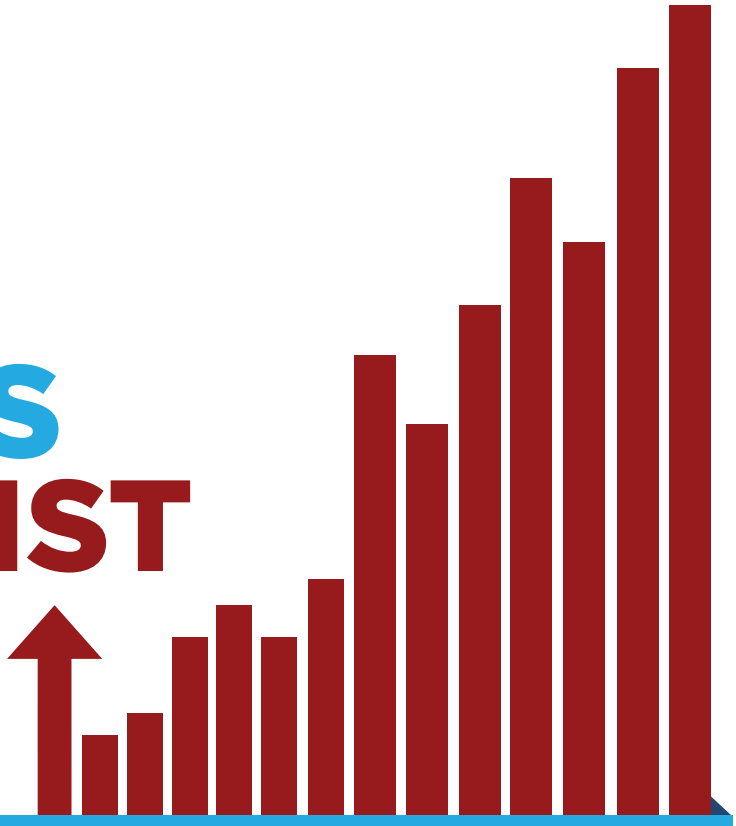
AAHPM
American Academy of Hospice and Palliative Medicine
Quarterly
WINTER 2012 | VOLUME 13 | NUMBER 4

DRUG SHORTAGES PERSIST IN 2012
—what's the cause?



PAGE 16

4 **President's Message:** AAHPM's 25th Anniversary: So Much Accomplished! (And So Far to Go...)

6 **Advocacy Update:** Opioid Prescribing Faces Increased Scrutiny

20 Congratulations, 2013 AAHPM Board of Directors

DRUG SHORTAGES PERSIST IN 2012—what's the cause?

GREGORY DYKE, BS RPH, AND ANDREW DESIO

Medications play an integral role in relieving suffering and supporting the best possible quality of life for many patients. Reliable availability of essential medications is of paramount importance. Unfortunately, the incidence of drug shortages has increased markedly over the past 16 years. In 1996, there were only three reported shortages.[1] There are about 230 reported drug shortages as of December 2012, leaving healthcare providers and patients questioning how these shortages are occurring, and what is being done about them.[2]

There are myriad reasons suggested as driving the shortages, including shortages of materials needed to produce products, manufacturing and quality improvement activities, and industry capacity constraints. A 2012 report to the US House of Representatives Committee on Oversight and Government Reform found that the widespread shortage of generic injectable medications is due to two main factors. The first is industry consolidation, which was accelerated by a provision in the Medicare Modernization Act (MMA). The second is increased Food and Drug Administration (FDA) enforcement and regulation, which has shut down a substantial amount of manufacturing capacity.[3] Glenn Ross, RN, senior director of pharmacy at VITAS Innovative Hospice Care, addressed these causes of drug shortages, stating that "when government agencies take certain actions, there is a ripple effect that can cause more drug shortages down the road."

Other drug shortage causes include manufacturing delays due to the availability of raw materials; problems with manufacturing equipment; changes in the location of manufacturing lines within a company; problems with product integrity, such as sterility and product potency; changes in formulation; and changes in demand. John Swegle, PharmD, clinical associate professor at the University of Iowa College of Pharmacy, reports that the shortages that his practice environment is experiencing include a number of the most common medications they use: morphine, hydromorphone, and fentanyl. "The morphine shortage is not as severe as it recently was, but widespread availability is sporadic. The unpredictable availability causes pharmacies to stock up, which is what everyone else does, exacerbating the problem. By far, the biggest frustration is not knowing how long the shortages will last," Swegle stated.

As seen in **Table 1**, drug shortages exist in many drug classes, although a predominant amount of the drugs in short supply are injectable. Because intravenous (IV) medications have strict sterility requirements and shorter expiration dates, these medications are particularly susceptible to shortages, and drug manufacturers are unlikely to stockpile them for extended periods. Strict FDA regulations on manufacturing can also limit the supply availability of these medications. Additionally, some older IV medications have become less profitable, prompting manufacturers to slow or stop production of these products. These factors lead to a large number of IV medication

Table 1.
SUMMARY OF CURRENT DRUG SHORTAGES

DRUG CLASS	SHORTAGES REPORTED
Antihistamines	1
Diagnostic Agents	6
Serums, Toxoids, and Vaccines	9
Anti-Infective Agents	29
Electrolyte, Caloric, and Water Balance	17
Smooth Muscle Relaxants	1
Antineoplastic Agents	19
EENT Preparations	4
Topical Agents	4
Autonomic Drugs	17
Gastrointestinal Drugs	5
Unclassified Therapeutic Agents	10
Blood Formation and Coagulation	5
Heavy Metal Antagonists	2
Vitamins	9
Cardiovascular Drugs	24
Hormones and Synthetic Substitutes	12
Central Nervous System Agents	39
Local Anesthetics	6
Other	9

Adapted from AHFS Drug Shortages Nov 8, 2012

shortages, despite the efforts of the FDA and others to control the problem.[4] Not to be overlooked, shortages of IV products disproportionally affect patients suffering from the most acute and difficult-to-manage symptoms.

Certain shortages are posing significant challenges in palliative and hospice populations (**Table 2**). A growing list of opioid shortages has made the management of pain even more difficult. Injectable hydromorphone is one example that illustrates how long a shortage can take to correct. First reported in March 2012, the injectable hydromorphone shortage was attributed to an increased demand—a testament to the narrow margins of inventory on which some of these medications operate. Recovery of the drug may not occur until the second quarter of 2013, depending on the specific hydromorphone product.[5] Many of these drug shortages are IV-dosage forms, including a multitude of chemotherapeutic agents, which is even more alarming. These shortages limit treatment options for patients who arguably have the greatest need for these medications. Lynn McPherson, PharmD, professor and vice chair in the Department of Pharmacy Practice and Science at the University of Maryland, echoes the challenges these shortages are creating. McPherson stated, "Right this minute, I am struggling to figure out what to do with a patient whose pain was finally controlled on IV methadone. Unfortunately, there is no more IV methadone in the state of Maryland."

Table 2.
DRUG SHORTAGES AFFECTING END-OF-LIFE CARE

ANALGESICS
Fentanyl, Methadone, Hydromorphone, Morphine
ANXIOLYTICS
Diazepam, Lorazepam, Midazolam
ANTIEMETICS
Metoclopramide, Prochlorperazine, Promethazine
MISCELLANEOUS AGENTS
Acetylcysteine, Bumetanide, Dexamethasone, Furosemide, Haloperidol, Octreotide

Shortages of single products frequently cascade throughout the therapeutic class, causing practitioners to use unfamiliar, and potentially less optimal, medications. Depleting availability of all drugs in a therapeutic class then causes increased use in another class—potentially creating a shortage there. Janice Scheufler, PharmD, reported that the recent unavailability of injectable benzodiazepines caused significant problems at Hospice of the Western Reserve. Scheufler stated, "Lorazepam and midazolam were unavailable at the same time, as well as phenobarbital. This created a dilemma for appropriately managing seizures, causing the hospice to use levetiracetam and increasing its costs."

The effect of economics cannot be overlooked. The Medicare Modernization Act changed the reimbursement rate for outpatient injectable drugs and capped the growth rate of reimbursement paid to providers by Medicare for administering these drugs. The impact of these pricing changes has significantly reduced the price of many older generic drugs, thereby affecting manufacturing margins.[3] Smaller margins cause manufacturers to reevaluate their product lines and lead them to exit the market.

Economics not only affect manufactures, but payers and providers, too, because the laws of supply and demand drive prices. Hospices, being reimbursed on a fixed per-patient per-day schedule, are sensitive to cost pressures. Velvet Cox, RPh, clinical pharmacy specialist in Hospice at Providence Home Services in Portland, OR, stated that methadone shortages have been very problematic. When certain methadone products were not available, Providence Home Services had to resort to compounding from raw powder, which significantly increased the cost of therapy.

An additional challenge facing manufacturers is effectively recovering from a shortage. Because of the limited growth of the total drug manufacturing capacity—despite

large growth in demand—manufacturers typically shift production to the drug in shortage to aid in recovery.[5] However, the process of repurposing manufacturing equipment to produce a different product can be lengthy and expensive. Manufacturers risk focusing too many resources on one shortage and causing a shortage of another drug. If they do not shift enough resources to correct a shortage, it could be months before they realize production needs to be increased to meet demand.

Further exacerbating the problem of drug shortages is the difficulty with reporting them in a timely manner. When a raw material is in short supply, manufacturers are unable to produce enough product, leading to reduced shipments to wholesalers. In an effort to manage the reduced inventory, wholesalers will reduce shipments to pharmacies that ordered the product. Pharmacies will eventually run out of these drug products and not be able to fill prescriptions in a timely manner. When the shortage finally reaches the prescriber, a great deal of time has passed, and the shortage may have escalated. Reporting drug shortages is the responsibility of all parties involved, but quick action by the manufacturers in reporting can go a long way to alerting prescribers of a potential shortage.

Because drug shortages are a great threat to proper patient care, action must be taken to help prevent them in the future. Efforts to prevent drug shortages should be directed toward short-term corrections with limited impact on other drug supplies, and long-term solutions that stop shortages from occurring in the first place.

It is essential to quickly control and recover from drug shortages. Efforts from several groups can be significant in preventing drug shortages. Manufacturers can play an important role by increasing transparency in their manufacturing processes. If manufacturers are experiencing problems obtaining the necessary raw materials, if there are any issues preventing the release of a large batch of medication, or if demand is increasing beyond what the current supply can support, manufacturers can report a potential shortage. The FDA can also play an important role; announcements from the FDA have a very high visibility to prescribers and could be a simple way to announce a potential shortage. With the information that a drug is approaching a potential shortage, prescribers can use their professional judgment to decide if a patient absolutely needs a particular medication or if there is a viable alternative that will be equally effective. Although most prescribers may opt to use the drug regardless, more information will help them make an informed decision about patients that will need a medication further down the road. According to the FDA, 195 drug shortages were prevented in 2011 due to FDA efforts,[6] and as of August 2012 the FDA reports it has prevented another 100 shortages.

Although actions in the short term can help deal with and even prevent some shortages, long-term steps must be taken. Drug manufacturers must play a very large role in these preventive measures. Because manufacturers are producing more drug products than ever before, it is also important to increase total drug manufacturing capacity. This will directly prevent drug shortages by increasing supply and allowing the manufacturers more flexibility to decide which products they want to produce in a larger supply without compromising the supply of other necessary medications. When manufacturers start taking this step, it is up to the FDA to help approve new manufacturing facilities to aid in this process. The FDA may have limited resources to do so, but focusing on approving new manufacturing space will be an important preventive measure to stop future drug shortages. Finally, practitioners can help prevent shortages by developing responsible guidelines that thoroughly explore alternative therapies for

CONGRESS ADDRESSES DRUG SHORTAGES *Sue Ramthun*

The 112th Congress focused on drug shortages as a critical public health concern and convened several hearings to examine the issue. In 2011–2012, several congressional committees with healthcare jurisdiction heard testimony from government agencies, physicians, patients, hospitals, and the pharmaceutical industry.

In response, Congress passed legislation to strengthen the FDA's role in addressing drug shortages as part of the Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144. Since the early receipt of information from manufacturers regarding drug shortages is critical to preventing and dampening shortages, Title X of the FDASIA mandates additional reporting requirements.

Notification

FDASIA broadens the scope of the early notification requirement by mandating that all manufacturers of covered drugs notify the FDA of potential discontinuances, regardless of whether the firm intends to discontinue a product permanently or is only facing a temporary interruption of supply. The law requires the FDA to publicize an up-to-date list of drugs in shortage, including the cause and estimated duration of the shortage, to physician organizations, patients, and others.

FDASIA also requires the FDA to establish a system for the reporting of drug shortage evidence to the Agency. The FDA must issue noncompliance letters to those manufacturers that fail to comply with the above requirements. This letter and the company's response will be made available to the public.

In addition, the secretary of Health and Human Services is required to coordinate with the attorney general to increase aggregate and individual quotas of the Controlled Substance Act to address shortage issues. The attorney general is required to report annually to Congress regarding the number of quota expansion requests received, approved, and denied, and the reasons why.

treatment. Although there are some examples of disease states that can only follow a single treatment path, there are often many viable alternatives that can be effective as either a temporary solution or a long-term replacement of standard therapies. Essentially what works for practitioners in both the short term and long term is receiving more information to make the most informed decision possible.

An important preventive step that anyone can take is to report to the FDA a drug shortage or supply issue as soon as it appears. The FDA has a system for reporting shortages and maintains a database of current and resolved shortages, as well as drugs that have been discontinued. Early reporting can help practitioners adjust their practice in light of supply issues. The FDA website directs to the Center for Drug Evaluation and Research to report drug shortages. Before contacting the FDA, it is important to have as much detailed information as possible about the drug product affected. Such information can include the name, strength, and dosage form of the product, and the manufacturer of the product or its National Drug Code (NDC) number. To report a shortage call 888.463.6332 or e-mail drugshortages@fda.hhs.gov. The FDA website is updated as information becomes available to reflect new reported drug shortages.

The American Society of Health-System Pharmacists (ASHP) website (www.ashp.org) also offers useful information, such as the length of time a shortage has been occurring and what actions must be taken in order to obtain a drug product that is in shortage. Please note, reporting a shortage to ASHP does not send a report to the FDA.

References

1. Fox ER, Tyler LS. Measuring the impact of drug shortages. *Am J Health Syst Pharm*. 2004;61(19):2009.
2. US Food and Drug Administration. Six month check-up: FDA's work on drug shortages. FDA Voice. http://blogs.fda.gov/fdavoice/index.php/2012/05/six-month-check-up-fdas-work-on-drug-shortages. Published May 3, 2012. Accessed November 29, 2012.
3. US House of Representatives: Committee on Oversight and Government Reform. FDA's Contribution to the Drug Shortage Crisis. Published June 15, 2012. http://oversight.house.gov/wp-content/uploads/2012/06/6-15-2012-Report-FDAs-Contribution-to-the-Drug-Shortage-Crisis.pdf. Accessed November 29, 2012.
4. US Department of Health & Human Services. Economic analysis of the causes of drug shortages. ASPE Issue Brief. http://aspe.hhs.gov/sp/reports/2011/DrugShortages/ib.shtml. Published October 2011. Accessed November 29, 2012.
5. US Food and Drug Administration. Current drug shortages e-k. FDA website. http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm314740.htm#hydromorphone. Published October 12, 2012. Accessed November 29, 2012.
6. US Food and Drug Administration. Prescription drug shortages: examining a public health concern and potential solutions. Published December 15, 2011. http://www.fda.gov/NewsEvents/Testimony/ucm282956.htm. Accessed November 29, 2012.

Resources

US Food and Drug Administration. Current Drug Shortages Index. Updated November 29, 2012. http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm.

The White House: Office of the Press Secretary. Executive order 13588—reducing prescription drug shortages. The White House. http://www.whitehouse.gov/the-press-office/2011/10/31/executive-order-reducing-prescription-drug-shortages. Published October 31, 2011.

Rajagopal, D. Sun Pharma to export version of cancer medicine Lipidox to US. The Economic Times. http://articles.economictimes.indiatimes.com/2012-02-23/news/31091184_1_generic-version-sun-pharma-global-fze-lipodox. Published February 23, 2012.

Vranken JH. Elucidation of pathophysiology and treatment of neuropathic pain. *Cent Nerv Syst Agents Med Chem*. 2012 Oct 2. [Epub ahead of print].

Gregory Dyke, BS RPh, is the president of Clinical Consulting at OnePoint Patient Care, a national Hospice PBM and local Pharmacy Services provider. He can be reached at gdyke@oppc.com.

Andrew DeSio is a fourth-year pharmacy student at the University of Iowa College of Pharmacy.

There are a number of other provisions in FDASIA related to drug shortages, including the requirement that prior to taking any action that could result in a disruption in supply, the FDA must evaluate the costs and benefits of taking such action and communicate their findings.

The FDA will be required to submit an annual report to Congress on drug shortages and the agency's efforts to address these shortages. The Government Accountability Office is also required to submit a report under FDASIA that examines the causes of drug shortages and makes recommendations to prevent and alleviate shortages. Finally, FDASIA requires the FDA to establish a task force that will, by January 2013, publish and submit to Congress a strategic plan to enhance the response to drug shortages.

Economic Incentives

Some in Congress remain concerned that more must be done to address the effect of government pricing policies on the drug supply, particularly for the generic sterile-injectable drugs that have been in such short supply. Before the close of the 112th Congress, Rep. Bill Cassidy, MD, (R-LA-6) introduced the Patient Access to Drugs in Shortage Act (H.R.6611). The bill would provide financial incentives that would be triggered any time a generic injectable drug is likely to become in short supply, encouraging manufacturers to continue production or brand companies to enter the market. To increase profitability, Medicare reimbursement for a single-source drug would be based on wholesale acquisition cost rather than average sales price. The legislation would also exempt manufacturers from Medicare and Medicaid discount and rebate agreements. Rep. Cassidy is expected to reintroduce similar legislation in the new Congress.

Sue Ramthun is a principal and senior vice president at Hart Health Strategies, which serves as AAHPM's Washington, DC-based government relations counsel.