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FDA Issues New Guidance on Supply-Chain Disruption Notifications During COVID-19 Emergency

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On March 27, 2020, the FDA issued new guidance, "Notifying the FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act: Guidance for Industry," in an effort to prevent or mitigate shortages of drug and biologics products during the COVID-19 public health emergency. The issuance of the new Guidance followed a month of disruptions of active pharmaceutical ingredient (API) imports from China and India directly related to COVID-19.

The new Guidance provides the FDA's current thinking on industry requirements to notify the FDA of discontinuances or interruptions in drug manufacturing, in compliance with Section 506C(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) and its implementing regulations (e.g., 21 CFR § 310.306; 21 CFR § 600.82). This is the first Guidance to interpret these notification requirements since Congress granted this authority to the FDA under Title X of the Food and Drug Administration Safety and Innovation Act (the FDASIA), which amended the FDCA to give the FDA additional authority to address the challenges of increasing globalization and supply-chain complexity.

The Guidance emphasizes the critical role that manufacturer notifications play in preventing and addressing drug shortages during the COVID-19 pandemic. The Guidance also explains the importance of providing the FDA with timely and detailed information, to decrease the number, impact, and duration of drug shortages and supply-chain disruptions.

What Triggers the Notification Requirement?

Section 506C(a) requires manufacturers of life-saving drugs to notify the FDA of a permanent discontinuance, or an interruption in manufacturing, of a life-saving drug that is likely to cause "meaningful disruption" in the supply of that product in the U.S.

Notification is required for discontinuance or interruption in the manufacture of prescription drugs (other than radiopharmaceuticals) and biological products that are life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition. Life-supporting or life-sustaining drugs include sedatives, anesthetics, analgesics, and anti-inflammatory drugs. A debilitating disease or condition is one associated with mortality or morbidity that has a substantial impact on day-to-day functioning.

The FDA interprets a permanent discontinuance to be the manufacturer's decision to stop manufacturing and distributing a life-saving drug indefinitely. All permanent discontinuances meet the requirements for notification to the FDA. A disruption in manufacturing operations is "meaningful" if it results in a decrease in supply of a drug product that is "more than negligible" and would affect the ability of the manufacturer to meet anticipated demand for the product. The Guidance states that each manufacturer should focus its analysis on its own operations and not take into account the ability of competitors to meet market demand.

The Guidance also requests a manufacturer to notify the Agency if it is unable to meet demand for a life-saving drug (e.g., "when there is a sudden, unexpected spike in demand"), even if the manufacturer is not experiencing a permanent discontinuance or a qualifying interruption. According to the Guidance, these types of notifications can provide an "important signal" to the FDA of the potential for a shortage. Notice of one such unexpected spike in demand (for Midazolam Injection, USP, which is used for sedation of patients on ventilators (e.g., COVID-19 patients)), led the FDA to add the drug to its shortage list on April 2, 2020.

When to Make a Notification to the FDA?

Manufacturers are required to notify the FDA (1) at least six months before the discontinuance or interruption; or (2) if six months' advance notice is not possible, as soon as practicable, but in no case later than five business days after the discontinuance or interruption. In any event, the FDA expects to be notified well before any supply issues occur. The Guidance also recommends that manufacturers provide the FDA with updates every two weeks, regardless of whether there is a change in the status of the interruption.

What Should Be Included in a Notification?

The Guidance instructs manufacturers that the notification should address certain questions beyond the basic background information required by statute and regulation.

A number of the FDA's questions relate to the timing and extent of the discontinuance/interruption. Manufacturers should tell the Agency how much inventory they have in their possession (including emergency reserves), when the discontinuance/interruption is anticipated to occur, when they anticipate the last batch will be distributed, and how long they think the current supply in the market will meet the current market demand. Manufacturers should also describe how many facilities manufacture the product, which facilities are affected by the discontinuance/interruption, and how the discontinuance/interruption will affect the manufacturer's ability to meet its market share. The Guidance also asks manufacturers to estimate the duration of an interruption, which could be particularly difficult during the current public health emergency.

The regulations require the notification to include a "description of the reason" for the discontinuance/interruption. The Guidance elaborates that the FDA expects a "detailed and thorough explanation" because the Agency needs as much information as possible to determine how to respond to the issue, and specifically asks manufacturers to provide the root cause of the discontinuance/interruption. Given that the FDA requires notification five business days after the discontinuance/interruption, it is possible that a manufacturer will not know the root cause of the problem at the time of notification.

Similarly, a manufacturer might not have a solution to the problem. The Guidance asks whether the manufacturer has a proposal for how the FDA can expedite the availability of a product, including whether the FDA can take any actions to mitigate or prevent a disruption. Section 506C(g) specifically provides the Agency with the ability to expedite (1) reviews of supplements to an existing application; and (2) establishment inspections, to address a likely drug shortage.

If a change would normally require an establishment inspection prior to approval, manufacturers should keep in mind the FDA's authority to request records in advance of or in lieu of inspections since the FDA has expressed its willingness to use this authority during the current postponement of domestic and foreign inspections.

Public Notifications of Failure to Comply

The FDA issues noncompliance letters to manufacturers that have failed to submit required discontinuance/disruption notifications, and manufacturers are required to submit a written response to such letters within 30 calendar days. The Guidance also indicates that the FDA intends to issue noncompliance letters when the FDA determines that manufacturers have not notified the FDA "as soon as practicable." The FDA maintains a "Drug Shortages: Non-Compliance with Notification Requirement" database, where it posts noncompliance letters as well as responses received for the letters. However, according to the Guidance, the FDA will not make such postings "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 the FDA as required."

Public Comments on the Guidance

The FDA implemented the final Guidance before allowing public comment and intends to keep the Guidance in effect until the COVID-19 public health emergency has ended. The FDA has indicated, however, that the Guidance reflects its current thinking outside the context of the public health emergency, and has established a docket (FDA-2020-D-1057) for public comments. The FDA plans to reissue the Guidance within 60 days after the conclusion of the public health emergency based on public comments and the FDA's experience implementing the Guidance.

Considerations Going Forward

As industry grapples with travel restrictions, measures to prevent the spread of COVID-19 within the workforce, and other supply-chain challenges, applicants and manufacturers should consider the following:

- A review of current quality agreements to ensure they are designed to meet the FDA's notification requirements, particularly as they relate to providing the FDA with the detailed information requested in the Guidance well before, or if advance notice is not possible, after any supply chain disruption.
- A review of current products to determine which are considered life-saving drugs, to make timely notifications to the FDA when there are manufacturing disruptions that affect life-saving drugs. Manufacturers should also consider integrating this information into their business continuity plans.
- Manufacturers should not delay notifications in order to gather additional information about a potential discontinuance/disruption. The regulations require prompt notification, and the FDA expects additional information to be submitted in follow-up communications.
- A notification should provide, if possible, a well-developed proposal for addressing the disruption. The FDA will take all reasonable steps to prevent or mitigate a potential drug shortage for life-saving drugs and has the authority to take certain actions, such as expedited review of supplements to address disruptions. Providing a potential solution to the problem will help the FDA fulfill its mission to ensure that patients have access to life-saving drugs.

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