

Drug Shortages Increasingly Take Toll on Care

In 2010, there were 178 products in short supply, which was up from 61 products in 2005.

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FROM A FOOD AND DRUG
ADMINISTRATION DRUG SHORTAGE
WORKSHOP

SILVER SPRING, MD. – With their increasing prevalence, drug shortages in the United States have led to delays in treatment, forced the use of less effective alternatives, and encouraged a burgeoning gray market that sells tough-to-obtain medications at highly inflated prices, according to stakeholders gathered at a recent FDA meeting.

Shortfalls in drug supply have increased in the United States, with 178 shortages of products reported in 2010, up from 61 in 2005, according to Dr. Edward Cox, coordinator of the FDA's drug shortage program. Disproportionately affected are generic drugs and sterile injectable products; the latter accounted for two-thirds of the shortages last year.

About half of the injectable shortages were caused by problems with product quality, followed by manufacturing delays (21%) and discontinuations (11%), and other issues including an increase in demand created by another shortage, he said at the meeting.

As with older generic drugs, there's little financial incentive to produce older sterile injectables such as propofol, which sell for as little as 48 cents for a 20-mL vial. In such cases, manufacturing glitches can often convince companies to pull the plug on a product, creating shortages.

Most hospitals aren't immune. A June 2011 survey of 820 nonfederal, short-term, acute care hospitals by the American Hospital Association found that almost 99% had experienced one or more drugs shortages in the first 6 months of 2011; 44% reported at least 21 shortages during that time. In addition, nearly half reported experiencing drug shortages on a daily basis, 40% on a weekly basis, and 13% on a monthly basis.

Almost all these hospitals (96%) had experienced shortages of anesthesia for surgery, followed by drugs used for emergency care (91%), cardiovascular care (90%), GI/nutrition (89%), pain management (88%), infectious disease (83%), and oncology (66%).

Drug shortages have hit the fields of oncology and anesthesiology particularly hard, often causing the delay or postponement of clinical trials of cancer treatments.

Shortages of propofol and succinylcholine have been common. Dr. Frederick Blum, past president of the American College of Emergency Physicians, who practices in Morgantown, W.Va., described being told there was no succinylcholine available when he recently requested it as he was about to intubate a trauma patient. When he asked for the next best drug, it wasn't available either

because supply had been depleted from the succinylcholine shortage. A third, less-than-ideal alternative was found. But Dr. Blum said that after 30 years of practice, during which time he probably has used succinylcholine thousands of times, he left that shift shaking his head about the need to resort to using a third-choice drug.

Before the shortage of succinylcholine was resolved earlier this year, shortages

are only two, and the FDA has asked another company to start manufacturing the colon cancer agent.

At St. Jude Children's Research Hospital, Memphis, 1-4 drug shortages were reported every month in 2009, but in 2011, an average of 22 shortages have been reported every month, peaking at 28 in July. Notable shortages over the past year have included every component of total parenteral nutrition (TPN) and multivitamin injections, with the latter resulting in a hospitalization of a patient who could not take oral multivitamins and developed neurotoxicity and a thi-



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To see a video about drug shortages and an interview with Michael R. Cohen, president of the Institute for Safe Medication Practices, scan the QR code below.

of the agent also resulted in postponed surgeries at Veterans Administration Medical Centers.

Dr. Len Lichtenfeld, deputy chief medical officer of the American Cancer Society, noted that many generic cancer drugs are in short supply. Such drugs, developed years ago, often are inexpensive and "remain mainstays of many currently available and effective cancer treatment programs," he said.

Generic cancer drugs that are in short supply include fluorouracil (5-FU), paclitaxel, daunorubicin, cytarabine, bleomycin, and cisplatin.

In many cases, such shortages are causing patients to have to travel further to get the drugs they need. Alternatively, they are treated with second- and third-line therapies that are not necessarily as effective, Dr. Lichtenfeld said. Many adult and pediatric trials of cancer treatments have been suspended when supply of the active control drug is no longer available, he added, and ACS is regularly contacted by patients and families who are looking for medications in short supply.

Exacerbating a shortage situation is the emergence of gray markets that trigger hoarding, he said.

Dr. Laura Porter of the Colon Cancer Alliance said that there have been shortages of 5 of 22 drugs used to treat for colon cancer, including 5-FU and leucovorin. Of the five, four are generic drugs. Last year, there were eight manufacturers of irinotecan, another drug used to treat colon cancer; today, there

are only two, and the FDA has asked another company to start manufacturing the colon cancer agent.

Shortages of chemotherapy drugs have increased over the past 2 years. At St. Jude, where 85% of the cancer patients are enrolled in clinical trials, enrollment in acute myeloid leukemia protocols were suspended because of a shortage of cytarabine and lymphoma protocols were modified because of the shortage of mechlorethamine (nitrogen mustard). He pointed out that with 10 drugs, about 90% of patients with childhood acute lymphoblastic leukemia, the most common childhood cancer, can be cured, but over the last decade, 8 of these 10 drugs have been temporarily unavailable.

Substitute drugs can often be more expensive and involve additional labor costs, adding up to an estimated \$415 million annually, according to Bryant Mangum, vice president of pharmacy services at Premier Healthcare Alliance, a network of over 2,500 hospitals in the United States.

An analysis of 636 unsolicited sales offers from gray-market vendors conducted by Premier found that the average markup of a drug price was 650%. Almost half the drugs were marked up by at least 1,000%, more than 25% were marked up by at least 2,000% – and a drug used to treat hypertension that usually costs \$25.90 was being offered at \$1,200, "a staggering increase," he said at the meeting.

The greatest markups were for drugs

used to treat patients in the areas of critical care sedation and surgery, chemotherapy, emergency care, and anti-infective drugs, he said.

Currently, the FDA's approach to drug shortages involves encouraging companies that make a product that is in short supply to ramp up manufacturing. The FDA also works with firms to address problems behind the shortage, such as manufacturing or quality issues. In rare cases, the FDA allows a product from an unapproved source to be imported into the U.S. temporarily, which was the case in 2010 for propofol and in 2011 for foscarnet, norepinephrine, leucovorin, and capecitabine.

Manufacturers have been giving the agency earlier notification about the potential for supply issues, a strategy that the FDA claims has successfully headed off some shortages. Such reports have helped prevent 99 shortages so far this year, an increase from 38 in 2010, Dr. Cox said at the meeting. Most of the prevented shortages (84) were derailed by expediting FDA review of new manufacturing sites, suppliers, and other issues that affected production of the drugs.

Other recommendations for resolving, preventing, and alleviating drug shortages now and in the future include creating stockpiles of certain drugs, similar to vaccine stockpiles; developing guidelines on treatment alternatives when there is a shortage of a drug, such as an antibiotic; and improving communications about drug shortages between FDA and stakeholders.

Clinicians need to be notified faster about shortages so they can be better prepared, according to several practicing physicians who spoke at the meeting. Of the hospitals that were surveyed by the AHA, 70% responded that the available information on how to manage drug shortages was not adequate.

Sources for such information include the American Society of Health-System Pharmacists, the FDA drug shortage website, and direct communication with manufacturers.

Dr. Blum, Dr. Cox, and Mr. Mangum had no disclosures. Dr. Lichtenfeld disclosed that he owns Johnson & Johnson stock and that the ACS receives grants from pharmaceutical companies and the foundations they oversee. Disclosure statements for Mr. Hoffman and Dr. Porter were not available. ■

FDA information on drug shortages, including current and resolved shortages, is available at www.fda.gov/drugs/drugsafety/drugshortages/default.htm. To report drug shortages, call 888-463-6332, e-mail drugshortages@fda.hhs.gov, or go to www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm142398.htm. To report shortages of biologic products (such as blood, vaccines, or allergens), call 301-827-4239 or e-mail CBERShortages@fda.hhs.gov.

