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Perspective

The Reality of Drug Shortages — The Case of the Injectable Agent Propofol

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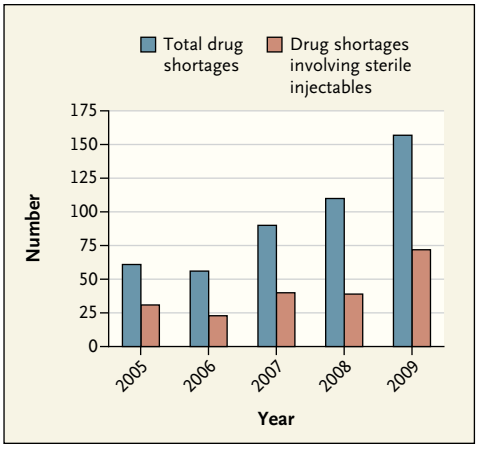
Over the years, physicians have come to rely on certain drugs as standards of care because of their unique clinical effects. Reduction in the supply of these drugs can have dramatic effects on medical practice, ultimately keeping patients from receiving the level of care they deserve and have come to expect. Drug shortages have therefore been a topic of some discussion within the medical profession.[1,2]

Recently, the supply of one drug — the sterile injectable drug propofol, a fast-onset, short-acting sedative–hypnotic agent used for the induction and maintenance of anesthesia or sedation — has become critically low.[3] In 2009, there were three manufacturers making propofol: Teva Pharmaceuticals, Hospira, and APP Pharmaceuticals. In early October 2009, Hospira recalled multiple batches of its propofol owing to the presence of particulate matter in the vials. In late October 2009, Teva recalled multiple lots of its propofol owing to possible microbial contamination. As of May 2010, Hospira had not yet returned propofol to the market and had expanded its recall to capture all product that might currently be in customers' inventories, and Teva recently announced that it would not be returning to the market. This confluence of events has left only one company to supply propofol to the entire U.S. market — an unrealistic expectation, given anesthesiologists' reliance on the drug.[3]

Although shortages can occur with any drug, sterile injectable drugs such as propofol are particularly susceptible. Data collected by the Drug Shortage Program of the Food and Drug Administration (FDA) show that of 110 shortages that occurred in 2008, 39 involved sterile injectables (35%), and in 2009, the proportion rose to 73 of 157 drug shortages (46%) (see graph). In recent months, there have also been shortages of neuromuscular blocking agents (injectable vecuronium, succinylcholine, atracurium, and cisatracurium), as well as of injectable metoclopramide, prochlorperazine, and ephedrine.

Several factors can contribute to shortages of sterile injectable drugs, especially those that, like propofol, have been on the market for some time. A limited number of companies are able to make sterile injectable products, since the process is complex and requires a relatively long manufacturing lead time. In addition, since a company's production lines are often used for many different drugs, any interruption in manufacturing can affect multiple products. And many of these drugs



Total Numbers of Drug Shortages and Shortages Involving Sterile Injectable Drugs in the United States, 2005–2009.

Data are from the Drug Shortage Program, Center for Drug Evaluation and Research, FDA, and do not include shortages of vaccines, immune globulin products, or other biologic products that are managed by the FDA's Center for Biologics Evaluation and Research.

are purposely manufactured in amounts that will satisfy current demand, which means that the supply chain has little, if any, excess inventory. This streamlined approach is efficient from a manufacturing perspective, but a sudden change in either the supply of or the demand for the drug can have catastrophic clinical consequences. If only a few companies make a drug and one of them encounters a manufacturing problem, the remaining companies may not be able to meet the demand.

In addition to these factors, a larger economic reality can contribute to drug shortages. When a drug goes off patent and generic versions become available or other companies develop competing treatments, the drug's price generally decreases. If the costs associated with making a drug begin to outweigh the profits, companies may wish to discontinue production of the drug in favor of a newer, more profitable product. If the number of companies making an older drug decreases, and there is a delay or problem in manufacturing, shortages can and do occur.

No one can dispute the fact that business competition has substantial benefits and certain drawbacks for health care. Furthermore, these benefits and drawbacks are intimately linked: competition drives the cost of drugs down; lower cost makes medicines more affordable for patients — a benefit to the public; but then lower profits may drive manufacturers to abandon production of a drug in favor of more profitable products, limiting competition. Although limited competition gives companies an incentive to continue making a drug, ensuring continued access for patients, it can also leave the supply of certain drugs vulnerable to shortages.

With patient care on the line, the health care community should quickly communicate with the FDA when a drug shortage occurs so that we can do everything within our legal authority to resolve the problem. (Drug shortages may be reported to the FDA by e-mail, at drugshortages@fda.hhs.gov.) The FDA cannot require a company to start or to continue manufacturing a drug or dictate how much of a drug must be manufactured, but we work closely with the health care community and the manufacturers to identify and address shortages as they occur.

The FDA has been working with the companies in question to resolve the manufacturing problems with propofol. To fill the gap in propofol supply, the agency has exercised its regulatory enforcement discretion and temporarily allowed the importation into the United States of the unapproved drug Fresenius Propoven 1%, a propofol product approved in other countries that is similar to the formulation used in this country. The FDA has inspected the manufacturing facilities producing Fresenius Propoven 1% to ensure that they are in compliance with current good manufacturing practices and has evaluated the quality of the formulation to assure its safety. These measures have ensured that the health care community continues to have access to propofol.

Since patient safety is of paramount concern to the FDA, we advise clinicians to continue to scrupulously adhere to label instructions for the use of a drug, even during a time of shortage. Risks associated with misusing a product cannot be ignored. Although this advice is true for drugs in general, it is especially important for sterile injectable products such as propofol. In the case of propofol, the FDA has received numerous reports over many years of adverse events resulting from multiple entries into single-use vials of the drug. This practice has resulted in life-threatening illness due to contamination. In a recent instance, practitioners at an endoscopy clinic in Nevada used 50-ml single-use vials of propofol to obtain multiple doses, contrary to label recommendations. Contamination of these vials led to an outbreak of hepatitis C infection, and approximately 40,000 patients were advised to be tested for potential infection with hepatitis B, hepatitis C, and HIV.[4] Patient safety must remain the highest priority,

and clinicians should carefully consider the risks as well as the benefits if they are considering deviating from the safe-use information in a product's label.

Drug shortages can have a profound effect on patient care, since they limit the treatment options available to prescribers and patients. It is the responsibility of everyone involved in the health care system — the FDA, the pharmaceutical industry, health care institutions, and clinicians — to identify shortages as quickly as possible, before they become critical. The agency posts notices of shortages of medically necessary drug products on its Web site,[5] which is periodically updated with information provided by the manufacturers regarding timelines for availability and other information.

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