCTS: GENERAL

■ 8. The authority citation for 21 CFR part 600 is revised to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 356c, 356e, 360, 360i, 371, 374; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa–25.

■ 9. Add § 600.82 to subpart D to read as follows:

§ 600.82 Notification of a permanent discontinuance or an interruption in manufacturing.

(a) *Notification of a permanent discontinuance or an interruption in manufacturing.*

(1) An applicant of a biological product, other than blood or blood components for transfusion, which is licensed under section 351 of the Public Health Service Act, and which may be dispensed only under prescription under section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(b)(1)), must notify FDA in writing of a permanent discontinuance of manufacture of the biological product or an interruption in manufacturing of the biological product that is likely to lead to a meaningful disruption in supply of that biological product in the United States if:

(i) The biological product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such biological product used in emergency medical care or during surgery; and

(ii) The biological product is not a radiopharmaceutical biological product.

(2) An applicant of blood or blood components for transfusion, which is licensed under section 351 of the Public Health Service Act, and which may be dispensed only under prescription under section 503(b) of the Federal Food, Drug, and Cosmetic Act, must notify FDA in writing of a permanent discontinuance of manufacture of any product listed in its license or an interruption in manufacturing of any such product that is likely to lead to a significant disruption in supply of that product in the United States if:

(i) The product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such

product used in emergency medical care or during surgery; and

(ii) The applicant is a manufacturer of a significant percentage of the U.S. blood supply.

(b) *Submission and timing of notification.* Notifications required by paragraph (a) of this section must be submitted to FDA electronically in a format that FDA can process, review, and archive:

(1) At least 6 months prior to the date of the permanent discontinuance or interruption in manufacturing; or

(2) If 6 months' advance notice is not possible because the permanent discontinuance or interruption in manufacturing was not reasonably anticipated 6 months in advance, as soon as practicable thereafter, but in no case later than 5 business days after such a permanent discontinuance or interruption in manufacturing occurs.

(c) *Information included in notification.* Notifications required by paragraph (a) of this section must include the following information:

(1) The name of the biological product subject to the notification, including the National Drug Code for such biological product, or an alternative standard for identification and labeling that has been recognized as acceptable by the Center Director;

(2) The name of the applicant of the biological product;

(3) Whether the notification relates to a permanent discontinuance of the biological product or an interruption in manufacturing of the biological product;

(4) A description of the reason for the permanent discontinuance or interruption in manufacturing; and

(5) The estimated duration of the interruption in manufacturing.

(d)(1) *Public list of biological product shortages.* FDA will maintain a publicly available list of biological products that are determined by FDA to be in shortage. This biological product shortages list will include the following information:

(i) The names and National Drug Codes for such biological products, or the alternative standards for identification and labeling that have been recognized as acceptable by the Center Director;

(ii) The name of each applicant for such biological products;

(iii) The reason for the shortage, as determined by FDA, selecting from the following categories: Requirements related to complying with good manufacturing practices; regulatory delay; shortage of an active ingredient; shortage of an inactive ingredient component; discontinuation of the manufacture of the biological product;

delay in shipping of the biological product; demand increase for the biological product; or other reason; and

(iv) The estimated duration of the shortage.

(2) *Confidentiality.* FDA may choose not to make information collected to implement this paragraph available on the biological product shortages list or available under section 506C(c) of the FD&C Act if FDA determines that disclosure of such information would adversely affect the public health (such as by increasing the possibility of hoarding or other disruption of the availability of the biological product to patients). FDA will also not provide information on the public shortages list or under section 506C(c) of the FD&C Act that is protected by 18 U.S.C. 1905 or 5 U.S.C. 552(b)(4), including trade secrets and commercial or financial information that is considered confidential or privileged under § 20.61 of this chapter.

(e) *Noncompliance letters.* If an applicant fails to submit a notification as required under paragraph (a) of this section and in accordance with paragraph (b) of this section, FDA will issue a letter to the applicant informing it of such failure.

(1) Not later than 30 calendar days after the issuance of such a letter, the applicant must submit to FDA a written response setting forth the basis for noncompliance and providing the required notification under paragraph (a) of this section and including the information required under paragraph (c) of this section; and

(2) Not later than 45 calendar days after the issuance of a letter under this paragraph, FDA will make the letter and the applicant's response to the letter public, unless, after review of the applicant's response, FDA determines that the applicant had a reasonable basis for not notifying FDA as required under paragraph (a) of this section.

(f) *Definitions.* The following definitions of terms apply to this section:

Biological product shortage or shortage means a period of time when the demand or projected demand for the biological product within the United States exceeds the supply of the biological product.

Intended for use in the prevention or treatment of a debilitating disease or condition means a biological product intended for use in the prevention or treatment of a disease or condition associated with mortality or morbidity that has a substantial impact on day-to-day functioning.

Life supporting or life sustaining means a biological product that is

essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.

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

Significant disruption means a change in production that is reasonably likely to lead to a reduction in the supply of blood or blood components by a manufacturer that substantially affects the ability of the manufacturer to fill orders or meet expected demand for its product, and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the manufacturer expects to resume operations in a short period of time.

Dated: October 28, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013-25956 Filed 10-31-13; 11:15 am]

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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-351]

Schedules of Controlled Substances: Placement of Tramadol Into Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.
ACTION: Notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration (DEA) proposes to place the substance 2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol, its salts, isomers, salts of isomers, and all isomeric configurations of possible forms including tramadol (the term “isomers” includes the optical and geometric isomers) into Schedule IV of the Controlled Substances Act (CSA). This proposed action is based on a recommendation from the Assistant

Secretary for Health of the Department of Health and Human Services (HHS) and an evaluation of all other relevant data by the DEA. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to Schedule IV controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities, or possess) or propose to handle tramadol.

DATES: Interested persons may file written comments on this proposal pursuant to 21 CFR 1308.43(g). Electronic comments must be submitted, and written comments must be postmarked, on or before January 3, 2014. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after midnight Eastern Time on the last day of the comment period.

Interested persons, defined as those “adversely affected or aggrieved by any rule or proposed rule issuable pursuant to section 201 of the Act (21 U.S.C. 811),” 21 CFR 1300.01, may file a request for hearing pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.45 and 1316.47. Requests for hearing, notices of appearance, and waivers of an opportunity for a hearing or to participate in a hearing must be received on or before December 4, 2013.

ADDRESSES: To ensure proper handling of comments, please reference “Docket No. DEA-351” on all electronic and written correspondence. The DEA encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the Web page or attach a file for lengthier comments. Go to <http://www.regulations.gov> and follow the on-line instructions at that site for submitting comments. An electronic copy of this document and supplemental information to this proposed rule are also available at the <http://www.regulations.gov> Web site for easy reference. Paper comments that duplicate electronic submissions are not necessary. All comments submitted to <http://www.regulations.gov> will be posted for public review and are part of the official docket record. Should you, however, wish to submit written comments in lieu of electronic comments, they should be sent via regular or express mail to: Drug Enforcement Administration, Attention: DEA Federal Register Representative/ODW, 8701 Morrisette Drive, Springfield, Virginia 22152. All requests

for hearing must be sent to Drug Enforcement Administration, Attention: Hearing Clerk/LJ, 8701 Morrisette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT:

Ruth A. Carter, Chief, Policy Evaluation and Analysis Section, Office of Diversion Control, Drug Enforcement Administration, 8701 Morrisette Drive, Springfield, Virginia 22152; Telephone (202) 598-6812.

SUPPLEMENTARY INFORMATION: *Posting of*

Public Comments: Please note that comments received in response to this NPRM are considered part of the public record and will be made available for public inspection and posted at <http://www.regulations.gov> and in the DEA’s public docket. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter.

If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made public, you must include the phrase “PERSONAL IDENTIFYING INFORMATION” in the first paragraph of your comment. You must also place all of the personal identifying information you do not want to be made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase “CONFIDENTIAL BUSINESS INFORMATION” in the first paragraph of your comment. You must also prominently identify confidential business information to be redacted within the comment. If a comment has so much confidential business information that it cannot be effectively redacted, all or part of that comment may not be made publicly available.

Comments containing personal identifying information and confidential business information identified and located as set forth above will be made available in redacted form. The Freedom of Information Act (FOIA) applies to all comments received. If you wish to personally inspect the comments and materials received or the supporting documentation the DEA used in preparing the proposed action, these materials will be available for public inspection by appointment. To arrange a viewing, please see the **FOR FURTHER INFORMATION CONTACT** paragraph, above.