FDA Strategies to Prevent and Respond to Drug Shortages
Finding a Better Way to Predict and Prevent Company Closures

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The FDA’s response to the Doxil shortage illustrates the limits of its reach. Doxil was still on the FDA’s critical-drug shortage list at the end of March. That list gave no indication of when the shortage might end, and no one knows all the details about the steps the FDA took earlier this year, much less their impact.

Bona E. Benjamin, BS Pharm, ASHP’s Coordinator of the Drug Shortages Resource Center, says that the consent decree that the FDA signed with Ben Venue was “somewhat out of the ordinary.” It allowed Ben Venue to start making Doxil again, despite serious concerns about systemic quality that the company had not addressed—again via a consent decree. Instead of promising to withhold enforcement action (normally used by the FDA to allow manufacturers to restart production lines when facility problems still exist), Ben Venue was apparently permitted to produce one lot of Doxil in January and another lot in March. Lisa Vaga, a Janssen spokesperson, referred a reporter to Ben Venue for answers to questions about how much volume was equivalent to a lot and about specifics of the “alternative” manufacturing process Ben Venue was using, which involved an unnamed supplier.

Marjorie Moeling, a Ben Venue spokeswoman, added that this is confidential commercial information and therefore the company cannot provide any additional information.

As to the availability of supplies of the recently FDA-approved Caraco generic medication, Mira Desai, speaking for Sun in India, said that Caraco started producing Lipodox 15 days after the FDA granted approval for the drug in the U.S. However, she declined to share details on the volume of Lipodox being produced. As a result, the extent to which the FDA’s response to the Doxil shortage improved the critical situation is far from clear.

Susan B. Joseph, Director of Good Manufacturing Practices (GMP) Compliance and Quality Assurance Systems at AstraZeneca, said: “The FDA may want to consider more clarity of required information and/or additional steps to help companies to provide more accurate information on drug shortage postings.”

She is one of a number of pharmaceutical industry executives urging the FDA to use provisions in the agency’s Safety and Innovation Act (FDASIA) of 2012 to step up its efforts to remediate drug shortages.

Rick Pollack, Executive Vice President of the American Hospital Association, said: “These drug shortages make the delivery of patient care more difficult and dangerous by causing delays in treatment and forcing the use of alternative drugs that may be less familiar to the provider.”

Shortages are also costly to hospitals in terms of staff time and other resources needed to manage the shortages, as well as the increased expense of buying alternative drugs “off contract.”
Shortages of Doxil, methotrexate (Rheumatrex, Wyeth/Pfizer), leucovorin (e.g., Wellcoverin, GlaxoSmithKline), risedronate (Actonel, Warner Chilcott), and atorvastatin (Lipitor, Pfizer) have resulted in delays of clinical trials.

Mr. Pollack added: “These shortages caused up to 9-month delays and/or stoppages in program enrollment along with concerns for patients already enrolled.”

Complicating life for hospital pharmacies, which cannot obtain supplies of some critically needed drugs, is the closure of some large compounding drug facilities over the previous 6 months. Hospital pharmacists use compounded drugs when the usual sources of distribution wither away, either temporarily or permanently (see page 242 for the Prescription: Washington column on compounding). Drug shortages also cause hospital pharmacies to become more vulnerable to receiving counterfeit products, which start popping up like weeds when lifesaving drugs become hard to get.

Michael A. Carome, MD, Deputy Director of the Public Citizen Health Research Group, said: “What may be less well understood is the role that companies representing themselves as compounding pharmacies have been permitted to play in addressing drug shortages.”

He explained that a number of these companies have taken advantage of the FDA’s lax regulatory environment by advertising themselves as suppliers when FDA-approved products are unavailable or in short supply. For example, he noted that the compounding pharmacy PharMEDium, with headquarters in Lake Forest, Illinois (see page 242), keeps an updated list of the most recent drug shortages on its Web site and encourages purchasers to contact its customer service department for additional assistance.

Concerns about the quality of drugs sold by large compounding manufacturers were not a factor for Congress when it passed several drug-shortage remediation provisions as part of the FDASIA in 2012. The bill became law before the outcry over the New England Compounding Center hit the front pages. The House and Senate were persuaded by a few “bad years” of escalating drug shortages. One provision in that bill allows the FDA to exempt hospitals from registering as manufacturers if the hospital repackages a short-supply drug in a central location. The ASHP’s Ms. Benjamin explained that the provision allows hospitals to do something they were not allowed to do before: centralize the repackaging of drugs in one location serving a number of hospitals within a system.

“This gives hospitals economies of scale,” she noted.

The FDASIA requires the FDA to publish guidance for hospitals on exactly how much latitude they have. The law contained no deadline for publication of that guidance, and the agency has not asked for comments on a draft.

Ms. Benjamin added, “It is not clear what the FDA will do here because pharmacy practice is regulated by the states, while manufacturing is regulated by the FDA.”

But a second provision has a much wider potential scope. It requires FDA to engage IMS Health, Inc., to collect data from manufacturers to compile sensitive production information. The GPhA plans to “more efficiently and effectively accelerate the recovery of manufacture and supply [that] voluntarily expand their operations to produce drugs vulnerable to, or in, a shortage or to reduce or waive required user fees.

Because drug shortages are expected to be with us for some time, being able to mitigate them faster, to the extent possible, is a worthy goal, of course. To that end, the Generic Pharmaceutical Association (GPhA) is developing a program called the “Accelerated Recovery Initiative” (ARI). The ARI will attempt ease the pain of shortages by providing the FDA with information that GPhA believes will enable the FDA’s staff to “more efficiently and effectively accelerate the recovery of critical drugs in short supply.”

A key element of the ARI is an agreement among competitors to compile sensitive production information. The GPhA plans to engage IMS Health, Inc., to collect data from manufacturers of short-supply drugs about their current and projected production and supply schedules. The IMS would use this information, along with market data it currently collects, to

AstraZeneca is not aware of any customers who are using quality metrics to drive purchasing or prescribing decision. Individual company quality metrics are internal tools to drive continuous improvement and promote visibility of system health and performance. They are not used to assess or determine individual batch quality. AstraZeneca believes assigning a quality rating system to individual sites or companies would be impractical to administer, cause confusion in the marketplace, and not add value in preventing drug shortages.

A company’s sagging grades on manufacturing quality metrics might be an indicator that it needs to spend some money to upgrade its processing lines or fix any number of problems, which could lead to a damning FDA inspection report and subsequent closure of those lines. The AHA’s Rick Pollack commented:

Inadequate investments in upgrading quality systems and a lack of redundancy in manufacturing operations are the Achilles’ heels of drug shortages. Particularly in the generic drug market, where price competition is the primary way to gain market share, economic incentives are stacked firmly against investing in plant improvements or redundancies. In the short term, there is little that the FDA can do to counteract these economic disincentives other than provide for expedited inspections and certification of manufacturers [that] voluntarily expand their operations to produce drugs vulnerable to, or in, a shortage or to reduce or waive required user fees.

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analyze whether, and to what extent, the anticipated supply of a given drug is likely to fall short of the projected demand over the next several months. This information would then be provided to the FDA.

Getting advance notice of supply shortages or remediating them quickly once they develop is one thing; preventing them is another. One option that the FDA tossed out for consideration is a “qualified contract manufacturer” program; companies would essentially be kept “on deck” in the event of a shortage and could quickly be deployed to produce those drugs in short supply. The Department of Health and Human Services (DHHS) already has a similar program—the Biomedical Advanced Research and Development Authority (BARDA)—which covers a relatively stable and limited number of products.

Alice E. Till, PhD, Vice President of Science Policy and Technology Affairs at Pharmaceutical Research and Manufacturers of America (PhRMA), said that the impact of a BARDA-like program is unclear and would need further evaluation.

“The same objective may be accomplished through the incentives that FDA can provide,” she commented.

For companies judged by the agency to have a holistic approach to and a demonstrated record of quality performance, the FDA could enable:

- faster, more streamlined approval of applications for new products.
- reduced regulatory oversight and requirements for changes to existing applications, including site transfers.
- the addition of back-up suppliers.
- improved manufacturing and testing procedures.
- a longer interval between routine GMP inspections.

Another option that could help to prevent shortages might be to institute a national medical material reserve program (NMMRP), managed by private industry. This is the darling of Jim Rush, Chief Operating Officer of JV Rush Health Readiness, Inc. Jim worked for years with the Department of Defense and the DHHS, including in the hospital-preparedness grant program, in positions related to the distribution of medical supplies in emergencies. An NMMRP could be merged into the Strategic National Stockpile (SNS), which is funded by the Centers for Disease Control and Prevention (CDC) and managed by the federal government in conjunction with local public health departments. The SNS has large quantities of medications and medical supplies to protect the American public if there is a health emergency (e.g., a terrorist attack, a flu outbreak, or an earthquake) that would be severe enough to cause local supplies to run out. As recently as March 2013, the Governmental Accountability Office (GAO) reported on how well (or not) the DHHS and CDC were managing the two grant programs underlying the SNS, the hospital-preparedness program, and Public Health Emergency Preparedness (PHEP). It wasn’t a glowing report, to put it mildly.

Jim Rush says that the CDC is spending more than $1 billion each year on the SNS program overall, which depends on the distribution of drugs through local public health offices. He claims that there is an argument to be made for turning that money over to private industry for management and allowing a private entity to run a combined SNS and a new NMMRP devoted to critical cancer drugs and others. Instead of relying on the federal DHHS health system to distribute drugs, the private distribution system would be deployed.

Given concerns about shelf life and potency, keeping critical drugs in an inventory wouldn’t be as simple as storing oil in a strategic stockpile. Giving the FDA the authority to quickly inspect foreign manufacturers that are selling a short-supply drug (which might not be approved in the U.S., as with Sun’s Lipodox) might be helpful, especially in this current budget environment of federal staffing reductions.

Ram Balani, founder of FDASmart, an offshoot of an Indian company, thinks that the FDA could quickly inspect potential foreign suppliers of generic sterile injectable drugs operating in places like China and India. Leveraging existing wireless, Internet-based technologies and allowing an FDA inspector in Rockville, Maryland, to “walk through” a plant in India via a telecommunications hookup, could accomplish this. Mr. Balani said that FDASmart already prequalifies foreign sources for Pfizer and Bristol-Myers Squibb.

Of course, the ultimate solution is to prevent drug shortages in the first place. Manufacturers stop producing certain categories of medications for the same reason companies in other industries stop making products: they are unprofitable. Profit margins can be extremely narrow when several generic drug companies jump in to make a product when the brand-name medication goes off patent. Price competition is intense, and the margins don’t support administrative functions, not to mention capital investments in manufacturing, which often become an issue after the FDA inspects a plant.

Sandra M. Swain, MD, FACP, President of the American Society of Clinical Oncology, said:

Although legislation was passed in July 2012 that contained provisions on drug shortages, there has been no legislation passed or regulations promulgated that address the imbalance of market forces in the current system. At a minimum, these imbalances exacerbate ongoing shortages.

The key to preventing drug shortages might be to find manufacturers of high-quality products and pay them enough for their drugs so that they make a reasonable profit and can invest in their facilities when they need to. Chris Topoleski, Director of Federal Regulatory Affairs at ASHP, commented:

The ASHP proposes that purchasers and prescribers place a greater priority on the ability of a manufacturer to provide an uninterrupted supply of critical medications and would be willing to pay more for drugs with guaranteed availability. We believe rewarding reliability in supply indirectly incentivizes improved quality.

Maybe critical drugs need a “price support” system like the one that keeps American farmers in hay even in boom times. In fact, maybe it would be a good idea to take some of those wasted agricultural support payments that go to wealthy farmers and transfer them to the FDA, which could use those billions of dollars to supplement the price of critical sterile injectables produced by responsible generic drug companies that meet certain quality metrics.