REPORT 2 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-18)
Drug Shortages: Update
(Reference Committee E)

EXECUTIVE SUMMARY

Objective. This report updates information on drug shortages since the 2017 report was developed, specifically commenting on the increase in drug shortages due to hurricanes that have impacted the pharmaceutical industry in Puerto Rico as well as other relevant policy considerations regarding manufacturer processes recently brought to light which have implications for the United States health care system.

Methods. English-language reports were selected from a PubMed and Google Scholar search from September 2016 to February 2018, 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), the Institute for Safe Medication Practices (ISMP), 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. A recent roundtable report developed by ASHP also was consulted as a key resource.

Results. Drug shortages remain an ongoing public health concern in the United States and the FDA and ASHP continue to provide information regarding the topic. Although the rate of new shortages has decreased, long-term active and ongoing shortages are not resolving and critical shortages are impacting patient care and pharmacy operations. In late 2017, major hurricanes struck Puerto Rico which houses significant infrastructure for manufacturing critical pharmaceutical and other medical products. The FDA has issued multiple statements regarding the situation in Puerto Rico and has undertaken extensive efforts to avoid exacerbating critical drug shortages. In November 2017, AMA took part in an ASHP-convened meeting to review and identify new opportunities to address ongoing supply chain and patient-care challenges associated with drug product shortages. Eleven recommendations were crafted as a result of discussions at the roundtable.

Conclusion. Although recent natural disasters have increased the number of drug shortages only slightly, shortages of basic products such as saline and small-volume parenteral solutions, and their containers, are significantly impacting the health care system by affecting patient care, increasing the potential for drug errors, and influencing the manner in which health care teams function. Information and discussion at an ASHP-convened roundtable on current issues regarding drug shortages illuminated additional relevant policy considerations such as manufacturer transparency regarding production location and the cause(s) of shortages; quality of outsourcer compounding facilities; and the potential inclusion of vital drug manufacturing sites as critical infrastructure.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 2-A-18

Subject: Drug Shortages: Update

Presented by: Robert A. Gilchick, MD, MPH, Chair

Referred to: Reference Committee E
(Douglas Martin, MD, Chair)

INTRODUCTION

American Medical Association (AMA) 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 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 February 2018, 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), the Institute for Safe Medication Practices (ISMP), 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. A recent roundtable report developed by ASHP also was consulted as a key resource.[1]

BACKGROUND

The CSAPH has issued eight reports on drug shortages.[2-9] The findings and conclusions of the first five reports are summarized in CSAPH Report 2-I-15, "National Drug Shortages: Update."[7] The remainder of this report will update information on drug shortages since the 2017 report was developed, specifically commenting on the increase in drug shortages due to hurricanes that have impacted the pharmaceutical industry in Puerto Rico as well as other relevant policy considerations regarding manufacturer processes recently brought to light which have implications for the United States health care system.

CURRENT TRENDS IN DRUG SHORTAGES

Drug shortages remain an ongoing public health concern in the United States. Although the rate of new shortages has decreased, long-term active and ongoing shortages are not resolving and critical

Action of the AMA House of Delegates 2018 Annual Meeting: CSAPH Report 2
Recommendation Adopted as Amended in lieu of Res 517, and Remainder of Report Filed.

shortages are impacting patient care and pharmacy operations. Several commonly used products required for patient care are in shortage including sterile infusion solutions (e.g., saline, amino acids, dextrose), as well as diazepam, lidocaine, hydromorphone, and morphine.[10-12] Ongoing supply challenges of certain medications, typically injectable products that are off-patent and have few suppliers, persist. Causes of these shortages continue to remain largely unchanged and are mostly triggered by quality problems during manufacturing processes.

As noted in previous Council reports, the two primary data sources for information on drug shortages in the United States continue to be the Drug Shortage Program at the FDA and the Drug Shortage Resource Center maintained by ASHP in cooperation with the University of Utah Drug Information Service. According to the most recent data compiled by ASHP and the University of Utah Drug Information Service, the total number of new shortages in 2017 was 146 (compared with 154 in 2016) and the number of active shortages was 183 in quarter four of 2017. As of the end of 2017, the largest number of shortages belongs to the class of electrolytes, nutrition, and fluids; for 3% of the shortages, the reported reason was "natural disaster" (Appendix). The most recent metrics reported by the FDA are listed in the 2017 Drug Shortages: Update report.[9] Updated metrics from the FDA are anticipated in summer of 2018.

The FDA continues to utilize a mobile app to provide up-to-date access to drugs in shortage as well as notifications about new and resolved drug shortages and ability for physicians to report a drug shortage (Box 1). The ASHP drug shortage resource center provides a list of shortages and some guidance on managing critical shortages (Box 1).

STATE OF THE INDUSTRY

The U.S. Government Accountability Office (GAO) examined shortages of sterile injectable anti-infective and cardiovascular drugs in 2012, 2013, and 2014 and noted that the shortages were strongly associated with three factors:

1. A decline in the number of suppliers
2. Failure of at least one establishment making a drug to comply with manufacturing standards resulting in a warning letter
3. Drugs with sales of a generic version

These factors suggest that shortages may be triggered by supply disruptions and by market forces in which there are low profit margins for generic drugs, resulting in manufacturers being less likely to increase production.[11]

Legislation enacted in 2012, the Food and Drug Administration Safety and Innovation Act (Title X: Drug Shortages) (FDASIA) requires drug manufacturers to notify the U.S. Food and Drug Administration (FDA) "of any change in production that is reasonably likely to lead to reduction in supply" of a covered drug in the United States. Although this warning requirement has played a significant role in reducing the number of drug shortages, it has not solved the problem.[13]

Impact of Hurricanes Irma and Maria on Drug Manufacturing in Puerto Rico

In late 2017, major hurricanes struck Puerto Rico which houses significant infrastructure for manufacturing critical pharmaceutical and other medical products for worldwide distribution, including the United States. The FDA has issued multiple statements regarding the manufacturing situation in Puerto Rico. Extensive efforts have been undertaken to avoid exacerbating critical drug shortages and addressing challenges related to refrigeration, storage and transportation. FDA also has been working to relocate production in coordination with federal and local government colleagues and pharmaceutical companies. Additionally, the agency is paying particularly close

attention to the demand for empty containers, which are also produced on the island, as an alternative to filled infusion bags.[14,15]

A primary concern is the shortage of small-volume parenteral solution (SVP) products, including saline, due to production and supply-chain problems on the island. ASHP and the University of Utah Drug Information Service have developed a clinical resource on the conservation and management of SVPs (Box 1).[16] Additionally, emergency physicians from Brigham and Women's Hospital recently published an oral rehydration protocol for use to conserve sterile infusion fluids.[17]

ASHP DRUG SHORTAGES ROUNDTABLE

In November 2017, AMA took part in an ASHP-convened meeting to review and identify new opportunities to address ongoing supply chain and patient-care challenges associated with drug product shortages. The meeting served as a forum for several health care organizations to examine how FDASIA has impacted shortages and to address whether a need exists to build on the law with new recommendations.

FDA Drug Shortage Program Update

An update provided by staff from the FDA Drug Shortage Program confirmed that the notification requirement enacted as part of FDASIA is generally being followed and that most companies report to the agency when they anticipate or experience problems that may lead to a shortage. A few companies have failed to comply with reporting requirements suggesting the need for additional manufacturer education regarding their reporting responsibility. Timely notification enables the FDA to create solutions intended to prevent the onset of a shortage (e.g., work with other manufacturers behind the scenes to ramp up production, expedite the review of an abbreviated new drug application (ANDA) from another company, develop a work around for the production issue, or begin the process of controlled importation of a drug to meet demand). FDA staff reiterated that the requirement for manufactures to notify the FDA does not obligate them to disclose the problem for the interruption, its expected duration, or an estimated time frame for resolution. Additionally, under current US law, the agency cannot require a company to manufacture a drug, no matter how critical or life-sustaining it is.

While the FDA encourages companies to develop drug shortage contingency plans, few have them. More could be done to incentivize companies to develop such plans and establish manufacturing redundancy.

Outsourcer Compounding Facilities

In 2013, legislation was enacted to provide more regulatory oversight of compounding. The law created a new category of compounder, an outsourcing facility, which is regulated under Section 503B of the Food, Drug and Cosmetics Act. This category allows firms that compound drugs without a patient-specific prescription to be licensed and inspected by the FDA rather than the state board of pharmacy. These firms are not classified as pharmacies but more closely resemble drug manufacturers in their operation.

Several issues were discussed at the roundtable regarding 503B facilities and their ability to provide specific formulations in the event of drug shortages. It can take up to six weeks for 503B facilities to increase or begin production of a drug in shortage and they can do so only after the FDA adds the product to the shortage list. Because the products in short supply and the duration of the shortage cannot be predicted, not only can delays exist in initiating production, but inconsistent

fulfillment from 503B facilities is common. Additionally, many 503B facilities are not able to produce drugs from active pharmaceutical ingredients (APIs) and only repackage other commercially available formulations. Adding to this complication, 503B facilities currently cannot repackage SVPs because the empty bags needed to do so are also in shortage.

Several 503B outsourcing facilities have been issued an FDA Form 483, the FDA inspection review form issued to manufacturers at the conclusion of an inspection when an investigator(s) has observed any condition that may constitute a violation of the Food Drug and Cosmetic (FD&C) Act and related Acts.[18] However, no additional information is posted if or when a facility successfully addresses the deficiency detailed in the report. The uncertainty surrounding manufacturing quality among these facilities creates uncertainty for hospitals that may choose to rely on them to mitigate drug shortages.

Drug Manufacturing as Critical Infrastructure

The term "critical infrastructure" is defined in the USA Patriot Act of 2001 as "systems and assets, whether physical or virtual, so vital to the United States that the incapacity or destruction of such systems and assets would have a debilitating impact on security, national economic security, national public health or safety, or any combination of those matters."[19] Flowing out of Presidential Policy Directive 21 (PPD-21), titled Critical Infrastructure Security and Resilience, was the drafting of an update to the National Infrastructure Protection Plan (NIPP), published by the Department of Homeland Security (DHS). This update, titled NIPP: 2013, describes a national effort to identify and achieve critical infrastructure security and resilience and manage risk through partnership efforts and information sharing between public and private organizations.[20] Because the United States critical infrastructure is largely owned by the private sector, managing risk to enhance security and resilience needs to be a shared priority for industry and government. The Healthcare and Public Health (HPH) Sector-Specific Plan (SSP) tailors the strategic guidance provided in the NIPP to the unique operating conditions and risk landscape of the HPH sector.[21] The HPH SSP outlines how public and private sector partners will evaluate risks; coordinate plans and policy; and provide guidance to prevent, protect, mitigate, respond to, and recover from all hazards that pose a threat to the HPH sector critical infrastructure.

At the roundtable, the Office of the Assistant Secretary for Preparedness and Response (ASPR), Office of Emergency Management, part of the U.S. Department of Health & Human Services (DHHS), outlined its efforts to coordinate with DHS and public and private sector organizations involved in disaster response. The DHS list of critical infrastructure, which includes the HPH sector, and criteria for determining the vulnerability of the infrastructure, may be re-examined in the near future; the current plan has very specific parameters and few are HPH-related.

The discussion with ASPR focused on the potential for evaluating manufacturer locations and their cybersecurity as criteria for determining risk and inclusion within the list of critical infrastructure. The fact that several manufacturers were impacted by cyber events over the past year and that product shortages were worsened by the recent hurricanes impacting Puerto Rico, highlight the need to evaluate risk and hazard and disaster response for drug and medical product manufacturing. However, production location for specific drugs and other medical products is proprietary information and many manufacturers are unwilling to share this with DHHS and/or DHS. ASPR wants to work more closely with manufacturers and explain the benefits of information sharing and being included as critical infrastructure. Of note is that any information shared with DHS or DHHS is, by law, protected from public disclosure and used only in the context of preparedness planning and response. Additionally, DHHS in collaboration with DHS can provide analytical tools to help

manufacturers prepare for disasters, identify their dependencies such as power and water, and become more resilient.

Automation Difficulties

Many of the drugs currently in shortage are basic products required for patient care in all medical settings, such as saline and SVPs. Shortages of these basic products, and their containers, are significantly affecting patient care and healthcare providers because options to address these shortages are limited or risky.

Increasing automation and the use of informatics in hospitals and large healthcare centers has created efficiencies, but the use of devices such as infusion pumps and the utilization of electronic health records (EHRs) can be associated with problems in the case of drug shortages. Many devices are often designed to use specific products from specific manufacturers. When the required product is not available and alternatives must be used, it is burdensome and requires significant work to change parameters for device functionality, if it is possible at all. Many EHRs have specific drugs and doses prepopulated for streamlining patient care and care team collaboration. When shortages occur and other drugs or doses are the only options available, EHRs must be reprogrammed with the new options, often at each EHR station and for each patient individually.

Recommendations Resulting from the Roundtable

Eleven recommendations were crafted as a result of discussions at the roundtable (Box 2). Some of them are already reflected in current AMA policy on drug shortages including urging manufacturers to establish contingency plans or redundancies in production and requiring FTC review of manufacturer mergers to evaluate shortage risk. Other recommendations include a call for greater manufacturer transparency, more information on the quality of outsourcing compounding facilities, and the examination of drug shortages as a national security initiative resulting in the addition of vital manufacturing sites as critical infrastructure.

IMPACT OF SHORTAGES ON HEALTH CARE PRACTICE

ISMP Practices Survey

ISMP recently published the results of a drug shortage survey they conducted in late 2017, before natural disasters exacerbated the shortage problem.[22] Almost all respondents of the survey practiced in a hospital setting. Shortages were reported across all treatment categories. Approximately 55% of respondents indicated experiencing shortages involving more than 20 drugs within the last six months and most (66%) were affected by at least one shortage daily.

The survey results revealed concerning trends:

- Approximately 90% of respondents experienced rationing, restricting, and hoarding of drug supplies.
- Many commented on waste (for example, 250ml bags of insulin but only a small fraction is needed).
- Survey participants noted other strategies that are being employed including re-deploying medications used for crash carts, reusing vials, extending hang times for IVs, purchasing sterile products compounded from non-sterile ingredients from compounding pharmacies without evaluating the risk, and transitioning infusion devices to push IVs (changing nurse protocols).

- 15% admitted to purchasing drugs in short supply at great cost from a secondary gray market.

Most survey participants (71%) were unable, at times, to provide patients with the recommended drug or treatment for their condition due to shortages, which resulted in patients receiving a less effective drug and delayed treatments. Many participants also stated that they need full-time staff to manage drug shortages and commented that the tasks associated with this process reduce the time available for direct patient care. Additionally, many respondents provided examples of how recent drug shortages have led to unsafe practices that have increased the risk of, or contributed to, a medication error.

SUMMARY

Although recent natural disasters have increased the number of drug shortages only slightly, shortages of basic products such as saline and SVPs, and their containers, are significantly impacting the health care system by affecting patient care, increasing the potential for drug errors, and influencing the manner in which health care teams function. Box 1 is a compilation of resources available to assist physicians and hospitals in mitigating drug shortages.

Information and discussion at an ASHP-convened roundtable on current issues regarding drug shortages illuminated additional relevant policy considerations such as manufacturer transparency regarding production location and the cause(s) of shortages, quality of outsourcer compounding facilities, and the potential inclusion of vital drug manufacturing sites as critical infrastructure.

Given its role as the leading advocacy organization for physicians and a key advocate for patients, patient care, and the public health, our AMA is concerned about the shortages of basic medical supplies such as sterile saline, medications for which the vehicle for intravenous administration is sterile saline, and any containers for sterile saline or injectable medications which are a component of our nation's drug shortage problems. The AMA welcomes the application of critical infrastructure terminology and policies to the drug shortage challenges clinicians face each day.

RECOMMENDATION

The CSAPH recommends that the following policy be amended by addition and deletion to read as follows:

Policy H-100.956 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 <u>are in short</u> supply ~~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 <u>the U.S. Department of</u> Health and Human Services <u>(DHHS)</u> 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, including the impact of group purchasing organizations on drug shortages, 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 federal Centers for Medicare & Medicaid Services (CMS) 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 society partners and other stakeholders 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.
10. Our AMA urges the FDA to require manufacturers to provide greater transparency regarding production locations of drugs and provide more detailed information regarding the causes and anticipated duration of drug shortages.
11. Our AMA encourages electronic health records (EHR) vendors to make changes to their systems to ease the burden of making drug product changes.
12. Our AMA urges the FDA to evaluate and provide current information regarding the quality of outsourcer compounding facilities.
13. Our AMA urges DHHS and the U.S. Department of Homeland Security (DHS) to examine and consider drug shortages as a national security initiative and include vital drug production sites in the critical infrastructure plan.
14. Our AMA considers drug shortages to be an urgent public health crisis, and recent shortages have had a dramatic and negative impact on the delivery and safety of appropriate health care to patients. (Modify Current HOD Policy)

Fiscal Note: Less than $500

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Box 1. Resources available to assist in mitigation of drug shortages.

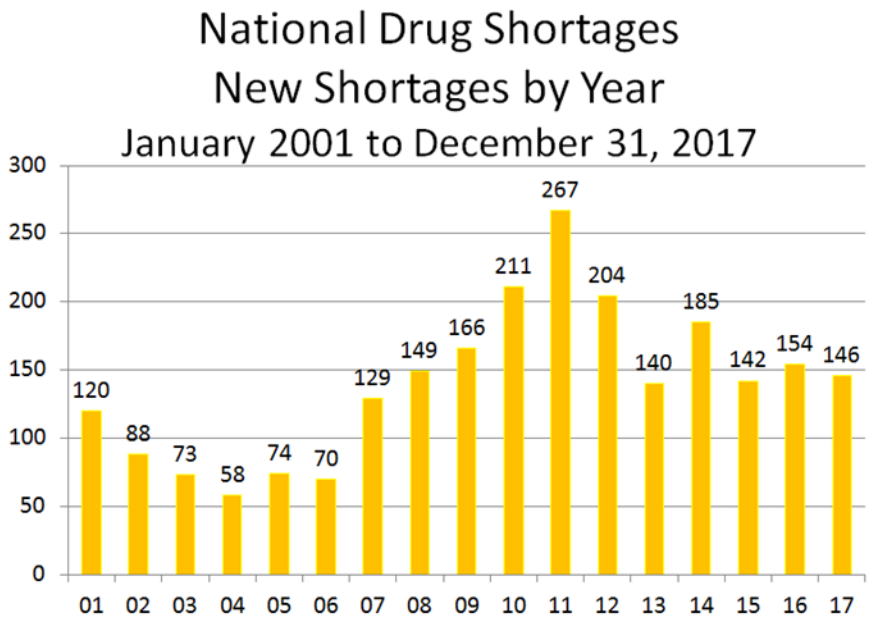
1. ASHP Resource Center
2. ASHP list of current shortages
3. ASHP and University of Utah guidance on small-volume parenteral solutions shortages
4. ASHP and University of Utah guidance on injectable opioid shortages
5. FDA Drug Shortages Page (includes current shortages list, mobile app, and additional information)
6. US Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response
7. ISMP newsletter on managing drug shortages
8. American Society for Parenteral and Enteral Nutrition guidance on shortages with parenteral nutrition components
9. NEJM article detailing Brigham and Women's Hospital Oral Rehydration Protocol[17]

Box 2. Recommendations resulting from the ASHP Drug Shortages Roundtable.

1. Manufacturers should provide the FDA with more information on the causes of the shortages and their expected durations.
2. Establish best practices for high-alert drugs.
3. FDA should require manufacturers to establish contingency plans and/or redundancies.
4. FDA should establish incentives to encourage manufacturers to produce drugs in shortage.
5. FDA should provide more information on the quality of outsourcing facilities' compounding.
6. Reconsider the purchasing process of saline.
7. Manufacturers need to be more transparent.
8. Examine drug shortages as a national security initiative.
9. Request electronic health records (EHR) vendors to employ changes to their systems to ease the burden of making drug product changes.
10. FDA should establish a quality manufacturing initiative.
11. FTC should include in its review of drug company merger proposals the potential risk for drug shortages.

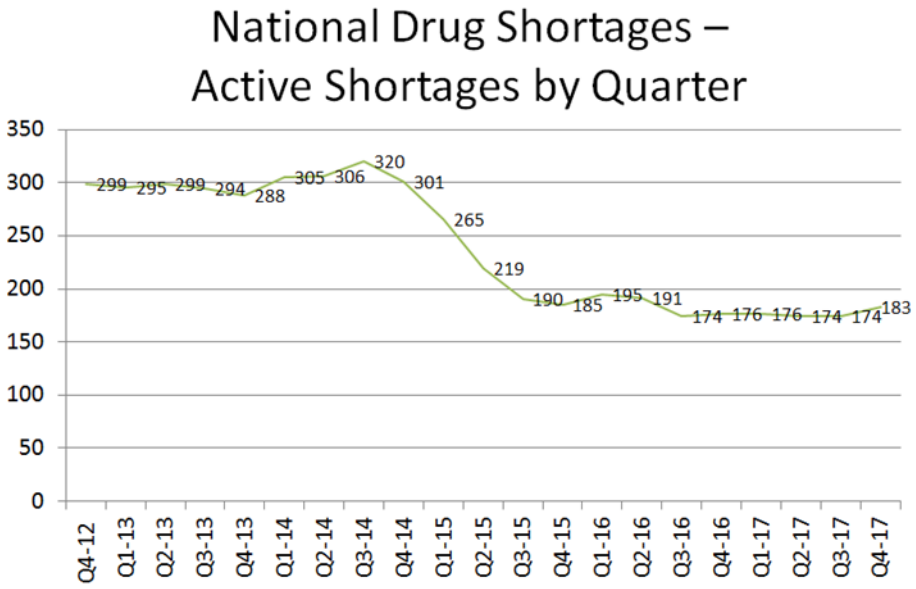
APPENDIX

Figure 1.



Note: Each column represents the number of new shortages identified during that year.
University of Utah Drug Information Service
Erin.Fox@hsc.utah.edu, @foxerinr

Figure 2.



Note: Each column represents the number of active shortages at the end of each quarter.
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Figure 3.

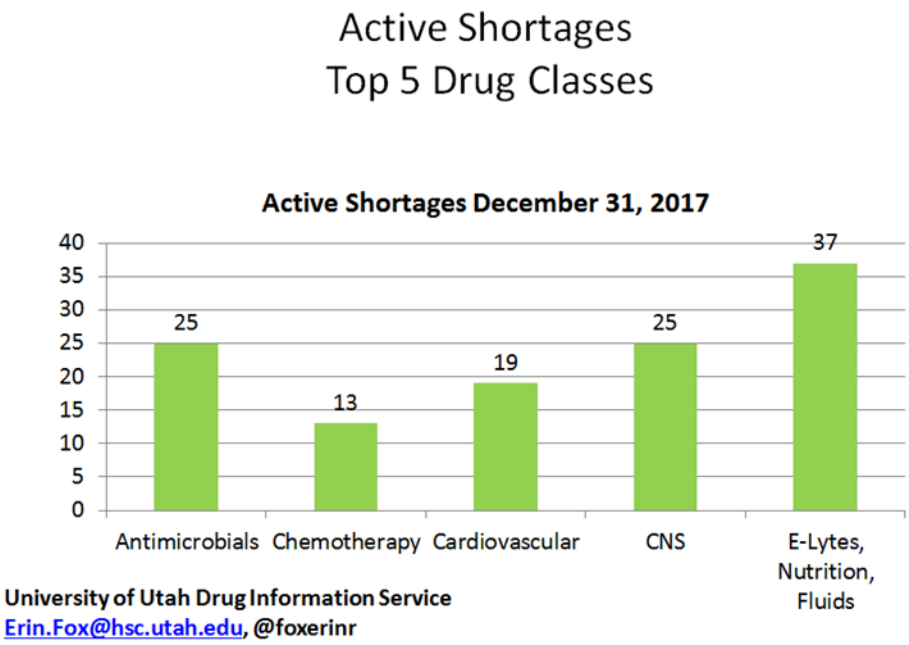

Figure 4.