Notifying FDA of a Discontinuance or Interruption in Manufacturing of Finished Products or Active Pharmaceutical Ingredients Under Section 506C of the FD&C Act

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Drug Shortage Staff, 240-402-7770, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

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Procedural

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Notifying FDA of a Discontinuance or Interruption in Manufacturing of Finished Products or Active Pharmaceutical Ingredients Under Section 506C of the FD&C Act Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA is issuing this guidance to assist applicants and manufacturers in providing FDA timely, informative notifications about changes in the production of certain finished drugs and biological products[2] as well as certain active pharmaceutical ingredients (API)[3] that may, in turn, help the Agency in its efforts to prevent and mitigate shortages.

The guidance discusses the notification requirements under section 506C of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356c) and FDA's regulations. Generally, section 506C of the FD&C Act requires applicants and manufacturers of certain finished drugs and biological products to notify FDA of (1) a permanent discontinuance in the manufacture of such products, (2) an interruption in the manufacture of such products that is likely to lead to a meaningful disruption in supply of those products in the United States, (3) a permanent discontinuance in the manufacture of API for such products, or (4) an interruption in the manufacture of API for such products that is likely to lead to a meaningful disruption in the supply of the API for those products. This guidance recommends that applicants and manufacturers provide additional details and follow additional procedures to ensure FDA has the specific information it needs to help prevent or mitigate shortages. In addition, the guidance

[1] This guidance has been prepared by the Drug Shortage Staff and the Office of Regulatory Policy in the Center for Drug Evaluation and Research (CDER), in conjunction with the Office of Compliance and Biologics Quality in the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For purposes of this guidance, a *finished drug* or *biological product* refers to a specific strength, dosage form, and route of administration of a drug or biological product. See 80 FR 38915 at 38919 and 38928; see also section 506C(h)(1) of the FD&C Act (defining "drug" for purposes of section 506C).

[3] For purposes of this guidance, *active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance (see 21 CFR 207.1).

explains how FDA communicates information about products in shortage to the public. When finalized, this guidance will replace the March 2020 guidance for industry *Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act*.

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

II. BACKGROUND

Title X of the Food and Drug Administration Safety and Innovation Act (FDASIA), enacted on July 9, 2012,[4] and section 3112 of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), enacted on March 27, 2020,[5] amended the FD&C Act to help the Agency address the problem of drug shortages in the United States, including by adding requirements related to notifying FDA about finished product and API manufacturing discontinuances and interruptions. While some supply disruptions and product shortages cannot be predicted or prevented, early communication and detailed notifications from manufacturers to the Agency play a significant role in decreasing the incidence, impact, and duration of supply disruptions and product shortages. Timely notifications that include specific information about the situation allow the Agency to evaluate the situation and determine an appropriate course of action.[6] When FDA does not receive timely, informative notifications, the Agency's ability to respond appropriately is limited.

Please note that notifications regarding discontinuances or potential manufacturing issues that are sent to FDA to meet other reporting requirements, for example, under section 506I of the FD&C Act (reports of marketing status) or 21 CFR 314.81(b)(1) (field alert reports), are not a substitute for the notifications required under section 506C of the FD&C Act. It is important that notifications pursuant to section 506C contain detailed information and be submitted to the appropriate staff in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) (as described in section III.E) to enable timely review and action by the Agency.

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[4] Public Law 112-144. The FDASIA amendments to section 506C of the FD&C Act took effect on July 9, 2012.

[5] Public Law 116-136. The CARES Act amendments to section 506C of the FD&C Act took effect on September 23, 2020.

[6] See CDER's Manual of Policies and Procedures (MAPP) 4190.1 Drug Shortage Management for information about CDER's policies and procedures for evaluating and managing drug shortage situations. CDER MAPPs can be found on the Manual of Policies and Procedures web page at https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp. See CBER's Standard Operating Procedures and Policies (SOPPS) 8506 Management of Shortages of CBER-Regulated Products for information about CBER's policies and procedures for evaluating and managing shortage situations. CBER SOPPs can be found on the Biologics Procedures web page at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-procedures-sopps.

III. NOTIFYING FDA OF A PERMANENT DISCONTINUANCE OR AN INTERRUPTION IN MANUFACTURING

Under section 506C of the FD&C Act and FDA's regulations,[7,8] certain persons must notify FDA of (1) a permanent discontinuance in the manufacture of certain finished drug and biological products, (2) an interruption in the manufacture of certain finished drug and biological products that is likely to lead to a meaningful disruption[9] (or, in the case of blood or blood components intended for transfusion, a significant disruption[10]) in supply of those products in the United States, (3) a permanent discontinuance in the manufacture of API for certain finished drugs and biological products, or (4) an interruption in the manufacture of API for certain

[7] Section 506C(i) of the FD&C Act (as amended by FDASIA) required FDA to issue regulations implementing section 506C of the FD&C Act. On July 8, 2015, FDA issued the final rule, "Permanent Discontinuance or Interruption in Manufacturing of Certain Drug or Biological Products" (80 FR 38915) to implement section 506C and other drug shortage provisions of the FD&C Act, as amended by FDASIA (see 21 CFR 310.306, 314.81(b)(3)(iii), and 21 CFR 600.82). Section 506C(i)(3) of the FD&C Act permitted FDA to apply the section, by regulation, to biological products (as defined in section 351 of the Public Health Service Act), including plasma products derived from human plasma protein and their recombinant analogs, if FDA determined that including these products would benefit the public health. FDA's 2015 final rule extended drug shortage notification requirements to applicants of certain biological products, including recombinant therapeutic proteins, monoclonal antibody products, vaccines, allergenic products, plasma derived products and their recombinant analogs, blood or blood components for transfusion, and cellular and gene therapy products (see § 600.82 and 80 FR 38915 at 38918).

[8] As noted above, the CARES Act amended section 506C of the FD&C Act by, among other things, adding requirements related to notifying FDA about discontinuances and interruptions in manufacturing of certain APIs. Prior to the CARES Act, section 506C contained notification requirements applicable to covered finished products (as described below in section III.A) only. As such, the regulations implementing section 506C, which FDA promulgated in 2015 (80 FR 38915), contain notification requirements applicable to covered finished products only. These regulations do not contain the notification requirements described in this guidance that are applicable to API for covered finished products; rather, such API notification requirements arise directly under section 506C, as amended by the CARES Act.

[9] With respect to finished product notifications under section 506C of the FD&C Act, *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 (see section 506C(h)(3) of the FD&C Act and §§ 314.81(b)(3)(iii)(*f*) and 600.82(f)).

[10] *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 (see § 600.82(f)). 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 (see 80 FR 38915 at 38920-21).

finished drugs and biological products that is likely to lead to a meaningful disruption[11] in the supply of the API for those products. Notifications under section 506C must include disclosure of reasons for the discontinuation or interruption.[12] The sections below describe the notification requirements under section 506C in greater detail and provide recommendations about the notifications, including the timing and contents.

A. Who Must Notify FDA and What Products are Subject to the Notification Requirements

The persons who must submit notifications under section 506C (collectively referred to in this guidance as *manufacturers*) are as follows:

- Applicants with approved new drug applications (NDAs) or approved abbreviated new drug applications (ANDAs) for certain finished drug products[13]
- Applicants with approved biologics license applications (BLAs) for certain finished biological products other than blood or blood components[14]
- Applicants with approved BLAs for blood or blood components for transfusion that manufacture a significant percentage of the U.S. blood supply[15,16]
- Manufacturers of certain finished drug products marketed without approved NDAs or ANDAs[17]

The notification requirement regarding discontinuances and interruptions in manufacturing of API under section 506C of the FD&C Act applies only to the *manufacturers* that are listed above; other entities in the supply chain for a drug, including third-party API manufacturers and suppliers, are not required to submit such notifications.

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[11] For purposes of this guidance, and with respect to API notifications under section 506C of the FD&C Act, *meaningful disruption* means a change in production that is reasonably likely to lead to a reduction in supply of an API by its manufacturer that is more than negligible and affects the ability of the API manufacturer to fill orders or meet expected demand for the API, and does not include interruptions in manufacturing due to matters such as routine maintenance or insignificant changes in manufacturing so long as the API manufacturer expects to resume operations in a short period of time.

[12] See section 506C(a) of the FD&C Act.

[13] See § 314.81(b)(3)(iii).

[14] See § 600.82(a)(1).

[15] See § 600.82(a)(2).

[16] 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 (see 80 FR 38915 at 38917).

[17] See § 310.306, which applies § 314.81(b)(3)(iii) in its entirety to covered drug products marketed without an approved NDA or ANDA.

The finished products for which notifications must be submitted under section 506C of the FD&C Act (referred to in the guidance as *covered finished products*) are prescription drugs and biological products[18] (including blood or blood components for transfusion) that are (1) life supporting, life sustaining,[19] or intended for use in the prevention or treatment of a debilitating disease or condition,[20] including any such product used in emergency medical care or during surgery or any such drug that is critical to the public health during a public health emergency declared by the Secretary under section 319 of the Public Health Service Act; and (2) not radiopharmaceutical drug products or any other products designated by FDA.[21,22] In addition, the manufacturers listed above must submit notifications under section 506C of the FD&C Act for API of covered finished products.[23]

In general, the notification requirements for covered finished products apply to each individual manufacturer regardless of market share, number of other manufacturers marketing products that are therapeutically equivalent, or the amount of product that may be in distribution.[24] Similarly, with respect to notifications for an API of a covered finished product, FDA recommends that a manufacturer consider its current API manufacturer's supply of the API, regardless of the API manufacturer's market share, the number of other API manufacturers marketing the same or similar APIs, or the amount of the API that may be in distribution. If a manufacturer is not certain whether the notification requirements under section 506C of the FD&C Act apply to the products it manufactures or the API(s) for the products it manufactures, we recommend that the manufacturer contact the Agency as described in section III.E below.

In the case of a covered finished product that is marketed under an approved application and API for such a product, the *applicant* is solely responsible for submitting notifications to FDA under section 506C of the FD&C Act concerning the covered finished product or API for the covered

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[18] See footnote 2.

[19] *Life supporting or life sustaining* means a 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 (see §§ 314.81(b)(3)(iii)(*f*) and 600.82(f)).

[20] *Intended for use in the prevention or treatment of a debilitating disease or condition* means a 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 (see §§ 314.81(b)(3)(iii)(*f*) and 600.82(f)).

[21] See section 506C(a) of the FD&C Act; §§ 310.306, 314.81(b)(3)(iii)(*a*), and 600.82(a).

[22] The notification requirement applies regardless of any determination with respect to whether the product is medically necessary (see generally CDER's MAPP 4190.1 Rev. 3).

[23] See section 506C(a) of the FD&C Act.

[24] As explained in the preamble to the final rule (80 FR at 38920), "…[T]he 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…Consistent with the statute, the rule does not require an applicant to predict the market-wide impact of an interruption in its own manufacturing…" But see above regarding the requirement for blood or blood components intended for transfusion which only applies to applicants that manufacture a *significant percentage* of the U.S. blood supply.

finished product, regardless of whether the product or API is manufactured *by* the applicant itself or *for* the applicant under contract with one or more different entities.[25] Accordingly, the applicant should establish a process with any third-party API suppliers, any relevant contract manufacturers, and other relevant entities to ensure that the applicant can provide a complete and accurate notification to FDA within the required time frame. Likewise, for a covered finished drug product marketed without an approved NDA or ANDA, the manufacturer should establish a process with any third-party API suppliers, any relevant contract manufacturers, and other relevant entities to ensure the manufacturer can provide complete and accurate notification to FDA within the required time frame.

B. When To Notify FDA

In general, manufacturers of covered finished products must submit a notification to FDA at least 6 months in advance of (1) a permanent discontinuance in manufacturing of a covered finished product, (2) an interruption in manufacturing of a covered finished product that is likely to lead to a meaningful disruption in supply of the product in the United States, (3) a permanent discontinuance in manufacturing of API for a covered finished product, or (4) an interruption in manufacturing of API for a covered finished product that is likely to lead to a meaningful disruption in supply of the API for the product.[26] However, if 6 months' advance notice is not possible, the notification must be submitted as soon as practicable thereafter[27]; furthermore, a notification concerning a permanent discontinuance or interruption in manufacturing of a covered finished product must be submitted no later than 5 business days after the discontinuance or interruption in manufacturing occurs.[28]

For covered finished products and API, FDA interprets a permanent discontinuance to be a decision by its manufacturer to cease manufacturing and distributing its product indefinitely for business or other reasons. Notification must be provided within the time frame described above.[29] Upon receiving such notifications, FDA assesses the potential public health impact of the reported discontinuance and, if appropriate, may request further discussion with the reporting manufacturer. With respect to covered finished products in particular, to the extent possible, manufacturers should not delay notifying FDA of a permanent discontinuance until after production has ceased; FDA should be notified well before any decline in supply occurs.

In the case of interruptions in manufacturing of a covered finished product, when assessing whether a meaningful disruption in supply is likely to occur, the relevant analysis is whether a change in production is likely to lead to a reduction in the supply of a product *by the manufacturer* that is more than negligible and would affect *the manufacturer's* ability to fill

[25] See §§ 314.81(b)(3)(iii)(*a*) and 600.82(a)(1).

[26] See section 506C(b) of the FD&C Act; §§ 310.306(b), 314.81(b)(3)(iii)(*b*)(*1*), and 600.82(b)(1).

[27] See section 506C(b) of the FD&C Act.

[28] See section 506C(b) of the FD&C Act; §§ 310.306(b), 314.81(b)(3)(iii)(*b*)(*2*), and 600.82(b)(2).

[29] See section 506C(a) of the FD&C Act; §§ 310.306(b), 314.81(b)(3)(iii)(*a*), and 600.82(a).

orders or meet expected demand for its product.[30] In other words, the assessment is to be based solely on the reporting manufacturer's capacity and supply. The manufacturer should not consider other manufacturers' or competitors' capacities or assumed capacities, or what it understands about market demand for the product.[31] To the extent it is possible to do so, manufacturers must notify FDA of an interruption in manufacturing that is likely to lead to a meaningful disruption in their own supply of the covered finished product in the United States prior to the interruption's occurrence.[32] In all cases, manufacturers should notify the Agency before a meaningful disruption in their own supply of a covered finished product occurs. For example, FDA should not first learn of a meaningful supply disruption resulting from an interruption in manufacturing when a manufacturer is unable to fill an order. Note that after providing the initial notification of an interruption in manufacturing of a covered finished product under section 506C of the FD&C Act, FDA recommends that manufacturers provide updates approximately every 2 weeks on the situation, including the expected timeline for resuming normal operations, even if the status remains unchanged. These updates are important to ensure that FDA remains informed and can act on the most current information. We recommend that such updates be submitted until the situation has been resolved.

If a manufacturer is unsure of whether to notify FDA of an interruption in manufacturing because the firm does not know whether it is likely to lead to a meaningful disruption in its supply,[33] FDA urges the manufacturer to submit a notification anyway. This would allow FDA to monitor the overall market and take timely steps, as necessary, to help prevent or mitigate any resulting shortage. In addition, if a manufacturer is considering taking an action that may lead to a meaningful disruption in the supply of a product (e.g., holding production to investigate a quality issue or transfer of ownership), FDA requests that the manufacturer notify FDA immediately through the process explained below in section III.E.

[30] See 80 FR 38915 at 38920. Manufacturers are not required to report 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 (see section 506C(h)(3)(B) of the FD&C Act).

[31] See 80 FR 38915 at 38920 (explaining that manufacturers are not required or expected to predict the market-wide impact of an interruption in their own manufacturing). But see section III.A (explaining that the regulatory requirement for blood or blood components intended for transfusion only applies to applicants that manufacture a *significant percentage* of the U.S. blood supply) (emphasis added).

[32] See section 506C(b) of the FD&C Act; §§ 310.306(b), 314.81(b)(3)(iii)(b), and 600.82(b).

[33] See footnote 9.

In the case of interruptions in manufacturing of API, a covered finished product manufacturer is required to notify FDA of interruptions in the manufacture of the API of such products that are likely to lead to a meaningful disruption in the supply of API. When assessing whether a meaningful disruption is likely to occur in this context, the manufacturer should consider whether a change in production of the API is likely to lead to a reduction in the supply of API *by the API supplier* that is more than negligible and would affect *the API supplier*'s ability to fill orders or meet expected demand for the API.[34] As noted in section III.A, to ensure the manufacturer is able to satisfy the notification requirement with respect to API, manufacturers should establish a process to ensure they receive sufficient, timely information about changes in production of their supplier's API.

As described above, the notification requirements under the FD&C Act and FDA's regulations are triggered by a permanent discontinuance or an interruption in manufacturing that is likely to lead to a meaningful disruption in supply of certain finished drugs or biological products or API for those products. However, FDA requests that manufacturers also notify the Agency when they are unable to meet demand for covered finished products, even in the absence of an interruption in manufacturing, for example, when there is a sudden, unexpected spike in demand. Though manufacturers are not required to report this type of situation to FDA, reporting under these circumstances provides an important signal to the Agency about a potential shortage and allows FDA to take appropriate steps to address the potential shortage.

C. What Information To Include in Notifications About Discontinuances or Interruptions in Manufacturing of Covered Finished Products

Under section 506C of the FD&C Act and FDA's regulations, notifications concerning a permanent discontinuance or interruption in the manufacture of a covered finished product that is likely to lead to a meaningful disruption in supply must include, at a minimum:[35]

- Name of the product, including the National Drug Code (NDC) number, or, for biological products, an alternative standard for identification and labeling if one has been recognized as acceptable by the Center Director.[36]

- Name of the applicant (for approved products) or manufacturer (for unapproved drugs).

- Whether the notification relates to a permanent discontinuance of the product or an interruption in manufacturing of the product.

- Description of the reason(s) for the discontinuation or interruption in manufacturing.

[34] FDA recommends that a manufacturer consider its current API manufacturer's supply of the API regardless of the API manufacturer's market share, the number of other API manufacturers marketing the same or similar APIs (including, for approved products, the number of approved API sources the manufacturer may have), or the amount of the API that may be in distribution.

[35] See section 506C(a) of the FD&C Act; §§ 310.306(b), 314.81(b)(3)(iii)(*c*), and 600.82(c).

[36] See § 600.82(c)(1).

- If an API is a reason for, or risk factor in, the discontinuation or interruption, the source of the API, and any alternative sources for the API known by the manufacturer.

- Whether any associated device used for preparation or administration included in the covered finished product[37] is a reason for, or risk factor in, the discontinuation or interruption in manufacturing of the covered finished product.

- The estimated duration of an interruption in manufacturing of the covered finished product.

As noted above, this information is the minimum that manufacturers must provide. However, to ensure that FDA is better equipped to help prevent or mitigate a drug shortage, FDA recommends that manufacturers provide additional details about the situation and has included below a list of types of additional information for manufacturers to consider providing in their notifications to FDA. This list is not intended to be exhaustive; it provides information that FDA generally finds helpful in assessing the situation and determining appropriate steps to help prevent or mitigate a shortage. The more information manufacturers provide, the better FDA will be able to assist.

We recommend including the following additional information, as relevant to the situation, when notifying FDA of a permanent discontinuance or interruption in manufacturing concerning a covered finished product:

- Whether the notification concerns an unavoidable supply disruption or a supply disruption that may be preventable.

- The underlying reason or root cause leading to this notification. (A detailed and thorough explanation beyond "manufacturing delay" or a recitation of the broad categories of reasons listed below in section IV is especially important and allows FDA to identify and use the most appropriate and effective mitigation tools.)

[37] For purposes of the notification requirement under section 506C of the FD&C Act, FDA considers the term *any associated device used for preparation or administration included in the drug* to be a device constituent part of a covered finished product that is a drug-led, drug-device or biologic-led, biologic-device combination product (i.e., a single entity, co-packaged, or cross-labeled combination product, as defined in 21 CFR 3.2(e)). Under section 506J of the FD&C Act, manufacturers of certain medical devices are required to notify the Agency of a permanent discontinuance in the manufacture of the device or interruption in manufacture of the device that is likely to lead to a meaningful disruption in the supply of the device in the United States. For more information about such device notifications, see section 506J of the FD&C Act. Regarding the shortage of a device, if you have questions about your notification, you can contact the Center for Devices and Radiological Health at CDRHManufacturerShortage@fda.hhs.gov and include "Question" in the subject line of the email.

- The estimated date of onset of the interruption in manufacturing or supply disruption for this product. If a supply disruption has already occurred, provide the estimated duration.[38]

- The anticipated time frame for all existing product (on hand and in distribution channels) to be exhausted if the notification is for a permanent discontinuance.

- The estimated market share for the product and whether the entire market share is affected by this issue.

- The estimated volume of historic monthly sales, usage, or demand, as applicable, for this product.

- Whether the product is manufactured on multiple lines or in multiple facilities.

- Amount of current inventory of product at the manufacturing facility or warehouse.

- If the notification is for an interruption in manufacturing, the date when the last remaining batch of finished product was or will be released into distribution and how long the supply is expected to last in the market without additional releases based on current demand.

- Whether there is an emergency or reserve supply of this product and whether allocation[39] of supply on hand or reserve supply is an option.

- Whether a redundancy risk management plan that identifies and evaluates risks to the supply of the drug is in place.[40]

- Whether public information has been provided or will be provided for stakeholders and patients regarding this actual or potential shortage (e.g., Dear Healthcare Provider (DHCP) Letters, supply or shortage information posted on the manufacturer's website).

- Whether a proposal is available for FDA to review that may help to expedite availability of the product or suggestions for FDA actions that may help prevent or mitigate a supply disruption or shortage.

Manufacturers need not have all of these additional details available before submitting a notification; notifications can be updated at any time to include such additional information.

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[38] Notifications of interruptions in manufacturing must include the expected duration of the interruption in manufacturing. See section 506C(a) of the FD&C Act. See also §§ 310.306(b), 314.81(b)(3)(iii)(*c*)(*5*), and 600.82(c)(5).

[39] *Allocation* generally refers to limiting the quantity distributed to customers to extend the life of the existing supply.

[40] See section 506C(j) of the FD&C Act.

Manufacturers must provide initial notification within the timeframe described in section 506C(b) of the FD&C Act and applicable regulations (see section III.B for further discussion), and FDA recommends that manufacturers update their notifications with additional information as it becomes available. As described further in section IV below, information that is submitted to FDA will not be disclosed except in accordance with applicable disclosure law, which includes restrictions on the release of confidential commercial information and trade secrets.[41] If FDA determines that a product is in shortage, the Agency intends to work with manufacturers to confirm the accuracy and appropriateness of information regarding the shortage before posting publicly on FDA's website.

D. What Information to Include in Notifications About Discontinuances or Interruptions in Manufacturing of API

Under section 506C of the FD&C Act, notifications concerning API must include, at a minimum:[42]

- Disclosure of reasons for the discontinuation or interruption in manufacturing of the API.
- Source of the API and any alternative sources for the API known by the finished product manufacturer.
- Expected duration of an interruption in manufacturing of the API.

To ensure these notifications provide information that is helpful to FDA in assessing the potential for a supply disruption or shortage, we recommend that manufacturers also include the additional information outlined below:

- Name(s) of the finished product(s) for which the API is used, including the NDC number(s), or, for biological products, an alternative standard for identification and labeling if one has been recognized as acceptable by the Center Director.[43]
- Name of the application holder (for approved products) or manufacturer (for unapproved drugs) of the covered finished product(s) for which the API is used.
- Number of any drug master file associated with the API.[44]
- Whether the notification relates to a permanent discontinuance of the API or an interruption in manufacturing of the API.

[41] See section 506C(d) of the FD&C Act.

[42] See section 506C(a) of the FD&C Act.

[43] See § 600.82(c)(1).

[44] See § 314.420.

- Estimated date of onset of the interruption in manufacturing or supply disruption for the API. If a supply disruption has occurred, provide the estimated duration.[45]

- Whether the discontinuance or interruption in manufacturing of the API has impacted or is expected to impact the supply of the covered finished product or ability to fill orders for the covered finished product.

E. How To Notify FDA

Manufacturers of covered finished products regulated by CDER should submit initial notifications about such products[46] and API for such products either via email to drugshortages@fda.hhs.gov or through the CDER Direct NextGen Portal at https://edm.fda.gov. Manufacturers of covered finished products regulated by CBER should submit initial notifications about such products[47] and API for such products via email to cbershortage@fda.hhs.gov. All additional updates should be submitted by email to the applicable Center (CDER or CBER), not through the NextGen Portal.

Manufacturers should submit a separate notification for each permanent discontinuance or interruption in manufacturing. A single initial notification may include a list of all affected covered finished products[48] or API. Manufacturers should not provide notification about a newly affected product (e.g., a new strength) in an update, even if the issue is related to a previously reported interruption in manufacturing. Rather, a separate initial notification should be submitted to ensure the newly affected product is tracked appropriately. In addition, as explained in section II, notifications submitted to FDA to satisfy other reporting requirements (e.g., under section 506I of the FD&C Act) are not a substitute for the notifications required under section 506C.

F. Failure To Notify FDA

If a manufacturer fails to provide notification with respect to covered finished products or API, as required by section 506C(a) of the FD&C Act and in accordance with the timelines set forth in section 506C(b) and the implementing regulations,[49] FDA will issue a letter to that manufacturer stating that the applicable notification requirement was not met (a "noncompliance letter").[50] Note that 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

[45] Notifications of interruptions in manufacturing must include the expected duration of the interruption in manufacturing. See section 506C(a) of the FD&C Act.

[46] Notifications for finished products under section 506C of the FD&C Act must be submitted to FDA electronically in a format that FDA can process, review, and archive. See §§ 310.306(b), 314.81(b)(3)(iii)(*b*), and 600.82(b); see also 80 FR 38915 at 38922.

[47] Ibid.

[48] See footnote 2.

[49] Section 506C(b) of the FD&C Act; §§ 310.306(b), 314.81(b)(3)(iii)(*b*)(*1*) and (*2*), and 600.82(b)(1) and (2).

[50] See section 506C(f)(1) of the FD&C Act.

failed to notify FDA "as soon as practicable," FDA will issue a noncompliance letter.[51] The manufacturer must respond to FDA's letter not later than 30 calendar days after its issuance, providing the reason for noncompliance and the information on the discontinuance or interruption required under section 506C(a) of the FD&C Act.[52] Not later than 45 calendar days after the issuance of the noncompliance letter to the manufacturer, FDA will post that letter and any response received on FDA's website,[53] with appropriate redactions to protect trade secrets or confidential commercial information.[54] However, FDA will not post the noncompliance letter and any response it receives if the Agency determines that the noncompliance letter was issued in error or, after review of the manufacturer's response, that the manufacturer had a reasonable basis for not notifying FDA as required.[55]

IV. HOW FDA COMMUNICATES INFORMATION ABOUT DRUGS AND BIOLOGICAL PRODUCTS IN SHORTAGE

Consistent with section 506E of the FD&C Act (21 U.S.C. 356e) and FDA's regulations,[56] FDA maintains public, up-to-date lists of finished drugs and biological products that FDA has determined to be in shortage in the United States.[57] These lists include:

- Established name of the product in shortage; brand name of the product in shortage, if applicable; the NDC number, presentation, strength(s), and package size, as available
- Name of each application holder (for approved products) or manufacturer (for unapproved drugs)
- Name of the distributor, if different from the application holder (for approved products) or manufacturer (for unapproved drugs)
- Reason for the shortage from the following categories:[58]

[51] Ibid.

[52] See section 506C(f)(2) of the FD&C Act.

[53] Links to noncompliance letters can be found at http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm403902.htm.

[54] See section 506C(d), (f)(3) of the FD&C Act.

[55] See section 506C(f)(3) of the FD&C Act.

[56] See section 506E of the FD&C Act; §§ 310.306(c), 314.81(b)(3)(iii)(*d*)(*1*), and 600.82(d)(1).

[57] See https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm for shortages tracked by CDER; see https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages for shortages tracked by CBER.

[58] The reason for the shortage identified is determined by FDA using the notification submitted and any supplementary information gathered, such as from manufacturing facility reviews conducted by FDA.

406
407 — Requirements related to complying with good manufacturing practices
408 — Regulatory delay
409 — Shortage of an active ingredient
410 — Shortage of an inactive ingredient component
411 — Discontinuation of the manufacture of the product
412 — Delay in shipping
413 — Demand increase
414 — Other reason
415
416 • Estimated duration of the supply disruption or shortage, anticipated date of availability,
417 and resolution dates (based on information provided by the manufacturer)
418
419 • Any additional information related to the shortage that the manufacturer chooses to share
420 (e.g., DHCP letters, informed consent forms, or patient letters)
421
422 FDA updates its lists regularly and strives to communicate in *real-time* so that patients and
423 healthcare providers have the most current information on product shortages in the United States.
424 A product is added to the CDER- or CBER-maintained list only after the Agency determines that
425 it is in shortage; products are not added to the list(s) immediately upon receipt of a notification
426 regarding a discontinuance or interruption in manufacturing. In cases where a shortage does not
427 occur or is prevented through FDA or stakeholder intervention, the product will not be posted on
428 the list. FDA generally considers a shortage to be resolved and removes the product from the
429 "current shortage" section of the list based on an evaluation of the entire market, assessing
430 whether all backorders have been filled and supply is meeting or exceeding demand. In making
431 this evaluation, FDA may consider, among other factors, affected market share, ability of
432 alternate manufacturers to cover the demand, and confirmed market stabilization.
433
434 The Agency does not include confidential commercial information or trade secrets in these
435 lists.[59] In general, FDA works with manufacturers to confirm the accuracy and appropriateness
436 of information before posting publicly on its website(s). FDA will continue to post information
437 on its website(s) consistent with section 506E of the FD&C Act and FDA's regulations,
438 regardless of any additional information manufacturers provide to the Agency based on the
439 recommendations in this guidance.

[59] See section 506E(c)(2) of the FD&C Act.