



4164-01-P

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: Final rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is amending 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 rule requires 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: The rule is effective [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

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### Executive Summary

#### Purpose of the 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 as 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. FDA believes this final rule will improve FDA's ability to identify potential drug shortages and to prevent or mitigate the impact of these shortages.

## Summary of the Major Provisions of the Rule

The rule modifies FDA's regulations to implement sections 506C and 506E of the FD&C Act as amended by FDASIA. Sections 310.306, 314.81(b)(3)(iii), and 600.82 (21 CFR 310.306, 314.81(b)(3)(iii), and 600.82) require all applicants of certain approved drugs or biological products,<sup>1</sup> including applicants of blood or blood components<sup>2</sup> 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. Applicants<sup>3</sup> are 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 rule requires 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

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<sup>1</sup> As used throughout this document, the term "biological product" refers to a biological product licensed under section 351 of the Public Health Service Act (42 U.S.C. 262), 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)). This rule does not apply to biological products that also meet the definition of a device in section 201(h) of the FD&C Act.

<sup>2</sup> As used throughout this rule, the term "blood and blood components" refers to blood and blood components for transfusion other than Source Plasma, which is outside the scope of this rule.

<sup>3</sup> 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 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.

practicable thereafter, but in no case later than 5 business days after the permanent discontinuance or interruption in manufacturing occurs.

The rule also provides that FDA will issue a noncompliance letter to an applicant for failure to notify FDA under the rule; specifies minimum information that must be included in the notification; codifies 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 defines 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 rule includes 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 removes § 314.91 related to reducing the 6-month notification period for "good cause," since it is no longer applicable under section 506C of the FD&C Act as amended by FDASIA.

#### Summary of the Costs and Benefits of the Rule

The rule imposes annual reporting costs of up to \$16,827 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 \$1.85 and \$5.94 million, and industry between \$2.97 and \$9.55 million. We also estimate annual costs for industry between \$9.57 and \$30.97 million associated with increasing production. Estimated total annual costs of the interactions between industry and FDA range between \$14.54 and \$46.92 million. Discounting over 20 years, annualized quantified benefits from avoiding the purchase of alternative products, managing product shortages, and life-years gained, would range from

\$30.45 million to \$98.65 million using a 3 percent discount rate, and from \$30.39 million to \$98.42 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.

## I. 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 new drug shortages significantly decreased in 2012 to 117 shortages, in 2013 to 44 shortages, and stayed at 44 new shortages in 2014, drug and biological product shortages still represent an ongoing challenge to public health.<sup>4</sup> 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.

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

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<sup>4</sup> Information on product shortages can be found at <http://www.fda.gov/drugs/drugsafety/drugshortages/default.htm> (for products regulated by the Center for Drug Evaluation and Research) and <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm> (for products regulated by the Center for Biologics Evaluation and Research).

supply of lifesaving medicines" and noting that "one important step is ensuring that FDA and the public receive adequate advance notice of shortages whenever possible" (Ref. 1). 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 and other stakeholders to successfully prevent numerous shortages by 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 regulatory flexibility and discretion in appropriate circumstances, if this would not cause undue risk to patients.

FDA was able to prevent just under 200 drug and biological product shortages in 2011, more than 280 such shortages in 2012, 170 shortages in 2013, and 101 shortages in 2014.

In July 2012, FDASIA amended the FD&C Act to modify existing drug shortages requirements and to add new drug shortages provisions. Section 506C(i) of the FD&C Act,

added by FDASIA, directs FDA to adopt a final rule to implement the drug shortages provisions. The final rule supersedes the IFR.

## II. The Proposed Rule

In the Federal Register of November 4, 2013 (78 FR 65904), FDA published a proposed rule to implement certain drug shortages provisions of the FD&C Act, as amended by FDASIA.<sup>5</sup> The preamble to the proposed rule explained that 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, 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.

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<sup>5</sup> Section 506C(i)(4) of the FD&C Act specifies that in promulgating a regulation to implement the FD&C Act's drug shortage provisions, FDA must issue a notice of proposed rulemaking that includes the proposed rulemaking and provide a period of no less than 60 days for public comment on the proposed rule.

- 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.

The Agency proposed 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) (see 78 FR 65904).

FDA provided 60 days for public comment on the proposed rule. Based on the comments received and FDA's experience to date receiving notifications, maintaining public lists of drug and biological product shortages, and working with manufacturers and stakeholders to prevent and mitigate drug and biological product shortages, the Agency is finalizing the rule as proposed.

### III. Description of the Final Rule

#### A. Persons Subject to the Rule

Sections 310.306, 314.81(b)(3)(iii), and 600.82 require notification to FDA of a permanent discontinuance or an interruption in manufacturing of a covered drug or biological product. The following persons are subject to these notification requirements:

- All applicants with an approved NDA or ANDA for a covered drug product (§ 314.81(b)(3)(iii)).
- All applicants with an approved BLA for a covered biological product, other than blood or blood components (§ 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 (§ 600.82(a)(2)).
- All manufacturers of a covered drug product marketed without an approved NDA or ANDA (§ 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 rule requires 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 rule an ANDA, NDA, or BLA applicant is 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 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 non-applicant entity that ensures the applicant's compliance with this rule.

Section 506C(i)(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, the rule applies only to applicants that are manufacturers of a "significant percentage of the United States blood supply." As described more fully in sections III.B.2.c and III.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 unnecessarily duplicating existing systems and without being unduly burdensome for industry. 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.<sup>6</sup>

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<sup>6</sup> Based on 2011 National Blood Collection and Utilization Survey (NBCUS) data, 10 percent or more of the U.S. blood supply would mean more than 1.5 million units of whole blood annually or approximately 125,000 units per month. We note, however, that these numbers may fluctuate year to year. See 2011 National Blood Collection and

## B. Products Covered by the 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 rule applies to all prescription drug products approved under an NDA or ANDA (§ 314.81(b)(3)(iii)), all marketed unapproved prescription drug products (§ 310.306), and all prescription biological products approved under a BLA (§ 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.<sup>7</sup>

FDASIA does not define the terms "life supporting," "life sustaining," or "intended for use in the prevention or treatment of a debilitating disease or condition," but instead requires FDA to define them (section 506C(i)(2) of the FD&C Act). Sections 314.81(b)(3)(iii)(f) and 600.82(f) define a "life supporting or life sustaining" drug or biological 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." As explained in the preamble to the proposed rule (78 FR 65904 at 65909), 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 pre-FDASIA section 506C (72 FR 58993 at 58994, October 18, 2007), and in medical device regulations (see 21 CFR 821.3(g)).

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Utilization Survey Report, available at <http://www.hhs.gov/ash/bloodsafety/nbcus/>.

<sup>7</sup> 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.

The final rule defines "intended for use in the prevention or treatment of a debilitating disease or condition" to mean "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" (§§ 314.81(b)(3)(iii)(f) and 600.82(f)). FDA equates "debilitating disease or condition" with "serious disease or condition" under this definition, and we have defined it according to the definition of "serious" found in § 312.300 (21 CFR 312.300), which governs expanded access to investigational new drugs. 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).

It is important to note that the 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 shortages of CDER-regulated products (CDER MAPP 4190.1 Rev. 2) (Ref. 2) and the existing Center for Biologics Evaluation and Research (CBER) Standard Operating Policy and Procedure (SOPP) on shortages of CBER-regulated products (CBER SOPP 8506) (Ref. 3). In general, FDA considers a product to be medically necessary under the internal MAPP and SOPP if there is no other product that is judged by CDER or CBER medical staff to be an appropriate substitute or there is an inadequate supply of an acceptable alternative, as determined by appropriate CDER and CBER personnel. In contrast, under this rule, an applicant is 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 or SOPP. Under the MAPP and SOPP, FDA uses the definition of medically necessary to prioritize the Agency's response to specific shortages or potential shortages and to allocate resources appropriately.

## 2. Biological Products

Section 506C of the FD&C Act, as amended, states that for purposes of section 506C, 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 (HHS) (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.

As proposed, FDA is applying 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. Shortages of biological products can have serious negative consequences for patients who rely on these products for their treatment. FDA

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

a. Plasma-derived products and their recombinant analogs. Under § 600.82(a), the requirements of section 506C of the FD&C Act apply 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). As explained in the preamble to the proposed rule (78 FR 65904 at 65910), 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.

FDA recognizes and greatly appreciates the efforts by PPTA to provide plasma product supply information to FDA and the public. However, as described in detail in the preamble to the proposed rule (78 FR 65904 at 65910), FDA concluded that it would benefit the public health for the Agency to receive direct notification under this rule from all manufacturers of these products. Because the PPTA program does not serve the same purpose as notification under this

rule, including plasma-derived products and their recombinant analogs in this rule will not duplicate the PPTA system. FDA believes that including these products within the scope of the 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. 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.<sup>8</sup> 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.<sup>9</sup> As explained in the preamble to the proposed rule (78 FR 65904 at 65910), 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

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<sup>8</sup>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>.)

<sup>9</sup>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>.)

approximately 30 percent of vaccines licensed in the United States are not subject to CDC notification.

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 has determined that including vaccines within the scope of this rule 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. The rule applies section 506C of the FD&C Act to blood or blood components, but in a more limited manner than for other biological products (§ 600.82(a)(2)). The rule requires 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. The rule is intended to require reporting of large-scale, permanent discontinuances, or interruptions in manufacturing of blood or blood components.

FDA anticipates that the rule will 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.

As explained in detail in the preamble to the proposed rule (78 FR 65904 at 65911), we are aware of two significant efforts to monitor local and regional supplies of blood or blood components: (1) America's Blood Centers (ABC) and the Blood Availability and Safety Information System (BASIS) and (2) 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 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 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, whereas the rule requires reporting.

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's 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 Task Force information 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 only capture short-term, day-to-day supply and distribution information. In addition, in contrast to this 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, the reporting requirements 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 III.A and III.C.1.

### 3. Scope of the Term "Product"

Under this rule, "product" refers to a specific strength, dosage form, and 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 § 314.81(b)(3)(iii), but the 100-mg strength continues to be manufactured without delay, under the 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.

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.

Sections 314.81(b)(3)(iii) and 600.82 require the applicant to report all permanent discontinuances of covered drugs and biological products to FDA. For purposes of this rule, we interpret 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.

i. Drugs and biological products other than blood or blood components.

Sections 314.81(b)(3)(iii)(a) and 600.82(a)(1) 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. Sections 314.81(b)(3)(iii)(f) and 600.82(f) adopt the statutory definition of "meaningful disruption in supply."

Consistent with the statutory definition of meaningful disruption, the rule requires 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 the 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 rule does not require an applicant to predict the market-wide impact of an interruption in its own manufacturing, which can be difficult to accurately assess and could lead to inconsistent interpretation of the regulation, less accurate predictions, and under- or overreporting.

Under the rule, reportable discontinuances or interruptions in manufacturing of a covered drug or biological product 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 is not required, under the 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 does 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 the rule and the applicant must 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 the list is not exhaustive. The rule requires that 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 be reported to FDA, even if not specifically described in this preamble.

ii. Blood or blood components for transfusion. Section 600.82(a)(2) requires 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 explained in section III.A, FDA intends to consider an applicant that manufactures 10 percent or more of the U.S. blood supply to manufacture a significant percentage of the U.S. blood supply for purposes of this rule.<sup>10</sup> Section 600.82(f) defines "significant disruption" as 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

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<sup>10</sup> Based on 2011 NCBUS data, this would be more than 1.5 million units of whole blood annually or approximately 125,000 units per month. However, we note that the number may fluctuate year to year.

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 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 1-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 whether 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 definition of "significant disruption" (interpreted to mean affecting 20 percent or more of an individual applicant's supply over a 1-month period) as applied to blood or blood components, in combination with limiting the 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 III.B.2.c of this document and in the preamble to the proposed rule (78 FR 65904 at 65911). 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 are unlikely to be identified and corrected by the

existing ABC, BASIS, and Task Force programs. The additional limitation of the 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.

Circumstances that trigger notification to FDA of a permanent discontinuance or an interruption in manufacturing of blood or blood components 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; 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 is not required under the 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 does 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 1-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 must be reported to FDA under the final 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 rule requires any permanent discontinuance or any interruption in manufacturing that is likely to lead to a significant disruption (as defined by the 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.

## 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 6 months' advance notice is not possible, as soon as practicable.

Consistent with the statute, §§ 314.81(b)(3)(iii)(b) and 600.82(b) 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, FDA expects 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 must 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 6 months in advance certain interruptions in manufacturing that are likely to lead to a meaningful disruption. 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 rule requires that the applicant 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 must 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 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 III.C.6 for further discussion of the consequences of failure to notify FDA). Additionally, it is important to note that an applicant that could have notified the Agency before 5 days had passed, but waited until the end of the 5-day period is in violation of the rule. Consistent with the statutory intent, whenever possible, applicants are 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. Sections 314.81(b)(3)(iii)(b) and 600.82(b) 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](mailto:drugshortages@fda.hhs.gov) (for products regulated by CDER) or [cbershortage@fda.hhs.gov](mailto:cbershortage@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." As described in the preamble to the proposed rule (78 FR 65904 at 65915), 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 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 eliminates § 314.91 in its entirety.

### 3. Contents of the Notification

Sections 314.81(b)(3)(iii)(c) and 600.82(c) 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 requires applicants to include the minimum information listed 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 III.C.4. We recognize that the duration of an interruption in manufacturing can be difficult to accurately predict. Therefore 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.

Along with the required elements of the notification, applicants are encouraged to include any other information in the notification that may assist the Agency in working with the applicant to resolve the permanent discontinuance or interruption in manufacturing. This 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 followup 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 of the FD&C Act 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 rule, the ANDA, NDA, or BLA applicant is 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 and biological product shortages lists the reason for the shortage, choosing from the following list of categories specified in the statute:

- 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 §§ 310.306(c), 314.81(b)(3)(iii)(d), and 600.82(d), FDA will 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 rule concerning the product in shortage. Sections

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)). As specified in the rule, the shortages lists will 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 rule for the drug or biological product, FDA will 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. Consistent with the statute, the Agency, not the applicant, is responsible for determining which categorical reason best fits a particular situation. In general, FDA intends to 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 final rule we 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 section 506C notification. This information will also assist FDA in responding quickly to the notification. If FDA has not received a notification under the rule, but becomes aware of a shortage through other means, FDA intends to 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, the final rule also adds an eighth category, entitled "Other reason." The Agency intends to choose "Other reason" only 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, although FDA may choose the "Other reason" category, the public shortages list will 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.

The final rule codifies, 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> (for products regulated by CDER) and <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm> (for products regulated by CBER).

The list of CDER-regulated products 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 § 314.81(b)(3)(iii)(d)); and Date Updated (last date FDA updated the information for that particular product). The list of CBER-regulated products includes similar information in fields for Product Name, Reason for Shortage, and Status.

## 5. Confidentiality and Disclosure

In general, as required by sections 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. Sections 314.81(b)(3)(iii)(d) and 600.82(d),

however, specify that FDA may choose not to make information collected under the authority of the 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 provisions closely track the statutory language in sections 506C(c) and 506E(c)(3) of the FD&C Act.

In addition, §§ 310.306(c), 314.81(b)(3)(iii)(d), and 600.82(d), as finalized, 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 § 20.61. These provisions provide appropriate protection for commercial and trade secret information protected by other Federal law and are consistent with 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). The final rule also implements a technical amendment to § 20.100 to include a cross-reference to §§ 310.306, 314.81, and 600.82. Section 20.100 describes, by cross-reference to other regulations, the rules on public availability of certain specific categories of information.

#### 6. Failure to Notify

Consistent with section 506C(f) of the FD&C Act, §§ 310.306(b), 314.81(b)(iii)(3)(e), and 600.82(e), as finalized, provide that FDA will 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 §§ 314.81(b)(iii)(3)(a) and 600.82(a) within the timeframe stated

in §§ 314.81(b)(iii)(3)(b) and 600.82(b). It is important to note that failure to notify FDA includes 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 will issue a noncompliance letter. 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," FDA will issue a noncompliance letter. Refer to section III.C.2.a for a discussion of the required timing for section 506C notifications.

As required by section 506C(f) of the FD&C Act, the rule provides the applicant with 30 calendar 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. Not later than 45 calendar days after the date of issuance of the noncompliance letter, FDA will make the letter and the applicant's response public, after appropriate redaction to protect any trade secret or confidential commercial information. FDA will 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. Comments on the Proposed Rule

The Agency received submissions from 34 commenters, including public health associations, pharmaceutical industry, hospital groups, consumer groups, and individuals. A summary of the comments contained in the submissions received and FDA's responses follow.

To make it easier to identify comments and our responses, the word "Comment," in parentheses, appears before the comment's description, and the word "Response," in parentheses, appears before our response. We have numbered each comment to help distinguish between different comments. Similar comments are grouped together under the same number. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received.

A. Persons Subject to the Rule

(Comment 1) One comment suggested that the notification requirement should be extended to API manufacturers. The comment stated that API manufacturers are further upstream in the drug development chain and that early warning of issues at this level, before they impact manufacturers formulating the drugs, would give FDA, other manufacturers of the drug, and programs more time to prepare and prevent shortages from affecting patients.

(Response) FDA does not agree that the notification requirement should be applied to API manufacturers. While interruptions in API supply may lead to a meaningful disruption in supply of the finished drug or biological product, they do not always have this effect. Therefore, notification to FDA of disruption in API supply would be premature and would not provide information that the Agency can take definitive action on. FDA believes that the notification requirement, which is derived from section 506C of the FD&C Act, generally provides the Agency with adequate notice to allow the Agency to work with the applicant and other stakeholders to prevent a shortage. As explained in section III.A, however, it is important that the applicant establish a process with any relevant contract manufacturer, API supplier, or other non-applicant entity to ensure that the applicant complies with this rule.

(Comment 2) One comment requested clarification on how a blood establishment will know if it is subject to the reporting requirements of the rule. The comment noted that the preamble to the proposed rule (78 FR 65904 at 65908) stated that FDA intends to consider a BLA-holder 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. The comment explained that the National Blood Collection and Utilization Survey (NBCUS) supplies the best data available nationally on collection and utilization of blood in the United States, but notes that the survey is voluntary and does not occur on an annual basis. The comment stated that it is not possible for a BLA holder to know what percentage of the U.S. blood supply it is collecting. Accordingly, the comment recommended that FDA identify an annual whole blood collection number to be used as the threshold for reporting.

(Response) FDA declines to identify an annual whole blood collection number to be used as a threshold for reporting because these numbers may fluctuate year to year. Because of their coordination with other BLA holders through the ABC, BASIS, and Task Force programs, we believe that BLA holders will generally be aware of whether they manufacture a significant percentage of the U.S. blood supply. Accordingly, we do not believe there will be significant uncertainty among BLA holders about whether they are subject to the notification requirements. If an applicant is unsure of whether it is subject to the notification requirements, we recommend that the applicant contact CBER at [cbershortages@fda.hhs.gov](mailto:cbershortages@fda.hhs.gov).

(Comment 3) One comment noted that the proposed rule did not discuss the effect of the notification provision on product allocation systems. The comment explained that products with inherently limited supply have been historically put on allocation systems by manufacturers to prioritize the allocation of these products. The comment explained that these allocation systems

help manage and track product supplies, curb gray market distribution, and prevent price hikes. The comment stated that section 506(D)(d) of the FD&C Act directs FDA to establish a mechanism by which health care providers and other third party organizations may report to the Agency evidence of a drug shortage. The comment requested confirmation that a notification under section 506D(d) of the FD&C Act does not extend to situations where a receiving entity (e.g., a hospital) reaches its allocation limits.

(Response) The comment is beyond the scope of this rulemaking. The final rule implements sections 506C and 506E of the FD&C Act by amending §§ 20.100 and 314.81(b)(3)(iii) and adding new §§ 310.306 and 600.82. The rule does not address section 506D of the FD&C Act. Consistent with section 506D(d), however, we do encourage patients, providers, pharmacists, and other non-applicants to communicate with FDA about potential shortages or disruptions in supply by email at [drugshortages@fda.hhs.gov](mailto:drugshortages@fda.hhs.gov) (for products regulated by CDER) or [cbershortages@fda.hhs.gov](mailto:cbershortages@fda.hhs.gov) (for products regulated by CBER), so that the Agency can take appropriate steps to address these situations.

#### B. Products Covered by the 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

(Comment 4) In the preamble to the proposed rule (78 FR 65904 at 65909), FDA requested comment on the proposed definitions of "life supporting or life sustaining" and "intended for use in the prevention or treatment of a debilitating disease or condition" and in particular, whether the definitions might lead to "over-notification." The majority of commenters supported the proposed definitions and agreed that they are consistent with current understanding of these terms. Some commenters noted that there might be the potential for over-

notification but agreed that more information, rather than less, will enhance FDA's ability to prevent drug and biological product shortages. One comment stated that the definitions could lead to over-notification if they are broadly interpreted but noted that it is difficult to predict whether over-notification will actually occur. The comment suggested that within 1 year of implementation of the final rule, FDA can assess whether overnotification has occurred and can revise the draft guidance for industry entitled "Notification to FDA of Issues that May Result in a Prescription Drug or Biological Product Shortage" to include additional examples of products that are or are not likely to fall within the scope of products subject to the notification provision.

(Response) FDA appreciates the commenters' input. We continue to believe that the proposed definitions provide sufficient clarity without overly restricting the categories of products subject to the rule. We have therefore finalized the definitions that were proposed and believe that these definitions will result in appropriate notifications under the rule. If, however, FDA finds that over-notification has occurred, the Agency may consider further clarification in guidance or by other suitable means.

(Comment 5) Three comments stated that the proposed definitions were overly broad, potentially encompassing the majority of approved drug and biological products, and may be subject to inconsistent interpretation. Two comments recommended using definitions based on the definitions of "immediately life-threatening disease or condition" and "serious disease or condition" in § 312.300. One of those comments specifically proposed the following definitions:

- "A life supporting or life sustaining drug product means a drug product that is essential to, or yields information that is essential to, the restoration or continuation of a bodily function associated with a stage of disease in which there is a reasonable likelihood that

death will occur within a matter of months or in which premature death is likely without early treatment."

and

- "A debilitating disease or condition means a serious disease or condition associated with morbidity that has a substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."

(Response) FDA does not believe it is appropriate to incorporate the comment's proposed definitions or alternative definitions based on the definitions set forth in § 312.300. As explained in section III.B.1, under §§ 314.81(b)(3)(iii)(f) and 600.82(f) of this final rule, FDA equates "debilitating disease or condition" with "serious disease or condition," and we have defined "debilitating disease or condition" according to the definition of "serious disease or condition" found in § 312.300. In the Agency's view, the definitions suggested in the comment would be too restrictive and could exclude certain products, such as anesthetic products, that are critical to patient care and should appropriately be considered "life supporting or life sustaining" or "intended for use in the prevention or treatment of a debilitating disease or condition." As noted in the previous response, FDA believes that the definitions in this final rule provide sufficient clarity without overly restricting the categories of products subject to the rule. If, following implementation of the rule, it appears that further clarification is necessary, FDA will consider what type of clarification may be beneficial and take appropriate steps.

(Comment 6) Three comments suggested that FDA should consider providing a list, in guidance or otherwise, of examples of drug products or classes of drug products that are likely to meet the definitions of "life supporting or life sustaining" or "intended for use in the prevention or treatment of a debilitating disease or condition." The commenters suggested that such a list would provide greater clarity and facilitate compliance with the rule.

(Response) FDA does not believe it is appropriate to provide a list of products that are likely to meet the definitions of "life supporting or life sustaining" or "intended for use in the prevention or treatment of a debilitating disease or condition." Such a list would be difficult to maintain and keep up to date as products come off the market and new products enter the market. We are also concerned that applicants and the public may misinterpret the list as an exhaustive list of all products that would be subject to the notification requirement, rather than as examples of drug products or classes of drug products that are likely to meet the definitions.

If an applicant is uncertain whether a particular discontinuance or interruption in manufacturing of a drug or biological product should be reported to FDA, we encourage the applicant to proceed with notification. It is important to note that, under section 1001(b) of FDASIA, submission of a notification will not be construed as: (1) An admission that any product that is the subject of the notification violates any provision of the FD&C Act or (2) evidence of an intention to promote or market the product for an unapproved use or indication.

(Comment 7) One comment requested that FDA recognize attention-deficit hyperactivity disorder (ADHD) as an example of a debilitating condition. The comment stated that FDA could do so by adding to the definition in the final rule a list of some debilitating diseases and conditions and including ADHD in that list.

(Response) FDA has recognized ADHD as an example of a debilitating condition. We note further that when products used to treat ADHD have gone into shortage, they have been included on FDA's drug shortages Web site. However, FDA declines to add a list of examples of debilitating conditions to the rule.

(Comment 8) One comment requested clarification that drugs used to treat a "debilitating disease or condition" include sedatives, anesthetics, analgesics, and anti-inflammatory drugs.

(Response) FDA has considered sedatives, anesthetics, analgesics, and anti-inflammatory drugs to be drugs that are intended for use in the prevention or treatment of a debilitating disease or condition.

(Comment 9) One comment suggested that the rule be modified to give FDA the option of including a statement in the approval letter for new NDAs, ANDAs, or BLAs indicating that the product is covered by the rule. The comment noted that this type of statement about the product's status would provide clarity and could be beneficial, especially to applicants entering the U.S. market for the first time.

(Response) FDA understands that including a statement in the approval letter that the product is covered by this rule would clarify that particular product's status. The Agency is concerned, however, that such action may create confusion about the status of other already-approved products where the approval letter does not include a statement regarding notification under this rule. Applicants and other stakeholders may believe that the notification requirement only applies with respect to products whose approval letter contains a statement about notification under this rule. Therefore, FDA does not think it would be appropriate to add a provision to the rule as suggested by the comment.

(Comment 10) One comment requested clarification that the definition of "medically necessary" in the drug shortage MAPP solely relates to the allocation of internal Agency staffing and resources and that it has no bearing on the scope of products subject to notification under the proposed rule or FDA's determination of an actual shortage and public notification of a shortage.

(Response) As explained in section IV.B.1 of this document and in the preamble to the proposed rule, under this rule, an applicant is 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.

(Comment 11) One comment expressed support for the inclusion of prescription drug products marketed without an approved NDA or ANDA and noted that such products are often critical to patient care.

(Response) FDA agrees that prescription drug products marketed without approved applications are important in patient care and accordingly § 310.306 is being finalized as proposed to ensure that the Agency is notified of a permanent discontinuance or an interruption in manufacturing of such products, as appropriate.

(Comment 12) Three comments raised questions about off-label uses. One comment requested clarification that off-label indications are not included within the scope of "marketed unapproved prescription drugs." Two comments noted that many prescription drug products used to treat children and nearly all prescription drug products used to treat neonates are not

labeled for use in those populations. Accordingly, those two comments stated that the rule should require notification based on off-label uses in addition to the uses in the labeling.

(Response) Off-label uses of drug and biological products are not included within the scope of "marketed unapproved prescription drugs." FDA is not requiring applicants to consider off-label uses when determining whether a product is a covered product for purposes of the notification requirement in section 506C of the FD&C Act and implemented in this rule. The Agency understands that off-label uses can, in certain circumstances, be an important part of patient care. In fact, as explained in the MAPP on drug shortages (CDER MAPP 4190.1 Rev. 2), FDA considers off-label uses when classifying products as medically necessary for purposes of prioritization. However, off-label uses are based on a practitioner's professional judgment about what will benefit an individual patient, and we do not believe it would be reasonable to expect applicants to take account of individual practitioners' therapeutic decisionmaking in assessing whether their products are subject to the notification requirement. We note that in many cases, though, products that would be covered by the rule if it applied based on an off-label use may nevertheless be covered products based on a labeled use, in which case the applicant would be subject to the notification requirement for that product.

## 2. Biological Products

(Comment 13) Many comments strongly supported applying section 506C of the FD&C Act to biological products. These comments expressed the view that early notification of a permanent discontinuance or an interruption in manufacturing of biological products would benefit the public health by facilitating prompt action on FDA's part to address, prevent, or mitigate a shortage of these products.

(Response) FDA appreciates these comments and agrees that extending the notification requirement to biological products will benefit the public health. Therefore, consistent with section 506C(i)(3), the Agency is finalizing § 600.82 as proposed.

(Comment 14) Two comments requested that the Agency make clear that biosimilars are subject to the provisions of section 506C of the FD&C Act. The comments stated that while the approval process for biosimilars is still under development, it is important that such products be included in the requirements of the final rule.

(Response) This rule applies to prescription biological products licensed under section 351 of the PHS Act,<sup>11</sup> including prescription biosimilar biological products licensed under section 351(k) of the PHS Act, 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 excluding radiopharmaceutical products.

(Comment 15) One comment expressed support for the inclusion of blood or blood components for transfusion but requested clarification on how FDA will determine which blood or blood components would be exempt from the rule and how FDA plans to address shortages of products determined to be exempt. In particular, the comment sought clarification on whether the rule would apply to reagents used to cross-match platelets for transfusion. The comment stated that there have been shortages of these reagents recently, which has impacted patient care.

(Response) As explained in section III.B.2.c, the notification requirement applies only to applicants of blood or blood components for transfusion that manufacture a significant percentage of the U.S. blood supply, and only when there is a permanent discontinuance of

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<sup>11</sup> As noted in footnote 1 to the Executive Summary, the term "biological product" refers to a biological product licensed under section 351 of the PHS Act, other than a biological product that also meets the definition of a device in section 201(h) of the FD&C Act.

manufacture or an interruption in manufacturing that is likely to lead to a "significant disruption" in supply of that blood or blood component. As noted in footnote 1 in the Executive Summary, the rule does not apply to biological products that meet the definition of a device in section 201(h) of the FD&C Act. Accordingly, this rule does not apply to reagents or other products that CBER regulates as devices, such as products intended for screening or confirmatory clinical laboratory testing associated with blood banking practices and other testing procedures (e.g., blood typing and compatibility testing).

(Comment 16) Two comments stated that blood and blood components should not be included in the rule. The comments cited the current systems described in the preamble to the proposed rule (78 FR 65904 at 65911) that monitor local and regional supplies of blood or blood components and coordinate during domestic disasters. The comments noted that blood and blood components do not have a history of shortages and stated that given the existing reporting systems and acknowledged successful record of planning activities in the blood community, coordination among the major blood organizations, and cooperation with FDA and HHS during and following disasters, it is not necessary to add another layer of reporting that is unlikely to provide additional security.

(Response) As explained in the preamble to the proposed rule (75 FR 65904 at 65911) and in section III.B.2.c, FDA agrees that the information available from ABC and BASIS and the efforts by the Task Force are critical to public health, and the Agency appreciates the willingness of applicants to coordinate. However, there are limitations to these existing systems. These systems are voluntary, they do not result in a direct notification from an applicant to FDA, and they only capture short-term, day-to-day supply and distribution information. In addition, the existing systems are not equipped to predict large-scale, significant disruptions of blood or blood

components. We believe that including blood and blood components in the final rule will allow FDA to anticipate large-scale, significant disruptions of blood or blood components and take appropriate action. Accordingly, FDA has determined that including blood and blood components within the scope of this rule will benefit the public health by ensuring that the Agency is provided with information essential to FDA's efforts to address shortages of these products without duplicating existing programs.

(Comment 17) One comment stated that cellular and gene therapy products should not be included in the rule. The comment stated these are relatively new products and that the notification requirements are not necessary for them. The comment noted that BLA holders should be reporting to FDA, at least annually, what products are being manufactured under the license, and if an applicant is experiencing difficulty manufacturing a product, the applicant can communicate with FDA. The comment stated further that it is difficult to understand the "meaningful" process FDA would initiate if a report is received from a cellular or gene therapy manufacturer, and recommended that if cellular and gene therapy products are included in the final rule, FDA should provide a specific guidance document addressing these products.

(Response) FDA does not agree that cellular and gene therapy products should be excluded from the rule, nor do we agree that periodic distribution reporting or voluntary communication with FDA regarding manufacturing difficulties are adequate to allow the Agency to address shortages of cellular and gene therapy products. Shortages of biological products can have serious health consequences for patients who rely on these products for their treatment. Early notification of a permanent discontinuance or an interruption in the manufacturing of biological products is crucial for allowing FDA to take steps to prevent, or mitigate a shortage of these products.

The required distribution reports referred to in the comment do not provide sufficient notice for FDA to anticipate a shortage or take appropriate action to address a shortage. As explained in the preamble to the proposed rule (78 FR 65904 at 65911), under § 600.81, applicants are required to submit to CBER or CDER information about the quantity of product distributed under the license, including the quantity of product distributed to distributors. As part of the 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, 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. In addition, any distribution data received from the applicant at 6-month intervals may not be current. Accordingly, FDA has determined that including cellular and gene therapy products within the scope of this rule would benefit the public health by ensuring that FDA is provided with information that is essential to Agency's efforts to address shortages of these products. If, following implementation of the rule, it appears that guidance or further clarification is necessary for cellular and gene therapy products, FDA will consider what type of guidance may be beneficial and take appropriate steps in accordance with good guidance practices set out in 21 CFR 10.115.

(Comment 18) Two comments recommended that the rule not be applied to vaccines. The comments stated that, in response to the unique nature of vaccines, the CDC has successfully partnered with vaccine applicants to reduce, if not eliminate completely, impacts to public health that may arise due to a supply shortage. The comments stated that CDC continues to be in the best position to monitor and manage vaccine supply. The comments suggested that

the CDC should continue to act as a confidential facilitator of critical supply information that is provided by applicants or manufacturers, to maintain these data as proprietary and confidential, and to allow CDC to use the information so that other applicants or manufacturers can fill the gap in the event of an imminent shortage. In addition, the comments noted that, for over a decade, the vaccine industry has voluntarily strived to provide FDA with the requested minimum 6-month notice when making a determination to discontinue production of a particular vaccine, where such a decision was foreseeable.

Alternatively, the comments proposed that FDA consider limiting the scope of the proposed rule to cover only non-VFC vaccines since there already are effective notification and distribution systems in place under the VFC program. The comments noted that CDC maintains a stockpile of VFC vaccines as part of its vaccine shortage notification program. Due to the CDC's regular collaboration with vaccine manufacturers, this program has proven highly successful in mitigating or completely eliminating supply disruptions.

(Response) FDA does not agree with the commenters' suggestion that the rule should not apply to vaccines or, in the alternative, should only apply to non-VFC vaccines. 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. FDA does not intend this rule to disrupt the contractual process and procedures that exist between manufacturers and CDC. However, as explained in the preamble to the proposed rule (78 FR 65904 at 65910), approximately 30 percent of vaccines licensed in the United States are not subject to CDC notification, including vaccines for rabies, yellow fever, and typhoid. Even for the vaccines that are subject to CDC notification, the information collected by CDC is not adequate for purposes of this rule. 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 prevention of drug and biological product shortages. Although FDA and its HHS partners work together on vaccine supply issues, FDA believes that including vaccines within the scope of this rule is essential to fully support FDA's efforts to identify, address, prevent, or mitigate a vaccine shortage.

(Comment19) Two comments noted that by design, influenza vaccine is a seasonal product and consequently, is unavailable for a significant portion of each year. The comments stated that for this reason, both seasonal influenza and pandemic influenza vaccines should not be covered by the rule.

(Response) We acknowledge that some vaccines, such as those for influenza, are seasonal products by design and consequently may be unavailable for a significant portion of the year. It is important to note that "meaningful disruption" is defined as a "reduction in the supply of a drug...that is more than negligible and affects the ability of the manufacturer to fill orders or meet expected demand for its product." In the case of a seasonal product, we anticipate that demand would decrease during the off-season; therefore, we would not expect that an interruption in manufacture of a seasonal product would be likely to lead to a meaningful disruption in the off-season. Accordingly, we decline to exempt vaccines intended for seasonal and pandemic use. We believe shortages of biological products, including seasonal influenza vaccines, can have serious health consequences for patients who rely on these products. Early notification of a permanent discontinuance or an interruption in the manufacturing of these products will allow FDA to promptly take steps to prevent or mitigate a shortage of these products that could otherwise result in delayed patient access.

### 3. Scope of the Term "Product"

(Comment 20) Two comments noted that the proposed rule would apply individually to all strengths, dosage forms, or routes of administration for a given product regardless of the supply status for other presentations and dosages of the same product. The commenters suggested that the rule should allow greater flexibility and should not apply to a product if an alternate presentation of the same therapeutic product is available.<sup>12</sup>

(Response) FDA does not agree. As we explained in the preamble to the proposed rule (78 FR 65904 at 65912), we understand that the permanent discontinuance or interruption in manufacturing of a specific strength, dosage form, or route of administration can have a significant impact on the targeted needs of particular patients. The Agency strives to ensure the availability of appropriate treatment options for patients. We also note that 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, thereby exacerbating difficulties in obtaining the product. Furthermore, as explained in other comments on the proposed rule (available in Docket No. FDA-2011-N-0898), requiring notification based on the status of each strength, dosage form, and route of administration helps to ensure that patients and their health care providers have the most accurate information about potential shortages, and can make treatment decisions accordingly.

If the applicant has available an alternate presentation of the same product, the applicant should include that information in the notification as a proposal to mitigate the shortage.

(Comment 21) One comment requested confirmation that notification is not required when there is a shortage of a particular "count" of product but overall the quantity of that product

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<sup>12</sup> We understand the comment to mean that the rule should not apply to a particular applicant if that applicant has available the same product in a different presentation, e.g., a different strength.

is not in shortage (e.g., a manufacturer is in short supply of a 50-count bottle of 10-mg pills, but there are sufficient numbers of 25-count bottles of 10-mg pills to meet patient need).

(Response) FDA would not require notification in the situation described in the example provided.

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

#### 1. Notification

(Comment 22) One comment expressed concern about the notification requirement as applied to blood or blood components. The comment cited the proposed rule (78 FR 65904 at 65913) and stated that monthly reporting of a decrease in any blood component produced by an affected BLA holder is overly burdensome and would result in reports that are meaningless. The comment recommended that FDA provide information and recommendations in a draft guidance to more fully explain the goals of this particular data collection.

(Response) The rule requires the notification of a permanent discontinuance or an interruption in manufacturing of blood or blood components that is likely to lead to a significant disruption in supply of the product in the United States. 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 1-month period to "substantially affect" the ability of the applicant to fill orders or meet expected demand. Such an interruption would be considered a significant disruption in supply. The rule does not require manufacturers to submit or report monthly data. The rule, as applied to BLA holders for blood or blood components for transfusion, is intended to capture events that are likely to precipitate large-scale disruptions in an applicant's blood supply.

(Comment 23) One comment expressed concern that the requirement that applicants report an "interruption in manufacturing" that is likely to cause a disruption in the manufacturer's own supply of a drug or biological product could keep important information from being reported to FDA. The comment explained that a manufacturer that is not experiencing "an interruption in manufacturing," but rather is experiencing a lack of available product due to an increase in demand would not be required to notify the Agency. The comment suggested that FDA consider expanding the notification requirement to include those applicants experiencing a shortage in supply due to an increase in product demand.

(Response) FDA agrees that notification by an applicant lacking available product because of an increase in demand, and not because of an interruption in manufacturing, could be helpful in anticipating and addressing potential shortages. However, such a notification requirement is beyond the scope of section 506C of the FD&C Act implemented by the final rule. FDA does encourage applicants to communicate with FDA if there is an increase in demand that the applicant is not able to meet. We also note that if an applicant experiences an increase in demand because of another applicant's permanent discontinuance or interruption in manufacturing, FDA would expect to receive notification about the situation from the applicant that has experienced the discontinuance or interruption.

(Comment 24) Two comments recommended specific modifications to the definition of "meaningful disruption," believing it to be unclear and potentially subject to inconsistent interpretation. First, the comments stated that terms within the definition, such as "reasonably likely," "more than negligible," and "short period" are insufficiently precise and recommended that the terms be removed from the definition. Second, the comments stated that, under the definition, applicants would be required to notify FDA if any products are under allocation or the

demand for the product exceeds the available supply. Accordingly, the comments suggested adding language to the definition with the clarification that "meaningful disruption" means that the adverse impact to supply is unable to be remediated or minimized through allocation or other means of prioritization. Last, the comments noted that many factors could potentially affect the ability of applicants to fill orders, including some that are not within an applicant's control. The comments noted that applicants do not ultimately determine, nor can they in all cases accurately predict, volumes of orders or product demand. One of the comments accordingly recommended that FDA consider including language to clarify that the definition of "meaningful disruption" is intended to reflect situations in which the availability of a product to patients would be impacted. The comment suggested that the rule should clarify whose orders the applicant needs to be able to fill, in order to distinguish between the temporary inability to fulfill an order to a wholesaler, as opposed to the inability of a patient to obtain a prescription or receive appropriate therapy.

(Response) The final rule is being issued to implement sections 506C and 506E of the FD&C Act, consistent with section 506C(i). Section 506C(h) defines "meaningful disruption" as "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 that "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." The final rule adopts the statutory definition. In our view, the language used in the statute provides flexibility to accommodate the wide variety of circumstances that may result in drug or biological product shortages. If there is any uncertainty about whether a particular circumstance must be reported to FDA under the rule, we encourage applicants to submit a notification. Early

notification is FDA's best tool for addressing shortages. Moreover, submission of a notification will not be construed as: (1) An admission that any product that is the subject of the notification violates any provision of the FD&C Act or (2) as evidence of an intention to promote or market the product for an unapproved use or indication.

(Comment 25) One comment noted that the preamble to the proposed rule (78 FR 65904 at 65912 and 65913) provides a number of examples of reportable discontinuances or interruptions in manufacturing of a covered drug or biological product. The comment stated that not all of the examples would result in a shortage of product to patients and may result in industry "over-reporting" events to the Agency. Accordingly, the comment requested that FDA further clarify the requisite link between the examples provided and an actual "meaningful disruption" in supply.

(Response) The list of examples provided in the preamble to the proposed rule are intended to assist applicants in understanding what must be reported under section 506C of the FD&C Act. As implemented by the final rule, section 506C requires that applicants notify FDA of a permanent discontinuance in the manufacture of a covered drug or biological product or an interruption of the manufacture of the drug or biological product that is likely to lead to a meaningful disruption in the supply of that product in the United States, and the reasons for such discontinuance or interruption. The list of examples is not intended to include only situations that will necessarily result in a meaningful disruption in supply. The list includes examples of events (i.e., permanent discontinuance and interruption in manufacturing) that are likely to lead to a meaningful disruption in supply and therefore must be reported to the Agency.

(Comment 26) One comment suggested that FDA amend the rule to require blood component manufacturers to report a decrease in donations when it is due to their own decision

to close donation sites versus the natural ebb and flow of blood donation cycles. The comment stated that companies have the ability to create shortages with the purpose of increasing prices by closing donation sites.

(Response) FDA does not agree the suggested change is necessary or appropriate. As explained in the preamble to the proposed rule (78 FR 65904 at 65913), FDA need not 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 1-month period. We expect that this type of situation would be identified and resolved through the existing programs that coordinate local and regional supplies of blood or blood components (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 this rule.

(Comment 27) One comment noted that some of the quality issues subject to notification under the rule also would be subject to reporting under Field Alert Reports for drugs and Biological Product Deviation Reports for biological products. In an effort to avoid dual reporting requirements, the comment suggested that FDA attempt to coordinate these reports and the Agency's followup in order to minimize the burden on both FDA and applicants.

(Response) FDA recognizes that some quality issues that result in interruptions in manufacturing subject to this rule could also be subject to reporting under Field Alert Reports (FARs) for drugs and Biological Product Deviation Reports (BPDRs) for biological products.

However, FARs and BPDRs are not supply reporting programs and do not serve the same purpose as notification under this rule. Applicants with approved NDAs and ANDAs are required to submit FARs to FDA if they find any significant problems with an approved drug; the purpose of the Field Alert Program is to quickly identify drug products that pose potential safety threats. Similarly, BPDRs are used by biological product manufacturers to report biological product deviations that may affect the safety, purity, or potency of a distributed product. Problems reported through FARs and BPDRs may not lead to a shortage. Moreover, we note that the timing of these reports and the information provided in them may not be adequate for FDA to address potential shortages. Therefore, we have determined that requiring manufacturers of drugs and biological products to notify FDA under this rule will not duplicate existing reporting programs and will provide the Agency with necessary information and lead time to take appropriate action to prevent or mitigate a shortage.

(Comment 28) One comment proposed that additional factors be taken into consideration and used as "filters" when manufacturers report drug and biologics shortages in order to limit the reporting of potential supply chain disruptions that are not "true drug shortage" events. The comment stated that these factors might include market dynamics and duration of supply chain shortage. With regard to market dynamics, the comment stated that FDA should consider the number of active suppliers and the percentage of the market supplied by such active suppliers. The comment stated that using this as a filter would help alert FDA to identify suppliers that are providing a significant percent of the market and that truly have the potential to create a drug shortage. For example, a market supplied by 10 active suppliers of equal market share would not likely experience a drug shortage if 1 of the active suppliers had a supply chain disruption. According to the comment, the market void could be absorbed by the nine other active suppliers

via safety stock, additional production, etc. Therefore, the comment recommended the addition of a "primary suppliers" filter to separate those active suppliers who are supplying a significant percent to the market (i.e., such as 20 percent or more of the market).

In addition, the comment stated that the duration of a supply chain shortage should be taken into consideration and utilized as a filter regarding drug shortage reporting. This filter would consider the typical inventory levels carried in the retail and wholesale channels. For example, an active supplier may have a supply disruption (i.e., product out of stock) for 30 days; however, the market may not experience a drug shortage given the inventory levels in the retail and wholesale channels. Typical inventory levels within these channels could range from 30 to 60 days of supply; therefore, the comment proposed a 60-day potential supply disruption as the minimum duration for drug shortage reporting to avoid chances of inventory hoarding and artificial increases in market demand that ultimately undermine the intent of FDASIA.

(Response) FDA declines to adopt the "filters" proposed to reduce reporting under the rule. FDA does not agree that these proposed "filters" are consistent with the language or intent of FDASIA. As explained in the preamble to the proposed rule (78 FR 65904 at 65912), "meaningful disruption" means a disruption in the applicant's own supply. This interpretation avoids the problem of expecting an applicant to predict the market-wide impact of its own interruption in manufacturing, which can be difficult to assess and could lead to inconsistent interpretation and less accurate predictions.

(Comment 29) Two comments addressed the stockpile of VFC vaccines maintained by CDC as part of its vaccine shortage notification program and noted the success of the program in mitigating or completely eliminating supply disruptions. One of the comments requested that

FDA permit applicants to take into consideration the existence of a CDC stockpile in assessing whether an interruption in manufacturing is reasonably likely to disrupt supply chains.

(Response) We acknowledge the importance of the stockpile of VFC vaccines maintained by CDC. CDC and HHS are required to maintain a stockpile of routinely recommended vaccines for the United States in the event of vaccine shortages or other unanticipated supply problems. The national pediatric vaccines stockpile currently maintains 14 pediatric vaccines that protect infants, children, and adolescents from 15 vaccine-preventable diseases excluding influenza.<sup>13</sup> Where appropriate, FDA and the manufacturers work together with CDC and take into consideration the existence of a CDC stockpile in assessing the impact of supply disruptions and the likelihood of a shortage. However, for the purposes of reporting under this rule, we do not agree that applicants should be permitted to take into consideration the existence of the CDC stockpile. As explained in section III.C.1.b.i, consistent with the statutory definition of meaningful disruption, the rule requires an applicant to report an interruption in manufacturing that is likely to lead to a meaningful disruption in its own supply of a covered drug or biological product. The rule does not require an applicant to predict the market-wide impact of an interruption in its own manufacturing, which can be difficult to accurately assess and could lead to inconsistent interpretation of the regulation, less accurate predictions, and under- or overreporting.

## 2. Timing and Submission of Notification

(Comment 30) Three comments requested clarification of when the notification "clock" would start, in other words, exactly when the notification requirement would be triggered. Two of the comments explained that at the outset, a meaningful disruption might not appear "likely"

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<sup>13</sup> See <http://www.cdc.gov/phpr/documents/VacStockpileManual.pdf>.

but may become "likely" as the events progress. The comments expressed concern that the Agency and the applicant may disagree about which event would trigger the notification requirement if it was not obvious to the applicant initially that a meaningful disruption would be likely. The comments suggested that the appropriate trigger to start the notification "clock" is the date on which information becomes available to the applicant from which it could be reasonably determined that a meaningful disruption is likely to occur. Another comment noted that the notification clock could begin on the date of the event causing the interruption, or on the date the applicant becomes aware that an interruption could cause a shortage. The comment cautioned that if the latter were considered the trigger, it may be difficult to determine the exact point in time.

(Response) FDA expects that an applicant will notify FDA as soon as information becomes available to the applicant from which the applicant could reasonably determine that a meaningful disruption is likely to occur. As explained in section III.C.2.a of this document and the preamble to the proposed rule (78 FR 65904 at 65914), the applicant should not wait until the interruption in manufacturing actually begins to disrupt supply and affect patient access to the product. Early notification is the Agency's best tool for addressing shortages because it provides FDA with lead time to work with stakeholders to prevent the shortage or mitigate the impact of an unavoidable shortage. Accordingly, while not required, we encourage applicants to communicate with FDA even in situations where a meaningful disruption may appear to be possible though not necessarily likely.

We understand the commenters' concern that FDA and the applicant may disagree about which event would trigger the notification requirement. FDA has sent and intends to continue sending noncompliance letters when the Agency believes an applicant failed to notify FDA as

soon as practicable or within 5 business days of the discontinuance or interruption.<sup>14</sup> If an applicant receives a noncompliance letter but believes the failure to notify was reasonable, the applicant should provide a full explanation of the circumstances in the applicant's response to the noncompliance letter. Consistent with section 506C(f)(3) of the FD&C Act, FDA will carefully consider the explanation provided in determining whether there was a reasonable basis for not notifying the Agency. If FDA determines that there was a reasonable basis for not notifying the Agency in accordance with section 506C of the FD&C Act and this rule, we will not post the noncompliance letter or the applicant's response to FDA's Web site.

(Comment 31) Several comments addressed the proposal that if 6 months' advance notice is not possible, notification must be submitted as soon as practicable thereafter, but in no case later than 5 business days after the permanent discontinuance or interruption in manufacturing occurs. Some comments expressed concern that FDA would allow an applicant to report as late as 5 days after a permanent discontinuance or interruption in manufacturing occurs. One comment stated that this would significantly weaken the rule and limit its effectiveness. The comment further stated that for an unforeseen disruption or discontinuation, FDA should require immediate notification or should outline what situations could arise that would appropriately necessitate a 5-day reporting delay. One comment expressed the view that reporting 5 days after the interruption should only be considered acceptable in rare circumstances, such as natural disaster. Another comment stated that applicants should be required to notify FDA a minimum of 6 months prior to the discontinuance or interruption, the only exception being a natural disaster or catastrophic incident. The comment stated that the proposed language is vague and

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<sup>14</sup> As noted in section III.C.2.a, even if an applicant notifies FDA within 5 business days of the discontinuance or interruption, the applicant may be issued a noncompliance letter if FDA believes the applicant did not notify the Agency as soon as practicable.

lenient and creates a loophole in mandatory reporting that ultimately serves neither the public health nor that of patients, while shielding manufacturers from their own failure to plan adequately.

In contrast, some comments expressed concern that requiring notification no later than 5 business days after the discontinuance or interruption would not provide sufficient time for applicants to investigate and get a complete understanding of the issue. The comments explained that more than 5 business days may be necessary to confirm whether actions taken in response to the interruption will affect the manufacturer's ability to fill orders or meet expected demand. One comment stated that requiring notification before a full investigation has been completed is likely to lead to overreporting and less reliable information being provided to FDA. The comment stated that the "as soon as practicable" standard set forth in FDASIA provides the necessary flexibility and should not be altered by adding a 5 business day limit. One comment recommended that, if FDA believes a definite reporting timeframe is necessary, it should be no shorter than 15 days after the permanent discontinuance or interruption in manufacturing. Another comment proposed that if a timeframe is necessary, it could be extended to 15 days along with qualifying language, such as "once it can conclusively be determined that a manufacturing issue will adversely impact supply."

(Response) FDA's most powerful tool for addressing drug and biological product shortages is early notification, which provides lead time for the Agency to work with manufacturers and other stakeholders to prevent a shortage or to mitigate the impact of unavoidable shortages. Accordingly, we expect that applicants will provide 6 months' advance notice whenever possible. FDA understands, though, 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. In those situations, FDA requires notification "as soon as practicable," but in no case more than 5 business days after the interruption in manufacturing occurs. The Agency has determined that 5 business days is adequate time for an applicant to assess whether the discontinuance or interruption in manufacturing is likely to lead to a meaningful disruption. As the situation evolves, FDA expects that applicants will provide the Agency with appropriate updates that will facilitate FDA's efforts. We believe that this timeframe appropriately balances the need for early notification and the understanding that applicants may not be able to immediately assess the impact of an interruption in manufacturing.

If notification was required only when an applicant has confirmed that a meaningful disruption will occur, then it might be appropriate to provide additional time for applicants to make this determination. However, the statute requires notification when a discontinuance or interruption in manufacturing is likely to lead to a meaningful disruption. The statute takes account of the fact that there may be a degree of uncertainty about the outcome of the discontinuance or interruption. As such, we note that the qualifying language proposed by one comment (i.e., adding "once it can conclusively be determined that a manufacturing issue will adversely impact supply" to the notification requirement) would not be consistent with the statutory requirement to notify FDA when a discontinuance or interruption is likely to lead to a meaningful disruption. FDA believes it is reasonable for an applicant to make a determination about whether an interruption is likely to lead to a meaningful disruption in supply within 5 business days of the discontinuance or interruption. The Agency does not believe that 15 business days should be necessary to make such a determination, and a delay of 15 business days in notification could have a significant impact on FDA's ability to prevent or mitigate a shortage.

We note that if an applicant receives a noncompliance letter for failure to notify the Agency within 5 business days of a discontinuance or interruption in manufacturing and believes that it would not have been reasonable to expect the applicant to determine that the event was likely to lead to a meaningful disruption, such information should be provided in the applicant's response to the noncompliance letter. The Agency, in turn, will consider that information in determining whether the applicant had a reasonable basis for not notifying FDA within the required timeframe and therefore whether the noncompliance letter should not be made public.

(Comment 32) One comment suggested that the rule should specifically include "natural disaster" as a potential trigger for notification. The comment acknowledged that the preamble to the proposed rule notes that reportable interruptions in manufacturing may include natural disasters, but the commenter was concerned that the examples provided in the proposed rule were all circumstances under the control of the manufacturer.

(Response) A wide variety of situations may lead to a reportable interruption in manufacturing (including natural disasters, equipment failure, or a delay in acquiring APIs or inactive ingredients), and FDA does not believe it is necessary or appropriate to include specific examples within the regulation itself. The Agency believes that the information and examples provided in the preamble to the proposed rule are adequate to assist applicants in determining whether a given interruption in manufacturing must be reported to FDA.

(Comment 33) One comment recommended that FDA require manufacturers to provide periodic updates on actions they are taking to bring drugs that are in shortage back to the market. The comment stated that this would help FDA understand the reasons for any continued delays in delivering drugs into the supply chain and allow the Agency to work with manufacturers in a more informed manner to reduce shortages.

(Response) Once FDA is notified of a situation that might lead to a shortage, FDA is in frequent contact with the applicant to seek ways to prevent the shortage. At this time, we do not believe that requiring periodic updates would be necessary, because we do not anticipate that requiring such updates would provide information that the Agency does not already have.

(Comment 34) Two comments provided suggestions about the electronic submission of 506C notifications to FDA. One of the comments suggested that the rule should include the specific office within FDA that notifications should be sent to. The other comment noted that applicants currently submit information in a nonspecified format via email and stated that FDA should provide greater clarity on whether this practice is intended to continue once the rule goes into effect and whether FDA will be specifying a uniform process for applicants to follow when submitting notifications.

(Response) As explained in the preamble to the proposed rule (78 FR 65904 at 65915), applicants must email notifications to [drugshortages@fda.hhs.gov](mailto:drugshortages@fda.hhs.gov) (for products regulated by CDER) and [cbershortages@fda.hhs.gov](mailto:cbershortages@fda.hhs.gov) (for products regulated by CBER). In the future, the Agency may consider creating an electronic notification portal to facilitate submission of these notifications. At that time, the Agency would provide any instructions necessary to use the portal. Because we expect that such a portal would be available on FDA's Web site, we do not believe it is necessary or appropriate to include the name of a specific receiving office in the regulation itself.

### 3. Contents of the Notification

(Comment 35) Two comments recommended that information about mitigation be required in the notification. One of the comments suggested that FDA require the notification to include a description of the efforts by the applicant to prevent or mitigate the shortage. The

other comment recommended that FDA require the notification to include a mitigation strategy or, at least, suggestions for mitigation.

(Response) FDA agrees that input from the applicant about ways to prevent or mitigate the shortage is crucial. The Agency, however, does not agree that it is appropriate to require information about mitigation to be included in the notification. We are concerned that there could be a delay in the notification if applicants are required to develop a mitigation strategy to include in the notification while also working to resolve the underlying issue. Instead, we have determined that it is appropriate to require basic information that is necessary for the Agency to take action and that the Agency is required to include in the shortages list under section 506E of the FD&C Act. We strongly encourage applicants to provide additional information, including proposals to prevent or mitigate the shortage, inventory on hand or in distribution channels, allocation procedures and/or plans for releasing available product, market share, or other information that may assist FDA.

(Comment 36) One comment suggested that FDA require the notification to indicate whether the drug or biological product is being used in an FDA- or National Cancer Institute-approved clinical trial. The comment explained that many clinical trials, especially for cancer treatments, are designed to test the safety and efficacy of the standard of care against, or in combination with, a new treatment being investigated. Accordingly, drug shortages have an impact on clinical trials, not just on patients undergoing standard treatment.

(Response) FDA understands that drug and biological product shortages may have an impact on clinical trials in addition to patients receiving standard treatment. However, we believe that requiring an applicant to state, in its notification, whether the product is currently being used in a clinical trial would require additional investigation by the applicant and would be

unnecessarily burdensome. FDA updates the drug and biological product shortage lists regularly, and we encourage investigators to sign up for email updates or the RSS feed to make sure they are aware of the latest information regarding product shortages.

(Comment 37) One comment requested clarification on what information must be included in a notification provided by the manufacturer of a covered drug marketed without an approved application.

(Response) As required by § 310.306, manufacturers of a covered drug marketed without an approved application must provide the same information in a notification as do applicants under § 314.81(b)(3)(iii)(c).

#### 4. Public Lists of Products in Shortage

(Comment 38) Two comments requested clarification about whether FDA will maintain a single list that includes shortages of both drugs and biological products.

(Response) At the present time, FDA intends to maintain separate lists of CDER-regulated and CBER-regulated products that are in shortage. The lists are available on FDA's Web site at <http://www.fda.gov/drugs/drugsafety/drugshortages/default.htm> (for products regulated by CDER) and <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm> (for products regulated by CBER).

(Comment 39) One comment expressed support for the proposed addition of "other reason" to the list of statutory reasons for the shortage that FDA could choose from. The comment noted that the seven reasons outlined in FDASIA may be difficult to apply in certain situations.

(Response) FDA agrees that the categories provided in FDASIA do not necessarily cover certain quality or manufacturing problems that may result in a shortage. Therefore, the Agency is finalizing "other reason" as an additional category that the Agency may identify.

(Comment 40) Three comments requested clarification of whether FDA would include potential drug and biological product shortages in the public lists, in addition to actual shortages. The comments expressed concern that disseminating information about potential shortages could result in unintended consequences, such as hoarding.

(Response) Under section 506E of the FD&C Act, FDA maintains an up-to-date list of drugs that are determined by FDA to be in shortage in the United States. Section 506C(h)(2) of the FD&C Act defines a shortage as "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug."

(Comment 41) Two comments requested clarification on the process and criteria FDA uses to determine whether there is an actual shortage and the process and criteria FDA uses to determine whether to remove a product from the shortages list.

(Response) The MAPP on shortages of CDER-regulated products (MAPP 4190.1 Rev. 2, p. 14) and SOPP on shortages of CBER-regulated Products explain in detail the process and criteria FDA uses to verify if an actual shortage exists. The MAPP (p. 17) also explains the process and criteria FDA uses to determine whether a product should be removed from the shortages list.

(Comment 42) Several comments noted that FDA is responsible for determining whether, in fact, an actual shortage exists as well as the categorical reason for the shortage that best fits the particular situation. The comments requested that FDA consult with applicants about these determinations before making the information public. One comment noted that this has been

FDA's practice and requested that the Agency continue this collaborative approach. Another comment specifically requested that FDA develop a process by which the Agency shares its intended public communication prior to posting it on FDA's Web site to allow applicants the opportunity to make corrections, including those related to unintentional disclosure of confidential or proprietary information.

(Response) FDA verifies all information with the applicants prior to posting information on FDA's Web site. Applicants also review the information posted on the Web site regularly and provide updates to FDA as new information becomes available.

(Comment 43) One comment noted that the rule does not address how the estimated shortage durations are determined. The comment stated that the estimated duration of shortages of some common medications, such as injectable calcium and phosphate preparations, listed on FDA's Web site have been inaccurate, which has made it difficult to develop strategies to prioritize care for those patients most in need of these drugs. The comment also expressed concern that there are no consequences for gross underestimations of durations of shortages. The comment recommended that FDA address these issues in the final rule.

(Response) The estimated shortage duration that is provided on FDA's Web site is intended to capture the particular applicant's anticipated recovery time and is based on information provided by the applicant. FDA communicates with applicants on a daily basis and updates the Web site with estimated recovery time as information becomes available from the applicants. The Agency makes every effort to provide as much information as possible and works closely with applicants to ensure that the Web site lists the most current information.

(Comment 44) One comment expressed concern about including each presentation of a drug product (e.g., strength, dosage form, route of administration) that is determined to be in

shortage in the public shortage list when alternate presentations of the same product remain available. The comment stated that section 503B of the FD&C Act (21 U.S.C. 353b) permits a compounder to begin manufacturing a drug once it is on the section 506E shortage list. As such, the comment stated that compounders may begin manufacturing a product on the list, even if there are other available presentations that would be adequate substitutes. The comment stated that compounded products raise grave public health concerns and urged FDA to provide examples of situations in which the Agency will not list a drug or biological product because a suitable substitute is available. The comment stated that such a clarification would be consistent with the public health exception to the statutory requirement for FDA to publicly disclose, to the maximum extent possible, information on drug shortages.

(Response) The Agency does not agree that withholding particular presentations of a drug from the shortage list because other presentations are available would be appropriate or beneficial to the public health. Other comments received on the proposed rule, and our own experience, indicate the importance to health care professionals of being made aware of shortages of any presentation of a given drug product to ensure that they have the most accurate information about products in shortage and can make treatment decisions accordingly. We do not think the potential risk identified by the comment outweighs the benefit to health care providers and patients of having this information. We note further that while section 503B of the FD&C Act does permit compounding of drug products listed in the drug shortages list, only the specific presentations included in the drug shortages list may be compounded. Moreover, facilities that compound under section 503B must comply with the current good manufacturing practice requirements under section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)).

(Comment 45) One comment suggested that FDA communicate directly with physician organizations and affected specialty societies about shortages so that the impact of the shortage can be minimized.

(Response) FDA agrees that communication about products that are in shortage is essential to ensure that health care providers have the information they need to make appropriate treatment decisions. We note that in FDA's drug and biological products shortages Web pages, individuals may sign up to receive email updates of shortage information. Drug and biological product shortage updates are also available by RSS feed.

(Comment 46) One comment recommended that FDA establish a mechanism whereby physicians can receive shortage information about specific therapeutic categories via email updates, an RSS feed, or through a smartphone application. The comment stated that these targeted communications would allow physicians to receive only the information they need.

(Response) Physicians and other interested stakeholders can receive information about specific therapeutic categories or specific products via email updates and RSS feed by signing up on FDA's Web site. In addition, in March 2015, FDA launched a mobile application (app) designed to facilitate access to information about drug shortages. The app identifies current drug shortages, resolved shortages, and discontinuances of drug products. The app allows users to search by a drug's generic name or active ingredient and also by therapeutic category. The app is available for free download via iTunes (for Apple devices) and the Google Play store (for Android devices) by searching "FDA Drug Shortages."

(Comment 47) One comment stated that it would be helpful if the information contained in FDA's Drug Shortage Web site were categorized by specific classes of drugs in shortage that are relative to a particular area of research, such as oncology. The comment stated that by

categorizing the information in this way, FDA could quickly notify researchers of drug shortages in classes frequently used by researchers in a particular specialty.

(Response) FDA's Drug Shortage Web site, which was redesigned after publication of the proposed rule, currently lists products alphabetically as well as by therapeutic category. This enables health care providers and other interested parties to access information relevant to particular specialties more easily.

(Comment 48) One comment recommended that FDA include information on the shortages Web sites indicating whether the drug or biological products listed are being utilized in an FDA-approved clinical trial. The comment also stated a link should be provided to the [clinicaltrials.gov](http://clinicaltrials.gov) Web site for each clinical trial in which the product is being used.

(Response) FDA shares the commenter's concern about the impact that drug and biological product shortages may have on clinical trials that test investigational products against the standard of care. However, the shortages Web sites as well as [clinicaltrials.gov](http://clinicaltrials.gov) are updated regularly, and it would not be feasible, at this time, to maintain links between the products on the shortages lists and the separate Web site that lists clinical trials in which the products may be used. FDA encourages investigators and sponsors to sign up for email updates or RSS feed and to visit FDA's Web site for the most up-to-date information about drug and biological product shortages. We also encourage sponsors to discuss with the appropriate review division any contingency plans if there is a shortage of products being used in a clinical trial.

## 5. Confidentiality and Disclosure

(Comment 49) Two comments noted the provision in the proposed rule that "FDA may choose not to make information...available on the drug shortages list...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 drug to patients)." The comments stated that the provision presumes that FDA is uniquely qualified to determine the relative value and/or risk associated with public dissemination of information related to product supply and product shortages. The comments suggest that, at a minimum, FDA should incorporate applicants' input into the decisionmaking regarding public dissemination of information related to supply constraints.

(Response) The provision of the proposed rule referenced in the comment codifies section 506E(c)(3), which reflects Congress' intent that FDA should have the discretion not to make information public if the Agency determines that disclosure would adversely affect public health. We welcome stakeholder input on all shortage-related matters. However, consistent with the statute, it is ultimately FDA's determination whether disclosure of information would adversely affect public health.

#### 6. Failure to Notify

(Comment 50) Three comments requested that FDA establish a process for issuing and adjudicating noncompliance letters sent to an applicant for failure to notify FDA as required by section 506C(a) of the FD&C Act. The comments expressed concern about potential disagreements between the Agency and the applicant about what constitutes timely notification and stressed the importance of a dialogue between FDA and the applicant before a noncompliance letter is issued. One comment specifically requested a process by which an applicant may appeal a decision to issue a noncompliance letter and confirmation from FDA that it will retract and remove any noncompliance letter from the Web site if the appeal is successful.

(Response) FDA believes that the process set forth in section 506C(f) of the FD&C Act (and codified in the final rule) is sufficiently clear. The Agency will send a noncompliance letter

to an applicant for failure to notify FDA, which includes failure to timely notify FDA, of a permanent discontinuance or interruption in manufacture that is likely to lead to a meaningful disruption in the supply of a drug in the United States. As provided in the statute, not later than 30 calendar days following issuance, the applicant must submit a response to the noncompliance letter. If an applicant believes it received a noncompliance letter in error, the applicant should provide in its response a full explanation, including relevant dates surrounding the event in question, and any other information of which FDA should be made aware. The Agency, in turn, will consider the information provided in determining whether the noncompliance letter was issued in error or there was a reasonable basis for not notifying the Agency. If FDA determines that the original letter was issued in error or that the recipient had a reasonable basis for not notifying FDA, then the Agency will not post the noncompliance letter or response to the Web site. In light of the process and timeframes specified in section 506C(f) of the FD&C Act, FDA does not believe that a separate appeals process or any further clarification is necessary at this time.

(Comment 51) Two comments requested that FDA establish a process to ensure that no confidential or proprietary information is released when a noncompliance letter and the applicant's response is posted to FDA's Web site.

(Response) As required by section 506C(f)(3) of the FD&C Act, appropriate redactions will be made before a noncompliance letter and the applicant's response are posted to FDA's Web site. FDA has extensive experience redacting confidential and proprietary information, e.g., from NDA and BLA approval packages, before posting documents to the Web site. We believe that the systems the Agency has in place are adequate to address the redaction of noncompliance letters and any response submitted by the applicant.

(Comment 52) One comment requested confirmation that FDA intends to address the failure to notify through the noncompliance letter process and not by GMP inspections.

(Response) If an applicant fails to notify FDA as specified in the final rule, the Agency will address such failure through the process outlined in section 506C(f) of the FD&C Act and codified in this rule.

(Comment 53) One comment suggested that FDA should provide notice of noncompliance to the major news services as well as posting the information on FDA's Web site. The comment stated that in this way, consumers, distributors, and other stakeholders will have knowledge of which companies have not complied with the notification requirement.

(Response) Consistent with section 506C(f) of the FD&C Act, FDA intends to make noncompliance letters and any response to such letters public by posting them on FDA's Web site, unless FDA determines that the noncompliance letter was issued in error or, after reviewing the applicant's response, determines that the applicant had a reasonable basis for not notifying.

(Comment 54) One comment stated that FDA should be better empowered to enforce the notification requirement, potentially by being given authority to fine companies that are noncompliant.

(Response) As explained in the comment to the previous response, FDA will address noncompliance in the manner prescribed in section 506C(f) of the FD&C Act.

#### D. Other Issues Raised

(Comment 55) Multiple comments requested that FDA work with other Agencies and professional societies to develop treatment guidelines when drug and biological products are in shortage.

(Response) FDA does not typically develop treatment guidelines. We note that some professional societies, such as the American Society of Health-System Pharmacists, do provide treatment guidelines that interested parties may consult.

(Comment 56) Several comments stated that notification only of a permanent discontinuance or an interruption in manufacturing is not sufficient to address the drug shortage problem. The comments noted that steps need to be taken to address manufacturing problems that may lead to product shortages. The comments also suggested that, in addition to notification, there should be a plan in place to either import an equivalent drug from other countries or assign a firm to manufacture the drug.

(Response) FDA appreciates and shares the commenters' concern about the problem of drug and biological product shortages. However, these comments are beyond the scope of this rulemaking. The Agency is issuing the final rule to implement sections 506C and 506E of the FD&C Act, which require notification of a permanent discontinuance or an interruption in manufacturing of certain covered products and maintenance by FDA of a publicly available list of drugs that are determined by FDA to be in shortage. As explained in section I, consistent with FDA's authority under the FD&C Act, the Agency uses a variety of tools to prevent or mitigate drug and biological product shortages, and early notification is crucial to FDA's efforts. However, FDA does not have authority over an applicant's business decisions regarding the manufacture of particular products.

(Comment 57) One comment raised issues concerning the preliminary regulatory impact analysis and the Agency's assessment of the net benefit of the rulemaking.

(Response) Our response is provided in the full discussion of economic impacts available in Docket No. FDA-2011-N-0898 (Ref. 4) and at

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

## V. Legal Authority

FDA is amending its regulations to implement sections 506C and 506E of the FD&C Act 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)).

## VI. Economic Analysis of Impacts

### A. Introduction

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this final rule is 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, \$227, represents a small percentage of average annual sales (up to 0.10 percent). Although the final rule does not require specific mitigation strategies, for firms that choose to implement mitigation or prevention strategies, it is possible that additional costs of \$113,000 associated with implementing mitigation strategies could be significant: 2 to 7.8

percent of average annual sales for companies with fewer than 20 employees. In FDA's experience 4 to 5 small businesses entities per year have been affected by a shortage. The Agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

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 \$144 million, using the most current (2014) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

#### B. Summary

The final rule amends FDA's regulations to implement sections 506C and 506E of the FD&C Act, as amended by FDASIA. The final rule requires all applicants of covered, approved prescription drug or biological products other than blood or blood components for transfusion (referred to as 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 prescription 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 6 months in advance of the permanent discontinuance or interruption in manufacturing, or, if that is not possible, as soon as practicable,

but no later than 5 business days after the permanent discontinuance or interruption occurs. The final 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 final rule would impose annual costs of up to \$40.54 million on those applicants or entities affected by the rule, and up to \$6.38 million on FDA in preventive costs. Estimated total annual costs of the interactions between industry and FDA range between \$14.54 million and \$46.92 million. Discounting over 20 years, annual quantified benefits from avoiding the purchase of more expensive alternative products, managing product shortages, and life-years gained, would range from \$30.45 million to \$98.65 million using a 3 percent discount rate, and from \$30.39 million to \$98.42 million using a 7 percent discount rate. Annualized over 20 years, net benefits range between \$15.90 million and \$51.72 million using a 3 percent discount rate; they range between \$15.85 million and \$51.50 million using a 7 percent discount rate. The public health benefits, mostly non-quantified, include the value of information that would assist FDA, manufacturers, health care providers, and patients in evaluating, mitigating, and preventing shortages of drug 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 1.

Under the current environment all notifications provide meaningful information to identify a shortage or to prevent one, but there is uncertainty whether the scope of the rule could result in notifications that do not provide information about any shortage and lead to additional costs.

The full discussion of economic impacts is available in Docket No. FDA-2011-N-0898

and at

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>

(Ref. 4).

Table 1.--Summary of Benefits, Costs and Distributional Effects of Final Rule

Category	Primary Estimate	Low Estimate	High Estimate	Year Dollars	Discount Rate	Period Covered	Notes
Benefits							
Annualized Monetized (millions \$/year)	\$64.545	\$30.445	\$98.645	2013	3%	2015-34	There is uncertainty surrounding these estimates because some underlying estimates came from non-representative studies.
	\$64.408	\$30.390	\$98.425	2013	7%	2015-34	
Annualized Quantified					3%	2015-34	17-55 preventable shortages per year.
					7%	2015-34	
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)	\$30.731	\$14.540	\$46.921	2013	3%	2015-34	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.
	\$30.731	\$14.540	\$46.921	2013	7%	2015-34	
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	Based on the analysis small business entities covered by the final rule could incur small costs, \$227 per notification or up to 0.10 percent of their average annual sales. Although the final 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.

## VII. Paperwork Reduction Act of 1995

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

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

Description: Under the final 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) must 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 is 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 final rule requires that the notification 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 final rule, the notification must 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 must 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, FDA will issue a letter informing the applicant or manufacturer of its noncompliance. The applicant must 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 2) will 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 final rule. We estimate that these respondents will submit annually a total of approximately 305 notifications as required under §§ 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 final rule ("Total Annual Responses" in table 2).<sup>15</sup> 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 2). We also estimate that preparing and submitting these notifications to FDA will take approximately 2 hours per respondent ("Hours per Response" in table 2).

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<sup>15</sup> This estimate is based on the number of new notifications we anticipate receiving under the final 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 are not covered under any existing OMB control number, and thus must be captured in this PRA estimate. In contrast, the analysis of impacts of the final rule estimates the costs and benefits 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 final analysis of impacts.

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), 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).

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

Table 2.--Estimated Reporting Burden<sup>1</sup>

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
Notifications required under §§ 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

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

The information collection provisions of this final rule have been submitted to OMB for review, as required by section 3507(d) of the PRA. Prior to the effective date of this final rule, FDA will publish a notice in the Federal Register announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

## VIII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the Agency concludes that the rule does not contain policies that have federalism

implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

#### IX. 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.

#### X. References

The following references have been placed on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, 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 May 2015.

2. Center for Drug Evaluation and Research, Manual of Policies and Procedures 4190.1 Rev. 2, "Drug Shortage Management," September 3, 2014, available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079936.pdf>, accessed May 2015.

3. Center for Biologics Evaluation and Research, Standard Operating Policy and Procedure 8506, "Management of Shortages of CBER-Regulated Products," April 9, 2012, available at

<http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/pruceduressopps/ucm299304.htm>, accessed May 2015.

4. "Regulatory Impact Analysis, Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis for Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products"; Final 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, 21 CFR parts 20, 310, 314, and 600 are 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, 379k-1; 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, 379k-1.

6. Revise § 314.81(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 Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356c(c)) 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 drug to patients). FDA will also not provide information on the public drug shortages list or under section 506C(c) of the Federal Food, Drug, and Cosmetic 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) 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, 379k-1; 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 Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356c(c)) 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 Federal Food, Drug, and Cosmetic 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: July 1, 2015.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2015-16659 Filed: 7/7/2015 08:45 am; Publication Date: 7/8/2015]