SPECIAL FEATURE

FDA's role in responding to drug shortages

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The Drug Shortage Program at the Food and Drug Administration (FDA) is a division of the Center for Drug Evaluation and Research (CDER), one of the five centers within FDA. The four other centers include the Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, Center for Food Safety and Applied Nutrition, and Center for Veterinary Medicine. At the Drug Shortage Program, we strive to ensure that safe and effective prescription, over-the-counter, and generic drugs are available to the American public. Other products, such as vaccines, biologicals, veterinary drugs, devices, radiological products, and nutraceuticals, fall into the jurisdiction of the other four centers. The Drug Shortage Program was developed to respond to drug shortages that have a significant impact on public health. Our program has expanded in the past two years because of the increasing number and complexity of drug shortages.[1] In addition to two full-time project managers, individuals from the Office of Generic Drugs, the Office of Compliance, and CDER Drug Information share the responsibilities involving drug shortages. A coordinated effort is often required between manufacturers and various components within FDA to deal with a drug shortage. The purpose of this article is to discuss FDA's role in resolving drug shortages.

FDA's scope of responsibilities in drug shortages

Manufacturers often notify CDER's Drug Shortage team of potential or current shortages, although they are not required by law to do so. The information may also be relayed to us through interactions with other components of FDA and reports from health care professionals, patients, and professional organizations. All reports are verified with the appropriate manufacturer or distributors.

Once we verify a shortage and are certain that it is not transient or self-limiting, the CDER review division that has the requisite scientific and medical expertise regarding the product is notified and consulted to determine whether the drug product is medically necessary. A medically necessary drug is defined as a product used to prevent or treat a serious or life-threatening disease or medical condition for which there is no other available source with sufficient supply of that product or alternative drug available. On occasion, expert opinion from outside FDA is obtained to make such a determination. The approved and unapproved (off-label) uses of a product are considered as well as whether a reasonable alternative drug product exists.

We recognize that more than one manufacturer may be producing a particular drug. Alternative products may be available, but some pharmacies and hospitals may have a drug shortage because of contractual agreements with a specific distributor or manufacturer; these types of issues are beyond our purview. Similarly, issues regarding costs of alternative products are not within the regulatory authority of FDA. We primarily focus our efforts on products that are considered medically necessary, since shortages of these products have the greatest potential to affect public health. We do not usually investigate shortages that are expected to be temporary and self-limiting or those involving a specific strength or package size of a drug product because of finite resources and the transient nature of these shortages.

Once a shortage is identified and the product is deemed medically necessary, we determine the cause of the shortage and work with the manufacturer and other components of FDA toward resolving the problem.

Common causes of drug shortages

Manufacturing problems are of-

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ten the cause of drug shortages. Manufacturing issues may be brought to FDA's attention by the manufacturer or as a result of an FDA inspection. Products affected by manufacturing difficulties are assessed for the risk they pose to public health. A voluntary recall may be initiated by the company if the situation warrants this action.[2] When FDA considers an enforcement action against a manufacturer, which does not involve an immediate threat to public safety, the products potentially affected by such an action are carefully reviewed. Every attempt is made to avoid a shortage of medically necessary products.

Limited production capabilitiy is another reason for drug shortages. The activities related to increasing production usually require a great deal of time and planning for manufacturers. Manufacturers often use the same manufacturing equipment for multiple drug products, so it is difficult to suddenly increase production of a product in response to a shortage. Since a manufacturer's production line is usually devoted to other products in addition to the product in shortage, increasing the production of one product will most likely result in the manufacturing delay of another product. The manufacturer may need to increase production by buying more equipment for its facility or by contracting with other facilities to produce the drug at multiple sites. If all manufacturers of a product are notified that a potential shortage exists, they may be able to increase production and avoid a shortage.

Another factor responsible for recent shortages is the availability of drug substance, the raw material from which the finished drug product is made. Even if there are multiple manufacturers of a finished drug product, there may be only one producer of a particular drug substance. Any interruption in the supply of this raw material will affect all producers of the finished drug. Manufacturers may sometimes require assistance from FDA in locating an additional supplier of the required raw material.

While manufacturing issues remain an important cause of drug shortages and the cause most amenable to FDA assistance, other factors contribute substantially to the overall problem. A significant factor in the development of many shortages is related to the number of firms producing a specific product and their respective shares of the market. Drugs still under patent protection are almost always single-source products. Therefore, any interruption of their supply is likely to lead to a shortage. However, even when there are multiple sources, it is not unusual for individual companies to have a large market share. When a company with a dominant or large market share ceases production of a drug, other manufacturers producing the same drug may have difficulty compensating for the shortfall. This situation was the basis for the recent shortages of a number of products, including naloxone hydrochloride injection and diazepam injection.

Market concentration has contributed to many recent shortages, and many reasons exist for such concentration. For example, few companies have the capability to produce sterile injectable products. Therefore, injectable products are particularly susceptible to shortages. In addition, newer drugs often supplant older drugs because they may be more efficacious, have a better safety profile with fewer or milder adverse effects, or generate more revenue for the manufacturer. This leads to fewer manufacturers producing the older products and an increase in sole-source products. Vulnerability to drug shortages may be increased by the ongoing spate of mergers in the pharmaceutical industry.

Many products are manufactured by a few firms. Should one of these firms encounter difficulties or make a business decision to cease production, a shortage will almost certainly occur. While FDA does have flexibility in addressing difficulties related to the manufacture of a pharmaceutical, FDA has no authority over the business decisions made by drug manufacturers. Although FDA does not have the authority to require a firm to produce a product, it can encourage a manufacturer to produce a drug in shortage by expediting the review of data supporting a new or generic drug. In addition, FDA cannot require a manufacturer to provide notification when a decision is made to cease manufacturing a product (unless it is a sole-source drug used to treat a serious disease or medical condition).[3]

Resolving drug shortages

When a shortage involves a manufacturing problem, a change in the production process or additional sites or suppliers may be required to resolve it. FDA works closely with the manufacturer to correct the problems identified. Part of our role at CDER is to help identify and distribute medically necessary products in shortage and coordinate the review and approval of the manufacturing change so that production can resume. If a new manufacturing site needs to be added because of problems or limitations at the existing site or if a new supplier must be added, the review of data to support these changes may be expedited for medically necessary drug products. Another type of expedited review was used to resolve the recent shortage of penicillin G sodium for injection. Since this medically necessary product was in short supply, the review of data to support approval of a new generic drug product was expedited.

When a product is available but deviates from the specifications set by the manufacturer, FDA can work with the company to assess the potential health impact of such deviations. When necessary, an ad hoc committee of FDA scientists conducts a health hazard evaluation to

determine the risks associated with the product. If, however, no significant patient risk is identified, protocols for additional end-product testing may be used to monitor corrections in the manufacturing processes while continuing to make the product available. In circumstances in which no product is available or substantial risks preclude continued use of the product, we attempt to identify an alternative source of the product. This may involve encouraging other firms to initiate or increase production to meet patient needs.

In rare cases involving a shortage of a particular product, importation of the drug may be allowed until the shortage is resolved. A recent example of importation as a means to minimize a shortage involved naloxone hydrochloride injection. An overseas product was identified and temporarily imported to help supply the U.S. market until the shortage was resolved.

When a drug is in shortage, alternative drug products may be identified by the CDER review division responsible for that class of drug products. CDER's Drug Shortage Program can monitor supplies of the alternative product and can utilize market share data. Advance notice may be provided to companies that a drug closely related to their product has the potential for shortages. These companies may choose to increase production to avert a potential shortage because of heightened demands. Recent examples of shortages affecting supplies of related products include certain neuromuscular blocking agents and furosemide injection.

FDA may also assist manufacturers in instituting an allocation program to limit distribution of the remaining inventory until the shortage issues are resolved. Firms may distribute a product from a central location to better control how much product is released and place limitations on quantities sold or encourage the use of clinically feasible alternative products to conserve remaining supplies. In some cases, an allocation program may be initiated to ensure that a drug is available for patients on an emergency-only basis for life-threatening conditions for which no alternative therapy exists. Such an allocation program was coordinated in the past for repository corticotropin injection (H.P. Acthar Gel, Questcor Pharmaceuticals). Examples of other products recently on allocation include caspofungin acetate (Cancidas, Merck) and beta methasone sodium phosphate–betamethasone acetate (Celestone Soluspan, Schering).

Available resources

Information about shortages and limited distribution of medically necessary drugs is provided on FDA's Web site.[4] When FDA receives a notice of drug discontinuation from a manufacturer, it posts and updates this information. To report shortage of a drug product, the CDER Drug Shortage Program has an electronic mail account at drugshortages@cder.fda.gov.

Future efforts

CDER's Drug Shortage Program has received many proposals and suggestions from industry, professional organizations, private citizens, health care professionals, and government entities of how to resolve some of the complex issues leading to drug shortages. These proposals include improving communication with health care providers and professional organizations regarding shortages, reevaluating the definition of a medically necessary drug, and establishing regulatory requirements for early notification of potential shortages and plans for discontinuing products. Our program continues to work toward ensuring the availability of safe, effective drug products and look for ways to improve the service provided.

References

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