Subject: National Drug Shortages: Update

Presented by: Bobby Mukkamala, MD, Chair

INTRODUCTION

Policy H-100.956, “National Drug Shortages,” directs the Council on Science and Public Health (CSAPH) to continue to evaluate the drug shortage issue and report back at least annually to the House of Delegates (HOD) on progress made in addressing drug shortages in the U.S. This informational report provides an update on continuing trends in national drug shortages and ongoing efforts to further evaluate and address this critical public health issue.

METHODS

English-language reports were selected from a PubMed and Google Scholar search from September 2015 to August 2016, using the text term “drug shortages” combined with “impact,” “crisis,” “oncology,” “chemotherapy,” “antibacterial,” “pediatric(s),” “nutrition,” and “parenteral.” Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the U.S. Food and Drug Administration (FDA), American Society of Health-System Pharmacists (ASHP), Government Accountability Office (GAO), Pew Charitable Trusts, Generic Pharmaceutical Association, the Pharmaceutical and Research Manufacturers of America (PhRMA) and by direct contact with key FDA and ASHP staff who manage drug shortage issues on a daily basis.

BACKGROUND

The Council has issued six previous reports on drug shortages. The findings and conclusions from these reports are summarized in CSAPH Report 2-I-15. The remainder of this report will update current information on drug shortages since that report was developed.

CURRENT TRENDS IN DRUG SHORTAGES

The two primary data sources for information on drug shortages in the United States continue to be the Drug Shortage Resource Center maintained by ASHP in cooperation with the University of Utah Drug Information Service and the Drug Shortage Program at the FDA. For a reminder on how the ASHP and FDA information and statistics on drug shortages are developed, see Table 1. The ASHP defines a 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.” The FDA defines shortages as a period of time when the demand or projected demand for a medically necessary drug in the United States exceeds its supply. Medically necessary drugs are defined by FDA as “any drug product used to diagnose, treat, or prevent a serious disease or
medical condition for which there is no other drug that is judged to be an appropriate substitute or there is an inadequate supply of an acceptable alternative.”

Because their criteria differ (the main distinction being the FDA’s definition of a “medically necessary drug”), the ASHP site lists more drug shortages than the FDA site.

**American Society of Health-System Pharmacists**

As of September 13, 2016, ASHP’s Drug Shortage Resource Center identified 135 drugs in shortage, down from 180 at the same time in 2015. Among these drug shortages, 17 products were not commercially available at all. Sixty-nine manufactured drugs have been discontinued since 2010, an increase of 9 from a year ago. The top active shortages by drug class remain central nervous system agents, electrolytes and nutritional components, antimicrobials, cardiovascular drugs, and chemotherapeutic agents. For a longitudinal view of new drug shortages on an annual basis, and the number of active drugs shortages quarterly, see the Appendix. Active shortages include both new and unresolved drug shortages. According to ASHP, the number of new shortages continues to decrease, while the number of active shortages has stabilized to a certain degree.

**Food and Drug Administration**

As of September 13, 2016, the FDA reported that 61 drugs were currently in shortage (compared with 67 one year ago), and 10 had been resolved. The latter are closely monitored because they may be at risk for falling back into shortage. Based on passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, companies are required to notify FDA of a permanent discontinuance or an interruption in manufacturing of certain drug products six months in advance, or if that is not possible, as soon as practicable. The shortage notification requirement has apparently reduced the number of new shortages by allowing FDA additional time to work with manufacturers to prevent shortages. The FDA’s drug shortages website lists drugs that meet these criteria, reflecting shortage information supplied by manufacturers. A Final Rule published on July 27, 2015 provides further guidance on the notification process and adds biologic products to the requirements for notification about potential supply disruptions.

**Drug Shortages Metrics Reported by FDA.** The FDA’s third annual report on drug shortages (required by FDASIA) noted the following metrics during the first three quarters of calendar year 2015:

- FDA was notified of 131 potential shortage situations by 47 different manufacturers, comparable to the numbers reported in 2014.
- 128 new drug shortages were prevented in the first three quarters of 2015, a 64% increase over the comparable time period for 2014.
- The review of 102 generic abbreviated new drug or supplemental applications was expedited, comparable to the numbers reported in 2014.
- 11 inspections were prioritized to address a drug shortage, comparable to the number reported in 2014.
- 11 fewer new drug shortages occurred in the first three quarters of 2015 (22) compared with the same period in 2014 (33).
- FDA exercised regulatory flexibility and discretion in 19 instances affecting 37 medically necessary products. Most of these involved measures to mitigate risks such as removing particulate matter, extra testing for quality, third-party oversight of production, provision
of special instructions to prescribers and/or patients, or approval of foreign sources. With respect to the last of these mitigation strategies, the FDA now conducts regular virtual meetings with their international regulatory counterparts to share information on drug shortages and mitigation strategies impacting patients in other countries.

The FDA also has developed apps for both the iPhone and Android operating systems that provide access to drug shortage information as well as notifications about new and resolved drug shortages.

**Reporting a Drug Shortage**

Physicians can directly report a drug shortage via the ASHP drug shortage website. Physicians can directly report a drug shortage to the Center for Drug Evaluation and Research via email (drugshortages@fda.hhs.gov) or by phone at 240-402-7770.

**GAO REPORT**

In a follow-up to its 2014 report on drug shortages, the Government Accountability Office (GAO) evaluated trends in drug shortages from 2010-2015 in an effort to identify influential factors. This evaluation confirmed that the FDA had prioritized 383 new, abbreviated, and supplemental drug applications to address drug shortages, mostly for sterile injectable products. The use of this prioritization scheme was temporally associated with reductions in active and ongoing shortages. Analysis of selected categories (i.e., sterile injectable anti-infective and cardiovascular drugs) confirmed that shortages were strongly associated with previously identified key drivers, namely a decline in the number of manufacturers, existence of a generic product, and an emergent problem with manufacturing capability in at least one manufacturer that was sufficiently serious to cause a warning letter to be issued. Shortages were more likely to affect generic drugs with low profit margins, although drug price itself was not predictive in this study.

**GENERIC PHARMACEUTICAL ASSOCIATION**

Given that the majority of drug shortages involve generic products, the GPhA created a voluntary approach called the Accelerated Recovery Initiative in 2013 intended to accelerate the recovery of certain critical drugs in short supply. This multi-stakeholder approach relies on voluntary, confidential communication between an independent third party (IMS Health) and pharmaceutical companies involved in the manufacturing of generic injectable drugs in shortage. Additionally, wholesalers, distributors, and the FDA can provide information to assist companies with making timely decisions to help avert or mitigate a shortage. While this program is apparently still operational, there are no publicly available reports evaluating its degree of success.

**CLINICAL IMPLICATIONS**

Despite increasing success in preventing or mitigating drug shortages and an overall decrease in the number of new drug shortages, critical drug shortages continue to occur across multiple therapeutic categories. While the existence of a sole source manufacturer is a risk factor for shortages, it also has been the focus of some recent exorbitant drug price escalations. Reviews of shortages affecting the operation of emergency departments identified several intravenous formulations that remain in short supply and are affecting patient care including certain opioid analogesics, antiemetics, selected antimicrobials, benzodiazepines and other drugs used for rapid induction of anesthesia, electrolytes, and local anesthetics. Shortages of various antidotes also have been noted, and the implications of drug shortages for pediatric patients, those with cardiovascular disease or those
who are acutely ill have been studied.\textsuperscript{15-18} In some cases, work-arounds have been successful in maintaining patient safety and achieving satisfactory clinical outcomes.\textsuperscript{19}

**SUMMARY**

Manufacturers are notifying the FDA about potential disruptions in supply or shortages earlier than in the past and the FDA is expediting the review of new applications intended to address shortages. Accordingly, the total number of new drug shortages continues to decline and the extent of ongoing shortages has stabilized over the past two years. However, the drug supply for many acutely and critically ill patients in the United States remains vulnerable despite federal efforts.\textsuperscript{20} Some progress is being made, but permanent solutions remain elusive and beyond the control of individual practitioners and the health care system.
REFERENCES


Table 1. Contrasting the FDA (CDER) and ASHP Drug Shortage Websites

<table>
<thead>
<tr>
<th>Purpose</th>
<th>FDA</th>
<th>ASHP</th>
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<tbody>
<tr>
<td>Provides information obtained from manufacturers about current shortages, estimated duration, and discontinuations and provides information about FDA’s and other stakeholders’ roles in addressing and preventing shortages</td>
<td>Notification of new shortages and status of ongoing shortages; drug shortage management resources</td>
<td></td>
</tr>
<tr>
<td>Audience</td>
<td>Public</td>
<td>Healthcare practitioners</td>
</tr>
<tr>
<td>Scope of shortage list</td>
<td>All drugs are listed that are confirmed to be a national shortage by FDA. A shortage is considered to be the period of time when the demand for the drug within the United States exceeds the supply of the drug.(^a)</td>
<td>All drug and biologic shortages reported and confirmed with manufacturer that are national in impact.</td>
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<td>Source of shortage report</td>
<td>Manufacturers notify FDA of production disruption and voluntarily provide updates. Reports are also received from ASHP and from public via <a href="mailto:drugshortages@cdr.fda.gov">drugshortages@cdr.fda.gov</a> Note: Manufacturer-provided information represents shortage status at drug firm level.</td>
<td>Voluntary reports from practitioners, patients, pharmaceutical industry representatives and others Note 1: Information is updated based on release dates from manufacturers. Note 2: Reports reflect status at healthcare provider level.</td>
</tr>
<tr>
<td>Criteria for inclusion on list</td>
<td>Manufacturers cannot meet current market demand for the drug based on information provided by manufacturers and market sales research. Drug listed are defined as “medically necessary.”</td>
<td>(1) Shortage is verified with manufacturers and (2) affects how pharmacy prepares or dispenses a product, or (3) requires use of alternative drugs, which may affect patient care.</td>
</tr>
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<td>Criteria for resolving shortage</td>
<td>One or more manufacturers are in production and able to meet full market demand.</td>
<td>All manufacturers of the drug restore all formulations and dosage sizes to full availability. Note: Products are listed despite partial or restricted availability as supply chain disruptions can result in intermittent shortages at the provider or patient level.</td>
</tr>
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<td>Reason for shortage</td>
<td>Provided by manufacturers using reasons required by legislation.(^b) FDA encourages firms to provide additional information about reasons and other information which, if proprietary, is nondisclosable without the firm’s permission.</td>
<td>Provided by manufacturer, if willing to disclose. Note: May differ from FDA’s due to different sources of information and legislation requiring FDA to use specified reasons</td>
</tr>
<tr>
<td>Other information</td>
<td>Estimated duration, links to regulatory information such as recalls and Dear Healthcare Provider Letters</td>
<td>Estimated duration, list of available products, implications for patient care and safety, shortage management strategies, therapeutic alternatives</td>
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</table>

\(^a\) Note: A separate shortage webpage for vaccines and some biologics is maintained by the Center for Biologics Evaluation and Research.

\(^b\) Categories include (a) requirement related to complying with good manufacturing practices; (b) regulatory delay; (c) shortage of an active ingredient
APPENDIX

National Drug Shortages

Annual New Shortages by Year

January 2001 to June 30, 2016

<table>
<thead>
<tr>
<th>Year</th>
<th>01</th>
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Note: These data represent the count of active shortages on the last day of each quarter, and should not be interpreted as total shortages for that period.

University of Utah Drug Information Service
Contact Erin.Fox@hsc.utah.edu, @foxerinr for more information