Patients and physicians in the United States are currently experiencing a critical shortage of potentially life-saving drugs for the treatment of cancer (and other serious diseases). This growing threat – which is devastating for cancer patients – is also costly. According to a survey conducted by the Premier Healthcare Alliance, the shortage is costing U.S. hospitals at least $200 million annually due to the need to purchase more expensive generic or therapeutic substitutes for drugs in short supply.

In addition, the costs associated with the drugs experiencing shortages are going up by an average of at least 11% annually. Some pharmacy managers are resorting to purchasing drugs on the “gray market” at inflated prices, also raising direct costs of acquiring drugs.

These estimates are only based on direct costs of acquiring drugs and do not incorporate indirect costs, such as the amount of hours spent each day by staff of oncology practices and clinics trying to locate drugs or substitutes for drugs that are currently in short supply.

Physicians, professional societies, governmental agencies, and the U.S. Congress are keenly aware of these shortages, which are mainly restricted to generic versions of injectable sterile drugs that have been off patent for years, but are considered standards of care for many types of cancer.

The situation is not likely to improve anytime soon. To illustrate the growing threat of this problem, in 2010, the Food and Drug Administration reported that 178 drugs were in shortage, compared with 157 in 2009 and just 55 in 2005. Table 1 shows some of the widely used cancer drugs that are experiencing shortages.

In addition to anti-cancer agents, some drugs used for supportive care are in various levels of shortages, e.g., antibiotics and anesthetics, especially propofol and neuromuscular blocking agents vital for use in surgery and for ICU patients on ventilators.

There are no good substitutes for some of the drugs on the list, for example, doxorubicin in lymphoma, vincristine in childhood tumors, and leucovorin for colon cancer and as a rescue agent post high-dose methotrexate in childhood tumors; and even when an acceptable substitute exists, the correct dosage may not be clear, or if clearly known, may be different from the desired drug, as in the case of switching epirubicin for doxorubicin in treating breast cancer.

The widespread fallout from these shortages includes dosing errors, unexpected side effects, delay of transplant, triaging of patients, and in some settings, stockpiling drugs that may be in short supply in the future. Some hospitals report taking patients off palliative therapy and reserving any remaining drug for patients treated with a curative intent. Other hospitals have reported triaging

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among patients being treated with a curative intent as well, reserving the specific drug for the less sick patients with a better chance of cure.

One oncology practice’s experience at Berks Hematology Oncology Associates, Ltd., in West Reading, PA, serves as a microcosm of the dire situation regarding cancer drug shortages. This practice includes five physicians and three physician assistants and serves up to 220 patients each day.

“The situation regarding drug shortages has never been worse, and it’s not likely to get better,” stated Berks’ CEO Bob Orzechowski in an interview.

One year ago, it was rare that cancer drugs would be back ordered at Berks. Currently, 11 critical drugs are back ordered and these back orders are the main agenda points for bi-weekly meetings of the practice’s P & T Committee.

“The pool of distributors has shrunk to two major distributors – two 800-pound gorillas,” Orzechowski said. “Smaller distributors have fallen by the wayside, making it more difficult to get a drug in shortage.”

What happens when a drug is in shortage? “Endless hours on the phone trying to locate another source,” Orzechowski said, adding “We may need to go to a specialty pharmacy and pay retail or to a smaller distributor. In either case, we pay more than we get reimbursed by an insurance company.” The practice does not go to the grey market or order drugs from Canada.

“The problem is pervasive,” said Orzechowski. “It’s happening everywhere. Distributors are facing shortages themselves.”

**Why Is This Shortage Happening Now?**

According to Dwight Kloth, PharmD, Director of Pharmacy at Fox Chase Cancer Center in Philadelphia, “This problem has been crescendoing for the last couple of years. My sense is that a number of factors have converged to create a perfect storm.” These factors are interrelated and include manufacturing and distribution snafus, meeting strict regulation standards for safety and sterility, the consolidation of generic drug companies, and financial disincentives for generic companies to continue to manufacture injectable sterile drugs.

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In Kloth’s personal experience, shortages are leading to “heartbreaking situations” and “painful discussions” revolving around patients who are not being treated at Fox Chase, but may need specific drugs: for example, a patient who came to Fox Chase for a second opinion and went back to his medical center 70 miles away for treatment, but that center was out of the medication that was needed, so Fox was asked to supply the drug to the other hospital.

“I had to refuse this request, because my first priority is to conserve the meager supply of drugs for Fox Chase patients. I have also had to decline requests when I didn’t have enough of a drug to finish out the week. I could be inundated with requests like these, and it would not be fair to say yes to some hospitals and no to others,” he explained.

Kloth also related that he has heard similar stories from his counterparts at other NCI-designated cancer centers across the country. In late March 2011, Fox Chase Cancer Center was asked by another cancer center if they could trade one drug in shortage for another, as the other center was desperately in need of thiopental. Unfortunately, in this case Fox Chase’s supply of thiopental was equal to a few hours’ worth of supply for that other cancer center.

**Contributing Factors**

» Manufacturing Problems

One factor that has received little media attention is that an “astonishing” (according to Kloth) 80% of the active pharmaceutical ingredients (API) in these drugs are currently derived from the international market, mainly China and India. Data from the American Society of Health-System Pharmacists show that approximately 13% of APIs are manufactured in the U.S., compared to 39% in India, and 43% in China, Kloth said.
As with other imports from China and other countries with less stringent standard than those in the U.S., importing APIs from these countries may make it difficult for manufacturing companies of generic drugs in the U.S. to comply with strict FDA and OSHA regulations for safety and sterility. “How can companies in the U.S. compete with India and China and meet strict regulations and pay their workers fair wages?” Kloth asked.

If manufacturing problems occur when companies fail to meet their own standards for safety and sterility and/or meet FDA’s standards, the drug is taken off line (out of distribution), creating a shortage.

**Consolidation of Generic Companies**

The consolidation of generic drug companies is also causing shortages of some drugs. Compared with a decade ago, there is now roughly one third fewer generic drug manufacturers in the U.S. Kloth explained that consolidation brings the risk of shortages.

“When six different companies are making a generic drug and then only two or three companies are making it, the supply dwindles while the demand remains constant,” he said. Also, if only two companies are making a specific drug and one of them has a manufacturing or distribution problem, it will also lead to shortages.

In 2009, consolidation of generic companies as well as manufacturing issues led to a shortage of propofol, a non-cancer drug widely used for conscious sedation in minor surgeries. Two thirds of the supply chain [of propofol] was recalled over a short period of time [due to manufacturing issues] and two of the companies that manufactured it took the drug off line.

Then one of the companies decided not to re-enter the market, noted Kloth.

**Profit Margins**

Although this view has been called both cynical and simplistic, profit or lack thereof is at least one of the drivers of the current drug shortages. The lion’s share of shortages is for off-patent generic drugs, like leucovorin, costing about $20 per day. As one person interviewed for this article said, “We won’t be seeing shortages of drugs like bevacizumab, which costs about $10,000 per month by one estimate.”

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Generic drug companies have smaller profit margins than Big Pharma to begin with, which gives the larger pharmaceutical companies that manufacture newer expensive drugs more money to work with, whereas generic companies are squeezed.

Kloth suggested that one factor leading to some of the current shortages is the success of pharmacy directors working with national group purchasing organizations (GPOs) in negotiating the lowest price per drug. “Our success has pitted generic companies against each other, and their profit margins are potentially narrowed,” he noted.

**Distribution Factors**

Most cancer drugs are purchased from one distributor (i.e., “sole source”), and both sole source and bundled purchasing contribute to drug shortages because these practices leave little or no inventory to cushion the blow of short-term shortages. Other factors affecting distribution are regional and local differences in product availability due to contracts with wholesalers and GPOs. Although current systems are in place to address potential shortages by correcting product allocation, these systems often fall short due to unreliable information.

GPOs are not able to determine competitive pricing that would facilitate establishing multiple contracts for a specific drug. Smaller facilities and clinics do not have the business clout that larger facilities and health systems have for procuring products.

As alluded to previously, the gray market has pushed up the price for drugs in short supply, creating the potential for stockpiling and price gouging.

**Solutions**

The problem of drug shortages is multifactorial and complex; therefore, experts agree there will not be a simple solution. A Drug Shortage Summit was convened last November by the American Society of Health-System Pharmacists (ASHP), the American Soci-
ety of Anesthesiologists (ASA), the American Society of Clinical Oncology (ASCO), and the Institute for Safe Medicine Practices (ISMP), and pharmacy manufacturers, pharmacists, and physicians met to explore the problem in great depth and come up with recommendations for solutions.

Michael P. Link, MD, President-elect of ASCO was present at the summit. The following are some of the main recommendations he presented on behalf of ASCO and the summit co-conveners:

» Extend the expiration date for drugs that are in short supply but are still found to be active and safe.

» Develop regulatory and distribution partnerships outside the U.S. to identify additional supplies.

» Create an equitable distribution plan between community and academic medical centers without mark-up of the product in question.

» Improve communication about impending drug shortages.

» Develop a process whereby payers provide immediate reimbursement in the face of a shortage.

Link is gratified to see that Senator Amy Klobuchar of Minnesota has introduced a bill addressing some of the problems identified by the Summit. The Preserving Access to Life-Saving Medications Act (S. 296) broadens the definition of medically necessary drugs and gives the FDA expanded authority to enforce the current requirement for manufacturers to let the FDA know about impending shortages 6 months before they are predicted to happen.

“Without legislation, there is no way to enforce it [i.e., the rule let FDA know a shortage is expected in 6 months] strongly,” Link says. “The new bill could prevent/mitigate an emerging shortage and provide lead time to develop strategies for working around such a shortage so that patients don’t suffer.”

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But Link agrees that the new bill is not a cure-all and will not solve existing shortages. “I see no evidence that these shortages are going away,” he stated.

ASCO is not a drug manufacturer or a distributor; the Society’s main concern is patients. “From the point of view of the individual patient, if a shortage is looming, the patient needs to work with his/her doctor to develop an appropriate work-around,” Link stated.

“For now, we have to be aware of the global nature of the problem and the potential for shortages. At ASCO, we are collecting data to try to identify where the problems are so that we can reassure patients about an effective work-around. For the future, we need better interaction and communication with drug manufacturers and distributors. The lack of communication has greatly exacerbated the problem,” he noted. Overall, potential solutions are a work in progress and will have to come from several sources. A multi-dimensional problem requires multi-pronged solutions.”

Men under 65 with early prostate cancer had better survival odds if they had surgery right away instead of waiting for treatment only if their cancer got worse, a study in Sweden found. (USA Today, 5/5/11)

One of the biggest new drugs for 2011, listed by expected sales in 2015, is Johnson & Johnson’s Zytiga™ for prostate cancer at $436 million. (Thomas Reuters Pharma, consensus forecasts, 5/6/11)

Another of the biggest new drugs for 2011 is Bristol-Myers Squibb’s Yervoy™ for melanoma with expected sales of $931 million in 2015. (Thomas Reuters Pharma, consensus forecasts, 5/6/11)

A record 887 cancer medicines are in clinical trials or awaiting FDA review based on a new PhRMA report. (Pharmaceutical Research and Manufacturers of America, 4/5/11)

The FDA just approved both Pfizer’s Sutent® and Novartis’ Afinitor® for progressive neuroendocrine tumors of pancreatic origin (or PNET), a rare type of pancreatic cancer. (FDA press releases, 5/6/11 and 5/20/11)