



December 23, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane,
Room 1061
Rockville, MD 20852

Re: FDA-2011-N-0690; Center for Drug Evaluation and Research, Approach to Addressing Drug Shortage; Public Workshop; Request for Comments

Dear Sir/Madam:

The American Society of Health-System Pharmacists (ASHP) is pleased to submit comments to the Food and Drug Administration (FDA) as part of the Agency's open comment period following the public workshop held on September 26, 2011 at which ASHP presented. This comment period was announced in the Federal Register on September 29, 2011.¹ For more than 60 years, ASHP has helped pharmacists who practice in hospitals and health systems improve medication use and enhance patient safety. The Society's 35,000 members include pharmacists and pharmacy technicians who practice in inpatient, outpatient, home-care, and long-term-care settings, as well as pharmacy students. Pharmacists in hospitals and health systems are experts in medication use who serve on interdisciplinary patient-care teams. They work with physicians, nurses, and other health-care professionals to ensure that medicines are used safely and effectively.

Since 2006, shortages of primarily generic injectable drugs have dramatically escalated, increasing from 70 five years ago to over 230 as of November 2011. These drugs, which are fundamental and essential to care, affect this nation's hospitalized and most vulnerable patients. Without access to the preferred or most clinically appropriate drug treatment, healthcare professionals must use alternatives, which may be less effective or associated with increased risk of adverse outcomes. Examples of these events are described in detail in the Institute for Safe Medication Practices survey in September 2011. In this survey, 1,800 respondents reported over 1,000 adverse drug events caused by shortages. Twenty-five percent of these reports were medication errors; another 20 percent were adverse drug reactions. A survey conducted by the American Hospital Association in July 2011 also identified suboptimal care, indicating that 82 percent of

hospitals reported delayed treatment and more than half said they could not provide some patients with the recommended therapy.

Drug shortages also add to the cost of providing care. A study by Premier in March of this year suggested the cost of purchasing alternative therapeutic products to those in shortage to be \$200 million. In addition, a survey conducted by ASHP and the University of Michigan indicated that hospital pharmacists are spending eight to twelve additional hours per week dealing with shortages – time taken away from direct patient care. Further, the study estimated that additional annual labor costs to hospitals of managing shortages to be \$216 million.

For over a decade, ASHP, in collaboration with the University of Utah Drug Information Service (UUDIS), has been tracking drug shortages and making that information available to the public on the ASHP drug shortages web resource center, which is accessible to the public.² The list is regularly updated, as new drugs are discovered to be in short supply or changes occur among existing shortages. While the FDA has a similar listing of drug shortages, the Agency focuses on those drugs that are defined as “medically necessary” by the Agency, whereas the ASHP web resource center tracks shortages for all prescription drugs and biologicals. We define drug shortage as “a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent.”³

Causes of drug shortages are many and complex. Manufacturing issues that lead to drug shortages include product quality issues that result in production halts or recalls, product discontinuations, and unavailability of active pharmaceutical ingredients (APIs) or other raw materials. Secondary shortages—or shortages that occur based on shifts in market demand caused by an initial shortage of another drug—are also common. Other contributing causes to drug shortages include quality issues that arise from the ever-increasing reliance on foreign ingredient and manufacturing sources and a lack of FDA resources to expedite approval of supplemental new drug applications and conduct foreign inspections.

While not a cause of drug shortages, just-in-time inventory practices by product distributors and practice sites have removed the buffer previously provided by larger inventories and resulted in an immediate impact of drug shortages on patient care. While information on the root cause of each drug shortage is not always publicly available, the cause of many shortages can be traced back to manufacturing processes or facilities that result in substandard end products. These manufacturing issues are compounded by constraints on capacity over the last few years that have resulted in fewer manufacturers producing critical drugs. When one manufacturer experiences a production interruption, other companies must ramp up production of their product to

meet market needs. This increased production is sometimes, but not always, possible. In the case of sole-source drugs, this situation almost instantly results in a shortage situation.

ASHP continues to work with FDA, other health care provider groups and members of the supply chain to address the issue. According to FDA, in 2010 the Agency was able to avoid 38 drug shortages when they were made aware of production interruptions ahead of time, and so far this year, 101 shortages were avoided. This is especially true with single-source active pharmaceutical ingredient (API) products. This characteristic makes a drug more vulnerable to shortages and should prompt FDA requirements for contingency plans to ensure product availability. However, manufacturers are frequently reluctant to make this information available for confidentiality reasons. FDA should establish mechanisms that support confidential notification of sole-source API drugs, thereby alleviating manufacturer concerns about publicizing vulnerability to shortages and causing competition for scarce sources of API. Admittedly, knowledge of single-source APIs may not avert a shortage if there are no other viable API sources. However, knowledge of single-source APIs should prompt the Agency to develop emergency plans in anticipation of supply interruptions, including proactive identification of alternate API sources, expedited regulatory procedures, and feasibility of importation or inclusion of the product in a national stockpile of critical therapies.

Under current law, manufacturers are not required to report to FDA when they experience an interruption in the production of their products, unless that drug is deemed medically necessary by the agency. The same holds true when manufacturers choose to discontinue a product. Even in cases where the drug is deemed medically necessary and reporting is required; FDA has no meaningful enforcement mechanism to penalize a drug maker for failing to report these problems. This information could be extremely useful to FDA in the case of drugs with multiple suppliers where the Agency could urge alternate suppliers to step up production of a product to offset the decrease in supply due to the interruption or discontinuation of the initial product.

In 2010, FDA worked with APP Pharmaceuticals to help alleviate a shortage of propofol, a widely used anesthetic preferred by anesthesiologists because of its excellent safety profile compared to other available drugs. By enabling the company to work with its German counterpart to import the drug, FDA was able to substantially improve product availability after the shortage occurred. Using this example, if an acceptable foreign alternative could be identified before a shortage occurs through establishment of continuity of supply plans for vulnerable drugs, then importation could be expedited and the negative impact of a specific shortage on patient care could be minimized or averted. Importation represents an extreme example of contingency planning. In its simplest form, manufacturing strategies that include contracting with other

manufacturers, working with FDA to establishing back-up suppliers of raw materials and APIs, staging product releases to prevent hoarding, and creating alternative production capabilities that can be used as countermeasures would be a significant step forward to combating drug shortages. Contingency planning by companies producing drugs critical to patient care must be a standard of practice.

The importance of notification is highlighted by quality concerns associated with the increased globalization of pharmaceutical manufacturing. A number of drug shortages can be traced back to quality concerns with foreign-produced APIs. While FDA has increased foreign inspections, it still lacks the resources necessary to fully address this issue. Therefore, drug shortages precipitated by recalls caused by substandard APIs will continue and likely increase.

Further, shortages are occurring overwhelmingly among generic injectable drugs, where production processes tend to be more complex than their solid dosage counterparts. Low margins for these expired patent products coupled with complex manufacturing processes may lead some manufacturers to abandon production of these drugs altogether in favor of products with higher profit margins, thus reducing the number of potential suppliers of products critical to patient care. A way to offset this problem may be to explore incentives to encourage manufacturers to either stay in the market or enter the market with a new product line and we urge more research to identify potential incentives. In addition, other stakeholders in the supply chain need to provide input on the economic factors that influence production capability.

The FDA must find a way to abbreviate and prioritize approval processes for existing therapies that are unapproved, but widely used and essential for patient care. For these drugs, the Agency should encourage manufacturers to submit applications and fast track their approval for the U.S. market, especially in cases where the potential exists for those drugs to fall in short supply. Barriers to manufacturing and marketing these drugs must be minimized in order to foster production and availability of these drugs.

Finally, the DEA should collaborate with FDA to initiate actions that address Schedule II drug shortages, based on the Agency's assessment of the impact DEA's quota limits have on availability of these drugs. If DEA quota requirements are in fact burdensome for manufacturers seeking to increase production, both agencies should work to establish criteria and procedures for emergency authorization to increase quotas for controlled substances in short supply.

FDA serves a vital public health mission that impacts patients served by pharmacists who practice in hospitals and health systems. It helps ensure that medications are safe and effective while implementing new mandates dealing with biosimilars, strategies to

mitigate and evaluate risks as well as benefits, while responding to ever increasing drug shortages. Health-system pharmacists, their patients and consumers in general share the view that FDA cannot provide these and other functions without adequate funding. Science and innovation that produces leading edge medical care must take place with the assurance that FDA is providing the needed oversight to protect the public health.

AS FDA's responsibilities grow, so too must its resources. For decades, FDA has been chronically underfunded. Because of recent congressional appropriations, the Agency's budget has been increased. Yet, ongoing and increasing responsibilities place additional demands on the FDA's ability to respond globally. Therefore, we will continue to urge Congress to provide additional funding to the FDA through the appropriations process.

Additionally, ASHP supports bipartisan legislation (S. 296, H.R. 2245) that would require drug manufacturers to notify the Agency when they experience an interruption in the production of a drug product potentially resulting in a shortage situation and are pleased that the Obama administration supports passage of this legislation as noted in the October 31, 2011 Executive Order.⁴

The Society appreciates the opportunity to comment on the FDA's public workshop. Please contact me if you have any questions or wish to discuss our comments further. I can be reached by telephone at 301-664-8806, or by e-mail at ctopoleski@ashp.org.

Sincerely,



Christopher J. Topoleski
Director, Federal Regulatory Affairs

¹ Federal Register, Volume 76, No. 189. Page 60505.

² www.ashp.org/drugshortages

³ Fox ER, Birt A, James KB et al. ASHP guidelines on managing drug product shortages in hospitals and health systems. *Am J Health-Syst Pharm*. 2009; 66:1399-406.

⁴ Executive Order 13588 -- Reducing Prescription Drug Shortages; <http://www.whitehouse.gov/the-press-office/2011/10/31/executive-order-reducing-prescription-drug-shortages>