REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 4-I-17

Subject: National Drug Shortages: Update

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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 United States. 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 2016 to August 2017, 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 US Food and Drug Administration (FDA), American Society of Health-System Pharmacists (ASHP), Pew Charitable Trusts, the Association for Accessible Medicines, the Pharmaceutical and Research Manufacturers of America (PhRMA) and by direct contact with key FDA, ASHP, and Utah Drug Information Service staff who monitor drug shortages and related issues on a daily basis.

BACKGROUND

The Council has issued seven reports on drug shortages.[1-7] The findings and conclusions of the first five reports are summarized in CSAPH Report 2-I-15.[6] The remainder of this report will update information on drug shortages since the 2016 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.[8,9] Table 1 summarizes how the ASHP's and FDA's information and statistics on drug shortages are developed. 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

Action of the AMA House of Delegates 2017 Interim Meeting: Council on Science and Public Health Report 4 Recommendations Adopted, and Remainder of Report Filed.

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 August 7, 2017, ASHP's Drug Shortage Resource Center identified 133 drugs in shortage, approximately the same number as at the corresponding time in 2016 (135). In addition, 14 products are not commercially available at all.[9] Seventy-one manufactured drugs have been discontinued since 2010, an increase of two from a year ago. Nearly 85% of drug shortages are generic sterile injectable formulations. The top active shortages by drug class remain antimicrobials, electrolytes and nutritional components, central nervous system agents, chemotherapeutic agents and cardiovascular/autonomic drugs. For a longitudinal view of new drug shortages on an annual basis, and the number of active drug shortages quarterly, see the Appendix. Active shortages include both new and unresolved drug shortages. According to ASHP, the number of new shortages is currently on a par with 2016, and the number of active shortages has stabilized.

US Food and Drug Administration

As of August 7, 2017, the FDA reported that 46 drugs were currently in shortage (compared with 61 one year ago), and 13 other shortages had been resolved.[9] 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 the 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.[8] 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.[9]

Drug Shortages Metrics Reported by FDA. The FDA's fourth annual report on drug shortages (required by FDASIA) noted the following metrics during the first three quarters of calendar year 2016.[10]

- FDA was notified of 186 potential shortage situations by 67 different manufacturers, a 35% increase over the number of potential shortages reported in 2015.
- 64 new drug shortages were prevented in the first three quarters of 2016, a 50% decrease over the comparable time period for 2015.
- The review of 102 generic abbreviated new drug or supplemental applications was expedited, exactly the same as the number reported in 2015.
- 10 inspections were prioritized to address a drug shortage, comparable to the number reported in 2015.
- Three fewer new drug shortages occurred in 2016 (23) compared with 2015 (26); currently, FDA is working to resolve 24 ongoing shortages that began prior to 2016, which is a decrease from the 64 ongoing shortages tracked at the end of 2015 (Personal Communication, Valerie Jensen, RPh, FDA).

- FDA exercised regulatory flexibility and discretion in 25 instances affecting 15 medically necessary products.[10] Most of these involved measures to mitigate risks such as the use of filters to remove particulate matter, extra testing for quality, third-party oversight of production, provision of special instructions to prescribers and/or patients, approval of foreign sources, and expanded access to investigational drugs for treatment use. With respect to approval of new foreign sources, 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 continues its work to improve its system for data tracking and drug shortage analysis. The FDA released a new technology platform in 2017 for drug manufacturers/applicants to send drug shortage and supply notifications. The "Direct NextGen" platform allows users to login, enter their shortage information, and submit to the FDA. This approach is intended to "streamline day-to-day work to identify and mitigate shortages, including research, data entry, and data management."[10]

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

In late June 2017, the FDA took additional steps to increase competition in the market for prescription drugs and facilitate entry of lower-cost alternatives. The agency published a list of off-patent, off-exclusivity branded drugs without approved generics, and also implemented, for the first time, a new policy to expedite the review of generic drug applications where competition is limited.[11,12]

STATE OF THE INDUSTRY

Report from Pew Charitable Trusts

Potential economic drivers of drug shortages were previously evaluated by the Council.[2,5,7] A new report from Pew Charitable Trusts and the International Society for Pharmaceutical Engineering took a closer look at shortages of sterile injectable pharmaceutical products based on interviews with company executives; the main focus areas were market forces, business continuity planning, and supply chain management.[13]

The report confirmed that quality issues continue to be a driving force behind shortages. Examples included FDA-inspection-related delays, delays in active pharmaceutical ingredient acquisition, failure of final product quality to meet good manufacturing practices, and problems arising from transferring the product from development (or in transferring new technology for a legacy product) to commercial manufacturing site. Factors cited by companies that contributed to drug shortages other than quality included market withdrawals, supply chain design, lack of business continuity elements needed to protect against shortages, limited purchaser-manufacturer incentives, limited insight into future market demands, and regulatory challenges impacting facility expansion or upgrading equipment; the latter is especially pertinent for legacy products.

CURRENT PERSPECTIVE

Based on analysis by the Utah Drug Information Service, during the past 2 years, the number of new drug shortages affecting clinicians and patients has been declining, and the number of active and ongoing drug shortages has remained similar (Appendix, Personal Communication, Erin Fox, PharmD). Shortages have stabilized, but even though the number remains elevated, it is significantly lower than 3 to 4 years ago. The fact that a high number of shortages continues to exist has obscured to a certain degree the progress that has been made, largely attributable to manufacturer notification requirements and proactive steps taken by the FDA. These changes have substantially decreased the actual number of shortages by preventing a large number of new ones. Significant progress has been made overall, but this progress has remained largely unnoticed by hospital pharmacists and practicing physicians who continue to experience the effects of ongoing shortages on a daily basis.

Additionally, it is apparent that some difficult challenges to continued progress exist. As previously noted, most drug shortages involve generic sterile injectable formulations and the cause of these shortages is typically manufacturing and quality problems. The 2016 report from the Government Accountability Office (discussed in the 2016 Council report) identified a decline in the number of suppliers, failure of a supplier to comply with manufacturing standards resulting in a warning letter, and manufacturers operating at low profit margins for generic drugs as primary contributing factors.[14] A major contributing factor to this trend was the failure of Boerhinger Ingelheim's BenVenue manufacturing facility in Bedford, Ohio, in 2013, which at the time was one of the largest suppliers of sterile injectable drugs, including many cancer chemotherapy products. The failure occurred despite the investment of $350 million to upgrade the facility; facing projected deficits of at least $750 million, the facility was not profitable and was closed.[15]

Currently, the majority of sterile injectables for the US market are produced by Pfizer (Hospira), Fresenius Kabi (Akorn), Teva and Baxter; other contributors are American Regent (Luitpold), Sandoz, and Mylan. Pfizer completed its acquisition of Hospira, at the time the largest manufacturer of sterile injectable in the United States, in September 2015. Recent events have created a climate of worsening drug shortages for critical care and emergency medications as well as some of what would be considered "basic products" emanating from the Hospira portfolio. In April 2017, Pfizer notified clinicians about a shortage of pre-packaged emergency drug syringes including atropine, dextrose, epinephrine, and sodium bicarbonate. In June, Pfizer recalled 42 lots of sodium bicarbonate vials (approximately half of supplies) due to concerns that the product may not be sterile; succinylcholine was also impacted by this recall.[16] Most recently, Pfizer had to halt production of 30 different Carpuject™ products (morphine, hydromorphone, etc.) due to problems at a specific manufacturing facility. Vial substitutes exist for most of the Carpuject™ products, but there may be shortages later this year. In response, the FDA extended expiration dating for emergency syringes, approved another supplier of sodium bicarbonate, and also allowed imported sodium bicarbonate.[17]

Although attention remains focused on injectable products, shortages of some solid dosage forms, including atenolol, furosemide, and methylphenidate tablets also have created problems for clinical management this year.

CONCLUSION

The generic sterile injectable drug industry is fragile and some drug supplies for acutely and critically ill patients in the United States remain vulnerable despite industry and federal efforts. Until new and reliable production capacity for sterile injectables is developed, the situation will not

appreciably improve. Some progress is being made, but permanent solutions remain elusive and beyond the control of individual practitioners and the health care system. As long as a free market economy exists and no one entity, including the FDA can mandate that a company produce a specific product, drug shortages will exist into the foreseeable future as the industry continues to merge and contract (except for high cost specialty drugs), the number of drugs emerging off patent increases each year, and the profit margin for legacy products disappears. This dynamic is occurring at the same time that pharmaceutical companies are under increasing pressure to reduce drug costs. The recent acquisition of Hospira by Pfizer and the resulting shortages raises the issue of how such acquisitions or mergers might impact the likelihood of such shortages.

RECOMMENDATION

The Council recommends that Policy H-100.956 be amended by addition to read as follows:

National Drug Shortages

1. Our AMA supports recommendations that have been developed by multiple stakeholders to improve manufacturing quality systems, identify efficiencies in regulatory review that can mitigate drug shortages, and explore measures designed to drive greater investment in production capacity for products that experience drug shortages, and will work in a collaborative fashion with these and other stakeholders to implement these recommendations in an urgent fashion.
2. Our AMA supports authorizing the Secretary of Health and Human Services to expedite facility inspections and the review of manufacturing changes, drug applications and supplements that would help mitigate or prevent a drug shortage.
3. Our AMA will advocate that the US Food and Drug Administration (FDA) and/or Congress require drug manufacturers to establish a plan for continuity of supply of vital and life-sustaining medications and vaccines to avoid production shortages whenever possible. This plan should include establishing the necessary resiliency and redundancy in manufacturing capability to minimize disruptions of supplies in foreseeable circumstances including the possibility of a disaster affecting a plant.
4. The Council on Science and Public Health shall continue to evaluate the drug shortage issue and report back at least annually to the House of Delegates on progress made in addressing drug shortages.
5. Our AMA urges the development of a comprehensive independent report on the root causes of drug shortages. Such an analysis should consider federal actions, the number of manufacturers, economic factors including federal reimbursement practices, as well as contracting practices by market participants on competition, access to drugs, and pricing. In particular, further transparent analysis of economic drivers is warranted. The Centers for Medicare & Medicaid Services should review and evaluate its 2003 Medicare reimbursement formula of average sales price plus 6% for unintended consequences including serving as a root cause of drug shortages.
6. Our AMA urges regulatory relief designed to improve the availability of prescription drugs by ensuring that such products are not removed from the market due to compliance issues unless such removal is clearly required for significant and obvious safety reasons.
7. Our AMA supports the view that wholesalers should routinely institute an allocation system that attempts to fairly distribute drugs in short supply based on remaining inventory and considering the customer's purchase history.
8. Our AMA will collaborate with medical specialty partners in identifying and supporting legislative remedies to allow for more reasonable and sustainable payment rates for prescription drugs.

9. Our AMA urges that during the evaluation of potential mergers and acquisitions involving pharmaceutical manufacturers, the Federal Trade Commission consult with the FDA to determine whether such an activity has the potential to worsen drug shortages. (Modify Current HOD Policy)

Fiscal Note: Less than $500

REFERENCES

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5. Council on Science and Public Health Report 3. National drug shortages-Update. American Medical Association Annual Meeting, Chicago, IL. June, 2014.

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12. Manual of Policies and Procedures. Center for Drug Evaluation and Research. MAPP 5240. 3 Rev. 3. Effective Date: 06/27/2017. Policies and Procedures. Office of Generic Drugs. Prioritization of the Review of Original ANDAs, Amendments, and Supplements. https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf.

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17. CDER Statement: FDA updates on Pfizer drug shortages. https://www.fda.gov/Drugs/DrugSafety/ucm563378.htm. Accessed August 7, 2017.

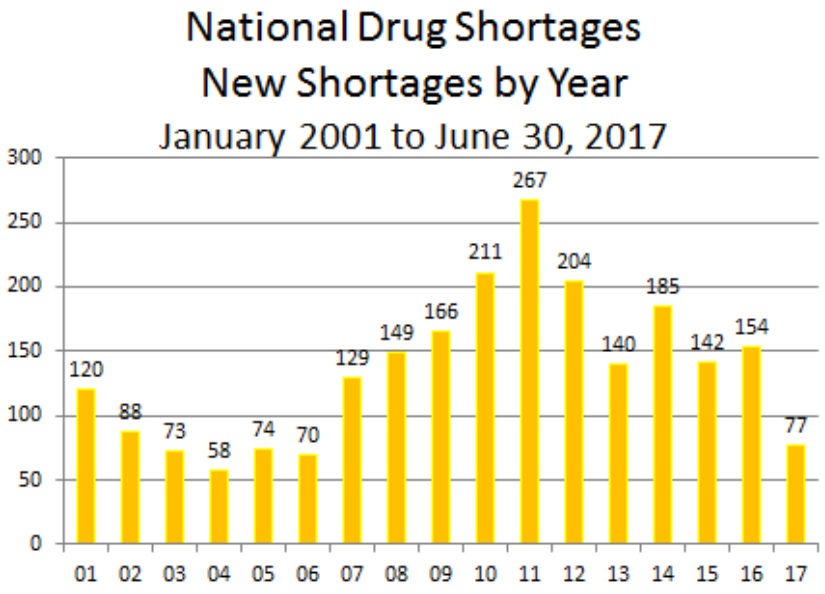
Table 1. Contrasting the FDA (CDER) and ASHP Drug Shortage Websites

	FDA	ASHP
Purpose	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	Notification of new shortages and status of ongoing shortages; drug shortage management resources
Audience	Public	Healthcare practitioners
Scope of shortage list	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]	All drug and biologic shortages reported and confirmed with manufacturer that are national in impact.
Source of shortage report	Manufacturers notify FDA of production disruption and voluntarily provide updates. Reports are also received from ASHP and from public via drugshortages@cder.fda.gov Note: Manufacturer-provided information represents shortage status at drug firm level.	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.
Criteria for inclusion on list	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."	(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.
Criteria for resolving shortage	One or more manufacturers are in production and able to meet full market demand.	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.
Reason for shortage	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.	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
Other information	Estimated duration, links to regulatory information such as recalls and Dear Healthcare Provider Letters	Estimated duration, list of available products, implications for patient care and safety, shortage management strategies, therapeutic alternatives

[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



Note: Each column represents the number of new shortages identified during that year.
University of Utah Drug Information Service
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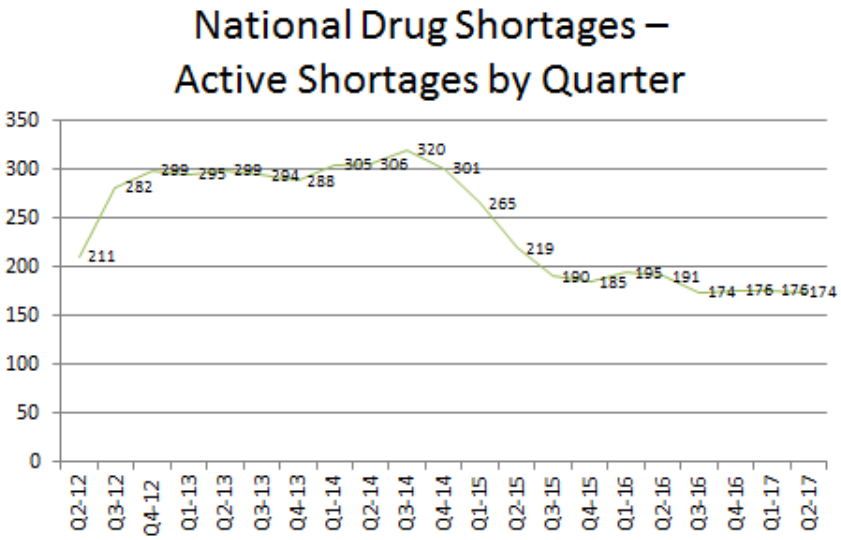

Note: Each column represents the number of active shortages at the end of each quarter.
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