Looking for the Treatment for Drug Shortages: Not a Simple Prescription

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When a patient arrives at your ambulatory surgery center at 6 AM expecting an uncomplicated outpatient procedure, how do you explain that a shortage of a critical anesthetic drug means that the operation will have to be postponed to another day? How do you tell a patient who has recently received a diagnosis of cancer that the first-choice chemotherapy agent is not currently available for his treatment? What can you say to the family of a patient who suffers a respiratory arrest because she received an overdose of an opioid that was being used at your institution because the usual drug is currently unavailable and an error was made because the practitioners ordering and administering the replacement drug were less familiar with its pharmacologic profile?

These are not theoretical questions but are some of the difficult ones that health care professionals in the United States have faced over the past few years as a result of the widespread shortage of multiple drugs. In this issue of *Mayo Clinic Proceedings*, Fox, Sweet, and Jensen[1] provide a detailed review of this public health concern. These 3 individuals are among the US experts most directly involved in our understanding of the effect of drug shortages and are also among those most active in addressing the causes of these shortages.

Although the authors explain that etiologies of drug shortages are multiple and complex, the initial "knee-jerk" response of most people who hear about the problem is to look toward the US Food and Drug Administration (FDA) to quickly find and implement a solution. However, the regulatory authority of the FDA is quite limited. The FDA, through its Center for Drug Evaluation and Research, is the government agency responsible for protecting the public health by regulating the manufacturing of prescription and nonprescription drugs and by ensuring that medication is safe and effective and meets specific quality and labeling standards. These roles are critical for health care delivery but do not provide the agency the authority to address all aspects of the shortage problem. The FDA cannot require a pharmaceutical company to make a specific drug or to increase the amount of a drug produced, and it has no authority to set drug prices or to determine to whom a drug is distributed.

Although the number and classes of drugs in short supply have increased over the past decade, drug shortages are not a new problem in the United States. The FDA Center for Drug Evaluation and Research Drug Shortage Program began in 1999, and the number of staff was recently increased to 11 in response to the greater workload caused by the growing number of shortages. The FDA staff has worked in conjunction with many stakeholder groups to raise awareness of the drug shortage problem and to seek solutions. Important milestones resulting from these relationships included the Drug Shortages Summit held in November 2010 (Bethesda, MD) and the Drug Shortage Public Workshop held in September 2011 (Silver Springs, MD). At the latter event, participants made several recommendations such as the need for improved communication among the FDA, stakeholder groups, and manufacturers.[2] Congressional interest in this important national health care issue was heightened at these meetings because of the presentations made by members of the public and representatives of medical specialty organizations.

The subsequent passage of the FDA Safety and Innovation Act (FDASIA) in July 2012 is an important milestone because the legislation contains requirements that address drug shortages in several ways.[3] There are expanded reporting requirements for manufacturers, thus helping the FDA better manage and track threatened shortages. Manufacturers of life-supporting or life-sustaining drugs must now notify the FDA of a "permanent discontinuance in the manufacture of the drug or an interruption of the manufacture of the drug that is likely to lead to a meaningful disruption in the supply" at least 6 months in advance or as soon as is "practicable."[3] This has been a

powerful tool that has enabled FDA staff to prevent or mitigate numerous shortages in 2012 and 2013 by working with the manufacturers as soon as the FDA is made aware of problems.

The FDASIA requires that the FDA distribute information on drug shortages to physician, health care, and patient organizations and that the FDA maintain an up-to-date list of drugs that are in short supply. The law also requires the FDA to create a task force on drug shortages and develop and implement a strategic plan for preventing shortages. A document outlining FDA adherence with the law was submitted to the Congress in October 2013.[4]

There is still vigorous disagreement on the specific causes of drug shortages, and therefore, the appropriate measures necessary to carry out fixes are often debated. In their recent analysis of shortages of generic sterile injectable drugs, Woodcock and Wosinska[5] point out several relevant facts: (1) Most of the sterile injectable drug shortages are due to the shutdown of the manufacturer's production for quality reasons. (2) The profit margin for this class of drugs is extremely small. (3) There is no redundancy in the manufacturing capacity, and there are no backup production lines for these drugs. (4) There are only a few firms producing generic sterile injectable drugs. (5) Many of the manufacturing lines and facilities used for generic sterile injectable drugs are quite old and are at increased risk for production or sterility problems that result in shutdowns. Some manufacturers are building new plants that will help with the production process and capacity, but other possible causes such as the supply chain issues and raw material sourcing remain.

The FDASIA required the Government Accountability Office (GAO) to conduct a study to examine the causes of the drug shortages and to provide recommendations on how to prevent or eliminate them. The GAO report is to be submitted to the Congress within 18 months after FDASIA was enacted, and it is hoped that this will shed sufficient light on the causes of the shortages so that new regulatory or legislative remedies can be implemented.

The problem of drug shortages is not confined to the United States, as documented in recent reports from Europe and Canada.[6-10] Although their health care systems differ from that in the United States, many of the root causes of the international shortages appear to be identical to ours. Hall et al[8] described how regulatory action against a Canadian manufacturing plant and later a fire at the facility resulted in one company significantly reducing the production of intravenous agents used in anesthesia, critical care medicine, and pain medicine. Because the company was a sole source supplier of 80% of these classes of drugs in Canada, this series of events had a catastrophic effect on the practices of anesthesiologists and critical care physicians in the country. To be cost-effective, most drug supply chains have adopted "just-in-time" delivery and the inventory reserves of manufacturers and suppliers are purposefully kept at a minimum. As such, the aforementioned Canadian disruption of drug production affected the supply chain and the end users extremely quickly, and the resulting shortage of drugs surprised most affected Canadian physicians.

To address this growing global problem, the International Drug Summit was held in Toronto, Canada, in June 2013. Stakeholders came from many countries to discuss root causes, effects, and solutions related to drug shortages.[11] Six recommendations were published from the summit, with a focus on international cooperation to track current shortages and the reasons for them. One recommendation was the development of an international list of "critical or vulnerable products." The group also encouraged countries "to develop evidence-based risk mitigation strategies which might include strategic buffer stocks and stockpiles, contingency planning, pandemic planning, and capacity redundancy appropriate to their national needs."[11]

Although FDA actions have successfully prevented or mitigated an increasing number of drug shortages in the United States, we look forward to the release of the upcoming report from the GAO containing its findings on the causes of this national health care problem and its recommendations on potential solutions. A resolution of this complex issue will not come quickly or easily; however, as health care professionals, we look forward to the time when we know that we will consistently have access to our full armamentarium of drugs and can use them to provide the best care for our patients.

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REFERENCES

1. Fox ER, Sweet BV, Jensen V. Drug shortages: a complex health-care crisis. *Mayo Clin Proc*. 2014;89(3):361-373.
2. US Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research, Approach to Addressing Drug Shortage; Public Workshop. September 26, 2011. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM274583.pdf. Accessed December 10, 2013.
3. Food and Drug Administration Safety and Innovation Act of 2012, 112th Cong, Public Law 112-144 (2012).
4. US Food and Drug Administration. *Strategic Plan for Preventing and Mitigating Drug Shortages*. Silver Spring, MD: US Food and Drug Administration; October 2013.
5. Woodcock J, Wosinska M. Economic and technological drivers of generic sterile injectable drug shortages [published corrections appear in *Clin Pharmacol Ther*. 2013;93(4):366 and *Clin Pharmacol Ther*. 2013;93(5):451]. *Clin Pharmacol Ther*. 2013;93(2):170-176.
6. Huys I, Simoens S. European drug shortages: a call for action! *Int J Pharm Pract*. 2013;21(1):1-2.
7. Ferguson K, Woodcock T. Ensuring a sustainable supply of drugs for anaesthesia and peri-operative care. *Anaesthesia*. 2012;67(12):1313-1316.
8. Hall R, Chisholm R, Cheng D, Murphy M, Campbell D. Drug shortages in anesthesia and perioperative medicine: Canada needs a better supply system. *Can J Anaesth*. 2012;59(7):629-635.
9. Bedard M. Drug shortages: can we resolve that problem? *Can J Anaesth*. 2013;60(6):523-527.
10. Hall R, Bryson GL, Flowerdew G, Grabowski-Comeau A, Turgeon AF; Canadian Perioperative Anesthesia Clinical Trials Group. Drug shortages in Canadian anesthesia: a national survey [published correction appears in *Can J Anaesth*. 2013;60(11):1170]. *Can J Anaesth*. 2013;60(6):539-551.
11. Canadian Pharmacists Association. Drug Shortages: International Summit. November 2010. http://www.pharmacists.ca/index.cfm/pharmacy-in-canada/advocacy-government-relations-initiatives/drug-shortages/drug-shortages-international-summit/. Accessed December 10, 2013.