An Overview of the FDA’s Drug Shortage Program

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BACKGROUND
The Drug Shortage Program (DSP), located in the Center for Drug Evaluation and Research (CDER) in Rockville, Maryland, attempts to resolve all problems relating to shortages of the products reviewed by the center and provides nonproprietary information about these drugs to the public. CDER is one of five centers within the Food and Drug Administration (FDA); the other four are the Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER), the Center for Food Safety and Applied Nutrition (CFSAN), and the Center for Veterinary Medicine (CVM).

CDER’s purpose is to ensure that safe and effective prescription, over-the-counter, and generic drugs are available to the American public. Other products, such as vaccines, veterinary drugs, devices, cosmetics, and medical foods, are under the jurisdiction of the other four centers. Until 1998, CDER did not have a standing drug shortage program. As the number and complexity of drug shortages increased, however, it became evident that a formal program was needed.

The current DSP was initiated with a coordinator and one part-time project manager; together they were known as the Drug Shortage Team. Following the terrorist attacks of September 11, 2001, and emergencies ranging from natural disasters to plant fires, the program became more proactive and expanded to address the availability of critical drugs, including those in the Strategic National Stockpile.

The DSP now consists of three project managers and a network of contacts from the Office of Generic Drugs, the Office of Compliance, the Office of New Drug Chemistry, and the Division of Drug Information. The DSP also maintains partnerships with several professional organizations, such as the American Society of Health-System Pharmacists (ASHP). This article provides an overview of the roles, processes, and limitations of the DSP.

RESPONDING TO SHORTAGES
The DSP receives information about shortages from a variety of sources, both inside and outside the FDA. Often the first reports of a shortage come from the public e-mail account maintained by the DSP. Reports may also originate from manufacturers, although there is no regulatory requirement for firms to report shortfalls unless the situation involves the discontinuation of “sole-source,” “medically necessary” drugs.

A medically necessary product is defined as one that is used to prevent or treat a serious or life-threatening disease or medical condition for which no other source of that product or an alternative drug is available in adequate quantities. A sole-source product, as the name implies, is available from only one supplier.

The ASHP, which maintains a comprehensive Drug Shortage Resource Management Center developed by the University of Utah Drug Information Center, regularly shares availability data with the DSP. CDER’s review divisions and the Office of Compliance frequently notify the DSP of potential shortages too.

After a report is received, the DSP takes several steps to determine whether a national shortage does exist. The DSP first determines the current manufacturer of the product and verifies that there is a disruption in the supply. It then assesses the severity and duration of the shortage, based on the firm’s reported capabilities and the problems involved. For products that are made by multiple firms, the DSP also evaluates market share data.

Next, the DSP contacts the medical experts in the appropriate CDER review divisions to determine whether the drug is medically necessary. A shortage involving medically necessary products would thus have a significant impact on public health.

On occasion, expertise from outside the FDA is also obtained for making these decisions. The approved and unapproved (“off-label”) uses of a product are taken into consideration in determining medical necessity.

In some cases, alternative products might be available, but pharmacies or hospitals might experience a shortage because of contractual agreements with a specific distributor or manufacturer. Neither these contractual issues nor cost differences among products are within the purview of the FDA. The program’s primary focus is on medically necessary products. However, shortages of other products or any shortage that is transient in nature or that is limited to a single strength or package size is monitored until the shortage is resolved or its status changes.

The most common questions that health care providers and patients ask the DSP are as follows:

- What is the reason for the shortage?
- How long will the shortage last?
- How can I access any remaining supplies?

After determining that a drug in short supply is medically necessary, the DSP posts information about the shortage on its "drug shortage" page of the FDA's Web site. The listing includes the name of the drug, the formulation, the manufacturer, the anticipated time frame for the agent’s availability, phone numbers for each company, and important communications such as "Dear Healthcare Professional" letters from manufacturing companies.

In addition to posting news on the Web page, the Drug Shortage Team personally answers each e-mail inquiry that it receives at its Drug Shortage e-mail account.
CAUSES AND SOLUTIONS

The causes of drug shortages are varied and may apply solely to a formulation or to an entire class of products. When shortages are first reported, the underlying reason is not always known. In such cases, the DSP contacts the manufacturer to discuss the lack of an agent’s availability and to determine potential solutions. Frequently, however, the firm may initiate a contact with the DSP to report an adverse situation, and it may request assistance from the FDA to resolve the problem. The actual reason for the shortage may involve matters related to proprietary information, such as current Good Manufacturing Practice (cGMP), which cannot be shared with the public. Therefore, such problems are reported to the public as general “manufacturing issues.”

The Office of Compliance may be the first to identify cGMP concerns as the result of an FDA inspection. This office then notifies the DSP so that a comprehensive evaluation of the impact of a shortage for the affected product can be made.

Sometimes there is a disruption of the raw material supply; this may be referred to as the “bulk drug” or the “active pharmaceutical ingredient” that is used to make the finished product. Several companies might make a particular finished drug product, but they might all use the same supplier of the raw materials. Therefore, if there is a problem with the supplier, all producers of the finished drug may be affected.

Discontinuation of a drug’s manufacture may cause a temporary or permanent shortage, depending on the market share represented by the firm. When a product is discontinued, even though it might not be medically necessary, a firm usually sends a notice to be posted on the FDA’s Drug Shortage Web site under the “discontinuations” section.

Natural disasters, such as floods, fires, and hurricanes, also affect manufacturing facilities. When these occurrences are reported to the DSP, the drugs produced at those facilities are evaluated (1) to determine whether alternate manufacturers or manufacturing sites can make up for any shortfall and (2) to establish a timeline for resolution of the problem.

Certain types of drugs are vulnerable to shortages because only a relatively small number of firms make these products. For example, a limited number of firms manufacture sterile injectable drugs. If one of these firms stops making one of these drugs, it is often difficult for the remaining firms to increase production because of the lack of available manufacturing capacity. Because significant time and resources are required to open a new facility or to approve an alternate site, long-term consequences may ensue because of the shutdown of one of these facilities.

The number of firms producing a particular drug can determine whether a shortage will develop. Products under patent protection are usually sole-source products, which by nature are more vulnerable to shortages. Even if several firms make a particular drug, if one firm suddenly ceases distribution, the rest of the companies might not be able to increase production quickly enough to avoid a shortage. This situation occurred recently with injectable methotrexate and is ongoing. Older drugs are often replaced by newer agents that are used for the same indication. As the demand for the older products decreases, fewer firms continue to manufacture them. Business decisions are often made to discontinue older products because of decreased profitability and also because of limitations on overall manufacturing capacity at the firm.

Mergers sometimes result in a company’s re-evaluation of the products made at its facilities, and a firm might decide to manufacture newer and potentially more profitable products to maximize revenue at its production sites. In the past, there have been shortages of injectable furosemide and injectable prochlorperazine as a result of the discontinuation of these older drugs. These problems were resolved by the Office of Generic Drugs’ expedited approval of new generic equivalents.

When shortages of medically necessary products occur, the DSP must determine the cause and must work with the manufacturer and appropriate FDA components (e.g., groups or individuals) to develop short-term and long-term management plans. Several approaches can be used to help prevent, alleviate, or resolve these problems.

Firms may need to make changes in their manufacturing sites, processes, or suppliers, and the DSP can often facilitate the FDA’s review of these changes. When the FDA is considering an enforcement action that would disrupt the drug supply, the products made at the facility are assessed; every effort is made to avoid any shortages of medically necessary products made at that site. Additional end-product testing or other steps may be necessary to ensure that the products that are released to the market quickly are safe and effective.

Sometimes product deviations resulting from a manufacturing problem are significant enough to warrant withholding the agent from the marketplace primarily because of concerns about safety or efficacy. When this happens, the firm might initiate a voluntary recall if it is warranted. The DSP works to identify alternate sources of the product; in rare situations, an overseas product might be temporarily brought into the U.S. to address a critical shortage.

This situation occurred with injectable naloxylo HCl, an opioid antagonist. One firm suddenly ceased production, and other manufacturers could not meet the market demand for this medically necessary product. Sufficient information was provided to the FDA to ensure that the overseas product was safe and effective, and the product was made available in the U.S. to meet patient needs during the shortage.

Another method of addressing drug shortages includes setting up limited distribution programs in order to reserve remaining quantities of products for medically necessary uses until supplies return to normal. When information is available regarding a limited distribution program or when other materials are provided to the DSP, such as a “Dear Healthcare Professional” letter from a manufacturer of a drug that is in short supply, or a discontinuation notice from a firm, these items are posted on the DSP’s Web site so that the public has access to all pertinent information about a drug’s unavailability or discontinuation. This Web site is updated whenever new information is received. The information regarding a particular shortage remains on the site until the shortage is reported to have been resolved.

When the DSP is notified in advance of a potential drug shortage or a planned discontinuation, the problem may be averted or its impact minimized. Early notification may allow the DSP to find a new firm to either increase production or to enter the market.
The FDA’s Drug Shortage Program

Additional tools for resolving shortages include expediting the FDA’s review of (1) data submitted by the firm that is needed to resume or enhance production or (2) a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) for a product in short supply. Usually, firms have worked closely with the FDA to ensure the continued availability of products needed for serious and life-threatening medical conditions, even for some products that were originally slated for discontinuation. Recent examples of such interventions include antibiotics, injectable anesthetics, and oncology agents.4

**AVAILABLE RESOURCES**

Health care providers and patients need timely information about drug shortfalls, including how to access remaining supplies. The DSP makes information available through various methods (e.g., on its Web site and through professional organizations). The FDA’s Web site lists shortages of medically necessary drugs and provides information about resolved shortages, drug discontinuations, and general communications.4

The DSP Web4 site lists only medically necessary CDER drug products, not products such as vaccines and medical devices, which are handled by other centers.

To report a drug product in short supply, anyone may use the DSP’s electronic mail account.2

The CDER Drug Shortage Web site4 is linked to the ASHP Web site,1 which maintains a comprehensive list of all products in short supply, not just those that are medically necessary, including vaccines.

The Centers for Disease Control and Prevention provides information about the availability of vaccines on its Web site.6

**SUMMARY**

The FDA has limited regulatory authority with regard to many of the aspects of drug shortages. The DSP primarily uses the tools of communication, facilitation, and negotiation to formulate and implement, in concert with regulated industry, effective plans for preventing and managing drug shortages.

Firms must report only discontinuations of some sole-source, medically necessary products to the FDA (see Exemptions in Section 506(c)),3 and even this regulatory requirement has no penalty component. In addition, there is no legal requirement for a firm to continue producing any drug, even one that is deemed medically necessary.

The CDER’s Drug Shortage Program is committed to making safe, effective drugs available to the public and encourages the cooperation of health care professionals, pharmacists, and pharmaceutical companies in achieving this goal.

**REFERENCES**

2. Center for Drug Evaluation and Research. Available at: drugshortages@cder.fda.gov.