Drug Shortages: Impact and Strategies

The drug shortage problem is well established, rapidly growing, and a symptom of current economic conditions. In June 2011, the FDA Web site listed 71 drugs that were not available, representing more than 200 individual products, including the oncology drugs bleomycin, cisplatin, cytarabine, daunorubicin, doxorubicin, etoposide, leucovorin/levoleucovorin, mechlorethamine, thiopeta, and vincristine. Last year, 178 drugs were on the FDA list (Figure 1), and today drug availability is a daily concern that requires constant vigilance and keeps many oncology professionals “up at night.” Hopefully, the current crisis will be a catalyst for significant changes in the future.

What’s Driving the Availability Problem?

“Fueling the problem are shortages of raw materials. Also, drugmakers are discontinuing older and off-patent drugs in favor of newer and more profitable ones, and issuing large recalls of drugs due to quality problems,” according to the FDA. Other reasons manufacturers state, listed on the FDA Web site, include increased market demand, manufacturing delays due to a change in manufacturing sites, a sub-contractor not meeting United States Pharmacopeia (USP) requirements, and issues associated with a new product launch. What is really behind these reasons and how they are interconnected?

Increased demand is the most frequently cited reason for shortages, often caused by competing manufacturers that have discontinued or withdrawn the product from the marketplace. Unavailability of raw materials is also frequently cited, not always because of a shortage from a foreign source. Unavailability can also occur because the manufacturer will not relinquish exclusive raw material contracts when the product is discontinued, thus driving the raw material supplier to contract with foreign drug manufacturers. The motive behind this strategy may be related to the original manufacturer having a “next generation” product that will capture greater market share if there is less competition from the “current generation” product.

There are also many acceptable reasons for product shortages, including facility and production line closures and product recalls that are required to ensure a safe drug supply. Expanded clinical indications based on new scientific evidence supported by payors can also increase market demand for a drug, as can information that is coupled with aggressive pricing resulting in appropriate therapeutic drug substitution.

Is There a Regulatory Solution?

Valerie Jensen, Associate Director of the FDA’s Drug Shortage Program, added reassurance, in various statements, that the FDA is “…doing everything we can within our current regulatory authority…working to resolve every drug shortage on our list” and that, “what we can do is work with a company on its manufacturing problems.” Other statements from the FDA include:

• “The FDA tries to resolve these as quickly as possible while ensuring public safety.”

• “Also, if a firm has expired inventory of a needed drug and it can give us data to support a longer expiration date, we’re glad to review that.”

• “Right now we just don’t have any authority at all to require companies to increase production or to require other firms to come on the market. We would like to have them report on all discontinuations and shortages, but that’s not something we can require, just encourage them to do.”

• “Many times we can resolve the issue before it becomes a shortage.”

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“The agency is especially concerned about the danger to consumers from shortages of injectable drugs, which represent more than half of the shortages reported in 2010.”

Ms. Jensen said the FDA is also seeing a large number of new drug shortages in 2011. “Companies have told us that these injectable drugs are older and not as profitable. They’ve told us it’s a business decision to discontinue production.”

Legislation titled Preserving Access to Life-Saving Medications Act (S.296), introduced to Congress, was intended in part to establish an “early warning system” whereby a manufacturer must notify the FDA of conditions that would likely result in a drug shortage. The legislation would also provide the FDA with power to impose financial penalties for manufacturers who fail to comply with required reporting. This is intended to give the competition time to “ramp up” production. However, S.296 as currently written requires a 6-month notice, when in reality another manufacturer would require 9 to 12 months to produce an FDA-approved product, provided they can access raw materials. This leaves a 3 to 6 month window when the product may be unavailable.

In these situations the FDA has other options to mitigate impact, such as expediting the review of submissions for new products or manufacturing changes that, if approved, may help increase availability of a currently short drug. The FDA can also work with manufacturers to identify sources of raw materials or encourage others to increase production of the drug. Finally, the FDA can use enforcement discretion to temporarily allow importation of a drug from other countries. The FDA, however, maintains that this last solution “will be rare, and only when absolutely necessary.”

**What’s the Immediate Impact of an Unavailable Drug?**

The most significant impact of a drug’s unavailability is the practitioner’s inability to provide the drug of choice for the unique patient situation, with whatever consequence that has on clinical outcomes and patient quality of life. Drug shortage significantly adds to the cost and possible decline in efficiency and quality of health care in several ways, including:

- the need to purchase drugs from a non-traditional source (“gray market”) at a higher price and at the risk of receiving counterfeit or tainted product;
• increased time to locate and purchase the product;
• substitution of a more expensive drug;
• need to develop drug rationing processes and the associated management costs;
• delay to treatment and the added cost of treating disease that has progressed;
• increased cost of managing inventory;
• increased cost of managing and changing computer codes;
• cost of educating people to the required changes; and
• cost of changing back once the situation has been resolved.

The impact on individual practitioners must also be considered, including time diverted from other responsibilities and potential safety issues that increase in unstable or stressful environments.

Can Something Positive Evolve?
Carefully documenting the impact of the situation and our actions is important. In some cases, we will find that a less expensive drug can be substituted with good results. Foreign-sourced drugs have already been allowed, so perhaps we will become more comfortable with a global drug supply, perhaps overseen by a “commonwealth” of national regulatory agencies such as the FDA and European Medicines Agency. Perhaps there will be better regulations and control over raw materials, including advance notice when they are not available. Perhaps an effective “early warning” system for product discontinuation will evolve. Perhaps compendia will provide better evidence-based information that supports therapeutic interchange decisions, and this will provide the knowledge and process needed to address the emerging issue of “biosimilar equivalence.” If these things happen, we will have new knowledge that can lead to future improvements in health care.

What Should Practitioners Do Now?
Considering the issues and finding solutions for each specific shortage is important. To do this, practitioners must collaborate with all stakeholders: manufacturers, distributors, group purchasing organizations (GPOs), professional standards organizations, providers, regulators and legislators, payors, news media, and (don’t forget) the patients. Each group must understand the issues and work toward a mutually beneficial end. I believe the key action steps for providers are:
• Stay informed by monitoring the FDA Web site (www.fda.gov/Drugs/DrugSafety/DrugShortages) and other professional sites such as the American Society of Health System Pharmacists (www.ashp.org/DrugShortages/Current/) to determine the drugs that will affect your practice. The FDA has an e-mail alert service that is recommended.
• When an actual or projected drug shortage becomes known, initiate your strategy. This can include proactive purchasing (no hoarding please), changing the order point and order quantity, sharing inventory between affiliates, developing and approving substitution policies, and implementing well-reasoned rationing policies that include patient and payor education.
• Establish who in your organization is accountable for managing the shortage and providing updates to all stakeholders through regular meetings, an intranet site, memos, or other communications systems. Some institutions maintain a virtual status board listing the drug, inventory available, number of potential
patient treatments available, and current number of patients under treatment. Your GPO can help forecast future product availability.

- Work with your GPO and wholesale distributor to secure (as best you can) adequate supply. Establish as many supply options as possible, even if they are non-traditional sources. If you purchase through a distributor that you are not familiar with, take measures to ensure the integrity of their product and their business ethics, by checking their business history through your GPO or state Attorneys General. Ask the distributor to provide evidence of a drug pedigree that certifies every step and possession of the drug from the manufacturer to final provider. Report unusual circumstances or unfair business practices to the Federal Trade Commission (www.ftc.gov/ftc/contact.shtm) and your state Attorneys General, or the National Association of Attorneys General (www.naag.org/current-attorneys-general.php). Finally, for product integrity issues, contact the FDA Office of Criminal Investigations (www.fda.gov/ICECI/CriminalInvestigations/default.htm) and the National Association of Boards of Pharmacy (www.nabp.net/boards-of-pharmacy/).

- Call the manufacturer to determine if an emergency supply is available for critical patients and the criteria required for release.

- Check on the supply of drugs likely to be substituted for the unavailable drug, because that may also soon be in short supply.

- Establish drug substitution rules and rationing criteria for your institution or practice through authorized bodies such as the Pharmacy and Therapeutics Committee. Build these rules into your drug formularies, ordering pathways, and protocols.

- Provide clinical needs and impact assessment information to the FDA to help them determine the seriousness of the shortage and if they can facilitate expedited review of a new product or manufacturing process that will offset the shortage, or approve the importation of the drug.

- Document the cost of each drug shortage—both the variance in cost among drug products and the professional time and patient impact—and include this in your institution’s budget analysis. This cost should also be considered in the operational or facility costs reported by your facility for CMS payments. Note that sometimes the manufacturer will negotiate “consideration to offset additional costs” for a product they could not provide.

- Collaborate with your information technology (IT) department to ensure they understand the importance and urgency of IT system changes that are required. Create a list of all IT systems that manage medication information, including the contact person and data fields that must be changed. The list should include systems related to 1) computerized prescriber order entry; 2) care sets and protocols; 3) pharmacy, nursing, surgery, radiology, and investigational drug systems; 4) formularies or catalogs associated with smart technology devices used for inventory, production, dispensing, or drug administration; and 5) patient billing.

- Document the impact of the drug shortage on patient care outcomes, addressing all relevant issues objectively and with solid evidence. Growing public and legislative concern must be addressed through education and accurate information as we seek to enlist understanding and support.

- When the situation is resolved, clearly communicate the impact and what the “new normal” is. Will drug usage patterns change back? Will IT technology be “re-set”? Will inventory be changed? What was the budget impact? Documenting the cost of returning to normal is also important, so sufficient resources can be planned for future occurrences.
Conclusions
The issue of drug availability appears to be getting worse and will continue to compromise the delivery and cost of health care. All stakeholders must collaborate so the best decisions are made on behalf of patients and all people involved are informed. Please document and publish your experiences, so the nation's health care enterprise can collaboratively work toward a positive solution and a better future.

References

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