Running on empty

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ABSTRACT

Pharmacists, physicians, and patients across the country have been asking, "Why?" Why have there been so many shortages lately? Why can some pharmacies get products, while others can't? Why are some prices skyrocketing? The FDA, state pharmacy boards, and groups such as ASHP have been hard at work looking for answers.
According to the FDA and ASHP, shortages can be caused by several situations. Manufacturers can spark shortages by abruptly discontinuing medications, either temporarily or permanently. Often, this is purely a financial decision. If a product is not profitable, there is not much incentive for a company to continue making it. When only two or three companies make a certain drug, discontinuation by one firm leaves the others holding the bag. Unlike other commodities, drug products can take months to manufacture. Even if the remaining companies scramble to step up production, it can be some time before they are able to fill the void. This situation has been aggravated by company mergers. After combining forces, companies look at their product lines and eliminate poor performers.

FULL TEXT

Headnote
COVER STORY
Headnote
What's behind the current rampant drug shortages?
Pharmacists want to know
Fentanyl, phenobarb, flu vaccine-- the mere mention of these drugs, and a host of others, sends chills down pharmacists' spines. Pharmacists everywhere have come to dread the sight of a delivery printout and the words product unavailable. One shortage after another in recent years has made a nightmare of the once innocuous task of ordering drugs.
Pharmacists, physicians, and patients across the country have been asking, "Why?" Why have there been so many shortages lately? Why can some pharmacies get products, while others can't? Why are some prices skyrocketing? The Food &Drug Administration, state pharmacy boards, and groups such as ASHP have been hard at work looking for answers.
According to the FDA and ASHP, shortages can be caused by several situations. The issue "is multifactorial ... and it doesn't look like it's going away," said Joe Deffenbaugh, M.PH., professional practice associate for ASHP.
Manufacturers can spark shortages by abruptly discontinuing medications, either temporarily or permanently. Often, this is purely a financial decision. If a product isn't profitable, there isn't much incentive for a company to continue making it. When only two or three companies make a certain drug, discontinuation by one firm leaves the others holding the bag. Unlike other commodities, drug products can take months to manufacture. Even if the remaining companies scramble to step up production, it can be some time before they are able to fill the void.
This situation has been aggravated by company mergers. After combining forces, companies look at their product lines and eliminate poor performers. Also, if both firms have been manufacturing a particular drug, they may consolidate production of that drug. According to ASHP, this makes the product more vulnerable to shortage problems by reducing the number of manufacturers that make it.
Still another problem is aging facilities. Deffenbaugh pointed out that most of the drugs in short supply have been

injectables. Manufacturing these drugs is complex and expensive. "What we've heard is that several manufacturers' sterile product facilities are getting old," he said.
As equipment ages, breakdowns are apt to occur more often. This stalls production as repairs are made. Some manufacturers are busy correcting the situation by building new plants. Others, when confronted with expensive major renovation requirements, have decided it's not worth manufacturing the product in question.
Unfortunately, no one has studied the phenomenon, so there is no way of knowing just how many plants need updating, said Deffenbaugh. Even worse, it's uncertain how many products may be affected in the future.
Manufacturers are not exactly forthcoming with their plans. How-- ever, corporations do inform their stockholders of changes that may affect earnings, and Deffenbaugh said these reports have been a good source of information.
Other causes of shortages are even more problematic because of their unpredictability Sudden, increased demand for a product can catch manufacturers by surprise. Raw material supplies are also vulnerable to a number of problems, as many suppliers are located in foreign countries. Natural disasters, wars, and disease in these countries can all inhibit or halt production of raw materials. These products may also undergo degradation or contamination before they reach the manufacturers, according to ASHP.
Can't the FDA do something?
In some cases, the FDA can help. In fact, the FDA has a department devoted to drug shortages. Mark Goldberg, M.D., is clinical coordinator of the department. Lisa Hubbard, R.Ph., and Valerie Jensen, R.Ph., are its project managers. Among other things, Hubbard, the senior project manager, and Jensen are responsible for communicating with R.Ph.s and the public about drug shortages. They maintain a Web site that highlights the shortages at www. fda.gov/cder/drug/shortages.
One of the main goals of Hubbard's department is to get shortage information to pharmacists as quickly as possible, so they can then explain it to their patients and physicians. At the Web site, RPh.s can sign up to receive notices and updates on drug shortages. You can also e-mail Hubbard and Jensen to let them know about a drug that's in short supply.
In addition to the Web site, Hubbard tries to have at least one contact person at all or most of the pharmacy organizations to better facilitate the dissemination of information. Her counterpart at ASHP is Deffenbaugh.
The FDA focuses on resolving shortages of medically necessary drugs, said Hubbard. She said that, believe it or not, most shortages are resolved before we even know about them. Only a small percentage ever becomes a pro lem. The agency continues to focus on the problem drugs until production is sufficient. While the FDA can't force companies to manufacture a drug, there are some things it can do.
For example, sometimes the FDA finds defects in facilities before manufacturers have had time to update them. The agency may have to halt production of a drug until the problem is corrected. If this seems likely to result in a shortage, and if the drug is medically necessary, the FDA will do what it can to alleviate the shortage.
In the case of updating facilities or correcting defects, the FDA can expedite inspections and application reviews. The agency can also look for alternative suppliers to help in the interim. In one case, a Canadian manufacturer was allowed to supply a drug while the original manufacturer got its plant up to par. When a sole supplier of a drug discontinues the product altogether, the FDA looks for manufacturers who may be willing to start making the drug.

One thing the FDA does not do is allow manufacturers to bypass steps that would affect drug quality. "The important thing to get out to the public is that we do not decrease our standards in any way," said Hubbard. Although the FDA is concerned about shortages, the agency is not willing to sacrifice drug safety and quality.
The problem is manufacturers are not in the habit of informing anyone in advance that they'll be discontinuing products. This means that no matter how quickly the FDA gets involved, there is likely to be a shortage until other manufacturers can meet the demand. For now, there's nothing more the FDA can do about this cause of shortages.

By law, only sole manufacturers of life-sustaining products that prevent a debilitating disorder are required to inform the FDA of intended discontinuation. In this case, manufacturers must give the FDA six months' notice

before ceasing production. The public has the Food &Drug Administration Modernization Act (FDAMA) of 1997 to thank for this requirement.

After several drug companies discontinued products, which, in turn, created shortages, many people have been saying the FDAMA requirement should be extended to include other manufacturers and medications. ASHP agreed. "We've asked Congress to consider changing the FDA's definition to be much broader and to require all manufacturers of medically necessary drugs [to have to give six months' notice]," said Deffenbaugh. While several Congressmen support such legislation, it's unlikely anything will be done about it this year. Drug shortages are not at the top of their priority list at the moment.

What manufacturers have to say

Not much, unfortunately. There's usually a lot of finger pointing, generally in the direction of the FDA or raw material suppliers.

Deffenbaugh said he understands why manufacturers are reluctant to inform the public of changes that may affect supplies. If a company is going to discontinue a product, he said, it is going to want to sell every-- thing it has. Informing buyers in advance may jeopardize this.

Shortages are one of the consequences of running a business, Deffenbaugh continued. In this country drugs are a commodity. Pharmaceutical manufacturers that have gone public (and most have) need to satisfy their stockholders. If a product isn't profitable, it's going to be dropped. This country wanted a free market system, and it got it. "So be careful what you ask for," he said.

Anatomy of a shortage

To better illustrate just how a shortage occurs, here are a few examples from the past year:

* Factor VIII-In November 2000 an FDA inspection of a Bayer manufacturing facility revealed bacterial contamination in some stages of recombinant Factor VIII (Kogenate FS) production. In January of this year, Bayer stopped distribution of the drug until the facility met FDA standards. More contamination problems in the spring led to another halt in production.

As Bayer's product became limited, demand for other Factor VIII products increased. Aventis distributes a Factor VIII, Helixate FS, but because it buys the drug from Bayer, the supply of this product also diminished. When Baxter stopped production of its version, Recombinate, the situation was aggravated even further. Baxter took a month this past spring to do some maintenance on its facilities. As if that weren't enough, Wyeth's albumin-free Factor VIII has also been limited because the company is updating its plant as well.

*Dexamethasone injectable-We can blame mad cow disease for this one. Dexamethasone used to be derived from beef protein sources. Because raw supplies were produced in other countries, and because mad cow disease was present in these countries, the importation of the product was halted. Switching to a plant source solved that problem, but it required FDA approval. The delays caused shortages until the plant-derived form of the drug could be produced.

*Influenza vaccine-With this one, things are even more complicated. There are "inherent difficulties in producing essentially a new vaccine every year," said Deffenbaugh. About "75 or 80 million doses are the maximum that could ever be produced [with the current system]. That is substantially less than would be needed to meet the FDA's 2010 goals."

Here's why: The manufacturers can't start making vaccine until the World Health Organization figures out what the strains will be. The strains differ by region, so vaccines must be made regionally. Also, the vaccine is polyvalent, so multiple strains are needed for each vaccine. The seed cultures are started in the spring, and the FDA supplies quality control reagents to the manufacturers. Then the vaccine is made during summer in preparation for fall deliveries.

A breakdown at any stage of this process means a delay in availability Last summer, a slow-growing strain was the first culprit Then, two manufacturers had problems making the vaccine. With this drug, Deffenbaugh said we would continue to have problems. In order to immunize all the atrisk people, both production and provider communication to patients will have to be increased. The Centers for Disease Control &Prevention and the FDA are

working on it, but "we still have too many preventable deaths from influenza," he said.

Life in the trenches

"I just spent days making phone calls," said Jane Younts, R.Ph., M.BA., M.H.A., director of pharmacy at Morehead Memorial Hospital in Eden, N.C. "The drug companies just won't tell you [anything]." She believes most customer service reps honestly don't know why a drug is not available, and they certainly can't give her a release date. She has found that most often she has to go through several people at a given company in order to get this information.

"We used to just order drugs and give them to the patients, and that was it," said Younts. Now, much of her time is spent trying to locate medications. "We're talking the basics," she said, citing dexamethasone and naloxone as examples. In addition, one of her technicians has also had to devote all of her time to purchasing.

"We essentially have been rationing drugs," Younts explained. "We're not using the word rationing, but that's what we're doing." For example, "We have a list of reasons you can give tetanus vaccine." After months of scrounging for information, Younts has become a very savvy customer. She knows Wyeth stopped making tetanus vaccine, and she knows the FDA asked Wyeth's competitor to increase production of the product. The frustrating part is that she also knows it takes 18 months to make new vaccine, and therefore relief is not imminent. "I have spent hours and hours just on tetanus vaccine."

Explaining all of this to the physicians in her hospital has been no easy task. "In the beginning, a lot of them didn't believe me," Younts said. The anesthesiologists, in particular, were quite difficult when fentanyl and succinylcholine were running short last fall. Referring to one anesthesiologist, she said, "I truly think he thought I could just go back into the pharmacy and whip something up." The physician did not believe that she could not get any fentanyl. While the pharmacy community was well informed about the shortage, she noted the American Society of Anesthesiologists didn't inform its members until the shortage was nearly resolved.

Charles Cancro, R.Ph., procurement specialist for the Ralph H. Johnson VA Medical Center in Charleston, S.C., had a similar problem with fentanyl. The physicians in his hospital were upset when he told them he was out of the drug. He had to explain that he couldn't just get it overnight because fentanyl is a [Schedule] CII, and there was a shortage of it at the time. Doctors think if you're out of a drug, you can just order it," he said. "They don't understand."

At least the oncologists at Morehead were easier to work with. Mounts said they worked around the dexamethasone shortage by switching to the oral (and readily available) form for routine, pre-chemotherapy use, and reserved the injectable for patients who still experienced nausea and vomiting after chemo.

Younts related a recent incident to illustrate her day-to-day battle with drug shortages: Because Wyeth has decided to no longer produce Antivenin (crotalide), an antidote for snakebites, her P&T committee selected CroFab (Savage Laboratories' new version of crotalide) as a replacement for the formulary. However, since the pharmacy still had some Antivenin in stock, the P&T committee agreed to use it up before switching to CroFab. Younts was satisfied another shortage problem had been avoided, until a patient came to the ER with a copperhead bite.

For some reason, the ER physician insisted on CroFab and would not use the Antivenin the pharmacy had in stock. Younts did not have any CroFab because the product was on back-order. Still unwilling to use anything but CroFab, the doctor ordered Younts to get a vial from a hospital 30 miles away. That hospital's pharmacist didn't want to loan her a vial because his supply was dangerously low. However his hospital also didn't want the patient, so in the end the vial was taxied over. But the patient recovered without needing the CroFab, and Younts had to send it back in another cab. She spent hours on this incident alone, not to mention a couple hundred dollars on cab fare, and couldn't charge the patient a dime because no drug was given.

On the retail side, shortages have also caused aggravation. Inhalers, especially, have been hard to come by So have some oral drugs, such as generic butalbital and Rocaltrol (calcitriol, Roche).

Trish, a retail pharmacist in the San Francisco area who doesn't want her name revealed, said she's been having trouble with Vancenase AQ (beclomethasone, Schering-Plough). "It is still not available," she said. "Even if it is the formulary drug, we have had to call doctors to change to something else, and then call the insurance company for

overrides. You know how much pharmacists like to spend time calling insurance companies."

The domino effect

When pharmacists find ways to deal with unavailable drugs, the shortages often worsen. "There is sort of a domino effect," said Deffenbaugh. "If you can't get your drug of choice, then you go to alternatives." Since these alternatives are usually limited, pharmacists and physicians often choose the same ones. It isn't long before the alternative drugs are also hard to come by.

A tragic example of this occurred in San Francisco this year. The dexamethasone shortage led to a shortage of other injectable steroids, including betamethasone. The shortage of betamethasone (Celestone, ScheringPlough) prompted an outpatient surgery center to obtain compounded betamethasone from a local pharmacy. The product was contaminated, and three patients died of meningitis after receiving epidural injections of it.

Cancro pointed out another problem: stockpiling. During a shortage, some pharmacies acquire as much of the drug as possible. This makes his job as procurement specialist very difficult. As some pharmacies order all the drugs they can find, this leaves the remaining pharmacies in the area with little supply.

Cancro commended his primary supplier, AmeriSource. The company didn't allow stockpiling and divvied up its supply of scarce drugs among all the orderers, said Cancro. "They wanted to make sure the patients got the drug."

A dug at any price

Many pharmacists, with irate patients and doctors breathing down their necks, will pay anything to get needed drugs. And that's just what some distributors are counting on.

Trish has paid higher prices for certain brands of albuterol inhalers. "We couldn't even get any from McKesson, our main wholesaler, so we had to get another brand from Majors, a secondary wholesaler." The inhalers from the second supplier were more expensive. She's had the same problem with phentermine. Her customers have suffered as well. "Fast Take test strips [for blood glucose meters] have been back-ordered for quite some time," she said. "And it has caused patients to have to go out and buy an entirely different meter because they couldn't get the strips."

Last year, ASHP received numerous complaints from hospital pharmacists about outrageous prices for flu vaccine. While hospitals waited for their supplies of flu vaccine, chain pharmacies in their areas held flu shot clinics. Then, the hospitals received faxes from small distributors offering the vaccine for $120 to $150 a vial.

Younts has had the same problem with dexamethasone. She used to pay $1.67 for one vial of the injectable. Now, a comparable dose sells for $167 a vial. That's 100 times the original price.

David Work, R.Ph., executive director of the board of pharmacy in North Carolina, has been investigating reports of price gouging in his state. Although the board does not have jurisdiction over pricing, Work has been working with the law enforcement agencies that do.

Also condemning price gouging is the AMA, which issued a statement denouncing the practice. The statement urged distributors to cease and desist.

The best-laid plans

Recognizing that the drug shortage is not going away, ASHP has published ASHP Guidelines on Managing Drug Product Shortages. The document, available from the organization and on its Web site gives practical, stepby-step advice on handling shortages.

The FDA continues to battle shortages and facilitate resolutions. The agency also encourages manufacturers and distributors to alleviate the domino effect by instituting allocation programs for drugs in short supply.

Meanwhile, Younts and Cancro are finding their own solutions. Younts has worked out an arrangement with the local health department regarding tetanus vaccine. Since physicians can't order the vaccine for their offices, they've had to send their patients to the emergency room for the vaccine. Now, Younts said, the health department has agreed to accept these patients so they can avoid the ER charges, at least during the week.

Younts is also giving physicians advance notice if it looks like a drug may be hard to get. Currently, she's having trouble with metoclopramide (Reglan, Whitehall-Robins Healthcare) injectable. Because this drug is used in the OR and recovery room, it's important that physicians know whether it's available before they order it.

When faced with a shortage, Cancro orders directly from the source. "We've called the manufacturer," he said. "Some of them do have emergency supplies [set aside]." And, when he orders, he tells the company, "I would like 10, but if you would ship me five, I'd be very happy."

Sidebar

Quick tips for drug shortage management

Sidebar

*Be very careful of dosing errors when using alternate drugs.
*Prioritize patients so that scarce drugs get to those who need them most.
*Order only what your pharmacy truly needs. Stockpiling makes shortages worse and ruins budgets.
*Communicate with other pharmacies in your area. You may be able to share resources and information.
*Report shortages to ASHP and the Food &Drug Administration.
*Maintaining relationships with pharmaceutical representatives may be helpful. They may be able to provide information about shortages.

Sidebar

*Be alert to any situation that may potentially cause a shortage. For example, warning letters to manufacturers are published on the FDA's Web site. Plant deficiencies sometimes lead to manufacturing delays. Stockholder reports can also provide information about manufacturing issues or production decisions. Poor profits may prompt discontinuation of slow-- movers. Also, drugs about to lose patent or switch to over-the-counter status sometimes become scarce. However, use caution when reacting to these situations-problems are often resolved before shortages occur. Source: Adapted from ASHP Guidelines on Managing Drug Product Shortages and other sources

Sidebar

On-line resources on drug shortages

Sidebar

Below are some Web sites that may offer useful information on drug shortages:

Sidebar

www.cdc.gov/nip/fiu-Centers for Disease Control &Prevention's flu vaccine site
www.fda.gov/cder/drug/shortages-Food &Drug Administration's shortage site
www.ashp.org/shortage-ASHP's shortage site

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