

Drug shortages roundtable: Minimizing the impact on patient care

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Background

Drug shortages are an ongoing public health concern in the United States. Although the number of newly reported drug shortages (170) is much lower than at the height of the shortage crisis in 2012 (305), clinicians continue to experience supply challenges for certain medications. These medications are typically injectable products that are off-patent and have few suppliers. The causes of these shortages do not appear to have changed since 2012, as shortages are largely the result of quality problems during the manufacturing process, which give rise to a halt in production in order to address the problem. In the case of a product with few competitors, this disruption in production cannot be absorbed by other companies, and demand outpaces supply. In the case of a sole-source manufacturer, no alternatives for production exist, and clinicians must either struggle to obtain a supply of the drug, compound the

drug when possible, or recommend an alternative therapy if one exists.

Legislation enacted in 2012 in response to the drug shortage crisis requires drug manufacturers to notify the 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.¹ This advanced-warning requirement has played a significant role in reducing the number of drug shortages, but it has not solved the problem.

A further complication occurred in late September 2017, as a major hurricane struck Puerto Rico, which houses significant drug manufacturing infrastructure. The result thus far has been a shortage of small-volume parenteral (SVP) solution products due to production and supply problems on the island. SVP solution products include saline bags, which are the foundation of basic i.v. compounding for hundreds of drugs that require further dilution, such as antibiotics, chemotherapy drugs, and electrolytes. They are also frequently used to start i.v. lines and administer blood products.

Overview

In November 2017, ASHP convened a meeting of healthcare professional organizations—the American Hospital Association (AHA), FDA, and the Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR)—to review and identify new opportunities to address the ongoing supply chain and patient care challenges associated with drug product shortages. The meeting

served as an opportunity to examine how the FDA Safety and Innovation Act (FDASIA), enacted in 2012, has affected drug shortages and to address whether there is a need to build on the law with new recommendations. Held at ASHP headquarters in Bethesda, Maryland, the meeting included attendees who represented not only a large part of the clinician community but also AHA, the Pew Charitable Trusts, and the University of Utah Drug Information Service. At the meeting, representatives from the American Society of Anesthesiologists, American Society of Clinical Oncology, American Medical Association, American Society of Parenteral and Enteral Nutrition, Institute for Safe Medication Practices, and Society of Critical Care Medicine discussed the ongoing challenges of drug shortages and their impact on patient care.

FDA

The meeting began with a presentation by Captain Valerie Jensen of the FDA Drug Shortage Program. Jensen reported that the notification requirement enacted as part of FDASIA is generally being followed and that most companies do report to the agency when there is a production problem. This reporting enables FDA to work with other manufacturers behind the scenes to increase production, allow for expedited review of another company's abbreviated new drug application, or, in extreme cases, begin the process of controlled importation of a drug to meet demand. Manufacturers are required to notify FDA 6 months in advance or, if that is not possible, as soon as practicable thereafter but in

no case later than 5 business days after the discontinuance or interruption in manufacturing. If a company fails to comply with the reporting requirement, FDA sends a letter notifying the company that it is not in compliance with the law. Jensen also noted that the requirement to notify FDA does not obligate the manufacturer to disclose the problem that led to the interruption, its expected duration, or an estimated time frame for resolving the problem.

In recent years, FDA has been working closely with international regulatory agencies to engage in controlled importation of drugs in short supply. This collaboration has not only resulted in more reliance on foreign inspection history but has also bolstered agency relationships with foreign sources. Jensen noted that controlled importation is not a long-term solution, as other countries also experience shortages.

During her presentation, Jensen also noted that while FDA can require advance notification of supply disruptions and product discontinuations, the agency cannot require a company to manufacture a drug, no matter how critical or life-sustaining it is. FDA believes that better reporting in terms of listing the actual production problems, as well as estimated timelines for resolution, would help. In addition, Jensen indicated that while FDA encourages companies to develop drug shortage contingency plans, more could be done to incentivize companies to develop such plans, including providing for manufacturing redundancy to have a backup system in place should a production line be taken out of service.

University of Utah Drug Information Service

Erin Fox, Pharm.D., of the University of Utah Drug Information Service also presented on drug shortages. Fox noted that the current shortage trend includes i.v. antibiotics, i.v. fluids (including 0.9% sodium chloride injection), and other widely used products, such as emergency syringes, sodium bi-

carbonate, Carpuject (Pfizer) syringes, amino acids, and parenteral nutrition products. One improvement is the significant decline over the past 5 years in the shortages of chemotherapy drugs. Fox emphasized that current shortages are impacting all areas of the hospital, from specialty to acute care centers.

Fox also cited a Government Accountability Office report from 2016 that identified the key factors in drug shortages, including few suppliers, poor manufacturing processes, and typically low-margin generic products.²

Many of the drugs in short supply are basic products needed to care for patients in hospitals, clinics, and other patient care settings. Shortages of these types are having a substantial effect on patient care, as options to address the problem are limited or risky. Further, while increasing automation in hospitals has created efficiencies, these systems are often designed to use with a certain product. When an alternative product must be used due to a shortage, the workload required to make such a change is burdensome. Fox cited the use of smart pumps and the labor-intensive process for changing a drug in the electronic health record (EHR). Further exacerbating the problem are the FDA requirements that prohibit the storage of drugs in syringes, yet syringe pumps are approved for use.

After Fox's presentation, Allen Vaida, Pharm.D., of the Institute for Safe Medication Practices (ISMP) described the results of an August 2017 drug shortage survey.³ The ISMP survey revealed that 55% of respondents indicated experiencing a shortage of 21 or more drugs within the previous 6 months. Roughly 27% reported weekly shortages, and 66% reported daily shortages. Ninety percent of respondents reported increasing inventory, hoarding, and rationing supplies of drugs in shortage. Other strategies being used by survey respondents included redeploying medications used for emergency resuscitation carts, reusing vials, extending hang times for i.v.'s, and transitioning infusion devices to i.v. push medications prepared

and administered by nurses. Survey respondents also described delays resulting from the labor-intensive re-entry of new drugs into computerized prescriber order-entry systems.

503B outsourcing facilities

In 2013, legislation was enacted in the wake of the New England Compounding Center tragedy to provide more regulatory oversight of compounding. The law created a new category of compounder, called an outsourcing facility, which is regulated under Section 503B of the Food, Drug, and Cosmetics Act.⁴ The new category allows firms that compound drugs without a prescription to be licensed and inspected by FDA rather than by the state board of pharmacy. These firms are not classified as pharmacies but more closely resemble drug manufacturers. Given this new category and the regulatory exception that allows compounding of drugs in short supply, the question was raised as to whether these 503B outsourcing facilities could fill the gap and produce drugs in short supply.

The group discussed the challenges associated with the 503B outsourcing market as a solution to the drug shortage problem. According to the group, the largest hurdle is the unpredictability of drug shortages. It is often not known ahead of time if a drug will be in short supply. Typically, it takes 5–6 weeks for 503B outsourcing facilities to increase the production of a drug, and they can do so only when a product appears on the FDA shortage list. This makes the marketplace uncertain for products compounded by outsourcing facilities, as they cannot predict which products will be in short supply or how long the shortage will last. In addition, many 503B outsourcing facilities are not equipped to produce drugs directly from active pharmaceutical ingredients.

The group noted that with respect to the situation in Puerto Rico, 503B facilities simply cannot make SVP solutions because the majority of empty bags needed to do so are

manufactured in Puerto Rico. In addition, extremely large volumes of these products are needed. For example, a 500-bed inpatient hospital can easily require 20,000 100-mL bags of 0.9% sodium chloride for injection for a single month. Many 503B outsourcing facilities have been issued an FDA Form 483, the FDA inspection form used when a facility is reviewed. These are posted online by FDA, but no additional information is posted to denote whether the facility has fixed the findings outlined in FDA Form 483. This creates uncertainty for hospitals attempting to select a facility and prevents 503B outsourcing facilities from playing a larger role in mitigating the impact of drug shortages.

Office of the ASPR

Laura Wolf, Ph.D., the Branch Chief of Critical Infrastructure Protection at the Office of the ASPR, Office of Emergency Management, described the Office of the ASPR's efforts to coordinate with other public and private sector organizations involved in disaster response, including the Department of Homeland Security (DHS). Wolf identified DHS's list of critical infrastructure, which includes public health and healthcare, and noted that DHS may reexamine the criteria for determining the vulnerability of that infrastructure.

In addition, the suggestion was made that manufacturing locations be evaluated and considered as criteria for determining risk. The situation in Puerto Rico underscores the need to track critical drug products and their manufacturers and evaluate the location of manufacturing. Wolf agreed that more timely information is needed during a disaster response regarding where drugs and other medical products are being produced and that currently such information is considered proprietary. She stated that the Office of the ASPR would like to work more closely with major manufacturers to explain the benefits of sharing such information with HHS. In other words, if manufacturers are identified as critical infrastructure, it would be

safe to share this otherwise proprietary information with HHS and DHS because, by law, this information sharing is protected from public disclosure and used only in the context of preparedness planning and response. In terms of benefits to drug manufacturers, Wolf noted that HHS works with DHS and can provide analytic tools to help manufacturers prepare for disasters and identify their dependencies (e.g., power, water) and how they can become more resilient.

Wolf also indicated that HHS is working with other federal partners to help identify additional authorities who can support FDA's drug shortage program efforts to prepare, prevent, and respond to shortages. She stated that HHS is convening discussions with the Department of Defense and the Veterans Health Administration, both of which purchase large amounts of drugs and other medical products. HHS is exploring whether such government customers can make changes in contracts to help support the resilience of these manufacturers.

Among other initiatives, due to predictions of an early and severe influenza season, the lack of 0.9% sodium chloride injection is a national security challenge. HHS is exploring what potential authority it has and what assistance it can provide through its various programs within the Office of the ASPR, and other government agencies. Finally, the Office of the ASPR is exploring whether it can predict future shortages, determine where future shortages might occur, and find ways to support manufacturers in implementing plans, such as ensuring that drug shortage contingency plans and enhanced redundancies in production and distribution are in place.

Development of a critical drug list

The group also discussed the need to develop a list of critical medications—perhaps the top 10 or 20 most commonly used, life-sustaining therapies deemed most critical to patient care. This list of medications

would be deemed a priority for the protection of public health, and special consideration could be given to maintaining the supply of these medications. The group noted the difficulty with this approach, as many products can be considered critical when in short supply. Further, participants noted the challenge of developing a list of drugs from the 2010 Drug Shortages Summit, a topic that was discussed during that meeting and later abandoned. One key difference between 2010 and 2017 is that the shortage of SVP solution products has generated significantly more panic among caregivers than have other shortages. It appears evident that the magnitude of this shortage is much more widespread than previous shortages. While consensus was not reached on developing a critical drug list, the group agreed that further discussion of this question may be warranted.

Key questions discussed by the group

1. What has worked in the past 4 years, and what has changed?

Early notification of discontinuances and interruptions has helped FDA mitigate the impact of drug shortages through behind-the-scenes work with manufacturers—some of them foreign sources—to expedite the approval of new suppliers, increase the production of alternative products, and arrange for the importation of supplies during an impending shortage. According to Jensen, while most manufacturers notify FDA in advance, as required, a few companies have failed to meet the reporting requirements. FDA suggested the need for additional manufacturer education regarding their responsibility to report possible interruptions to the drug supply.

In addition, many stakeholders question the accuracy of manufacturer reporting. There is a desire among the group to supplement existing laws by requiring manufacturers to report the specific manufacturing problem to FDA, including

an estimated timeline for resolution. If a manufacturer is stopping production for a significant amount of time, FDA has indicated that such information would be useful to the agency as it examines controlled importation or expedited review of another company. Currently, the provision of this information is not required under FDASIA.

2. Are there new trends with respect to shortages, new causes of shortages, or factors related to shortages that have emerged?

For the most part, drug shortages are still caused by manufacturing-quality problems and primarily affect generic, sterile injectable products. But there have been a few differences in the types of drug shortages over the past few years. First, the number of shortages of oncology products has declined significantly. The shortages of other drug classes, including antibiotics, amino acids, and total parenteral nutrition products, are nothing new. The more troubling shortages, however, are occurring with the most widely used products, such as 0.9% sodium chloride injection, as a large amount is needed. Such shortages affect nearly every area of hospitals and acute care centers.

While most shortages involve sterile injectable products, it was noted that a few oral products also appear on the shortage list. These shortages are less likely to be a result of manufacturing-quality issues and more likely to be based on marketplace factors, such as competitors withdrawing from the market. A related issue is how business decisions, such as mergers, impact drug shortages. The purchase of Hospira by Pfizer, for example, brings into question whether the new parent company is continuing to invest in new production capacities and facilities. The group suggested that the Federal Trade Commission (FTC) should consider an additional factor

when evaluating buyouts or mergers, specifically the potential effects such an action may have on the supply of drugs.

3. What recommendations, including policy options, may be needed to help prevent and mitigate shortages?

Throughout the day, the group discussed potential policy options. Listed below, these options range from improving the requirements in Title X of FDASIA to providing some type of contingency planning. It is important to note that the recommendations were the result of discussion among the nongovernment groups and cannot be attributed to either HHS or FDA.

Recommendations to help prevent and mitigate shortages

1. Manufacturers should provide FDA with more information on the causes of the shortages and their expected durations.

Current law requires manufacturers to notify FDA when there is a discontinuance or interruption in manufacturing. However, manufacturers are *not* required to disclose the problem causing the interruption or to provide a timeline for resolution. This lack of information hinders the ability of healthcare providers to plan for shortages. Title X of FDASIA should be strengthened to require these notifications to include disclosure of the problem causing the interruption and an expected timeline to address the shortage.

2. Health systems should establish best practices for high-alert drugs.

Best practices should be established for certain widely used and critical drugs. This will be helpful in the event of a shortage and, if widely applied, will also reduce waste throughout the healthcare system, thus helping to prevent shortage situations. Focus should specifically be placed on limiting i.v. fluid waste. Once best practices are established, a multi-

disciplinary educational component will need to be implemented to ensure that all medical professionals are trained and educated in these best practices for limiting i.v. fluid waste.

3. FDA should require manufacturers to establish contingency plans.

Manufacturers cannot always predict when a shortage will occur. Such shortages negatively impact patient safety and access to care. Therefore, it is recommended that manufacturers establish contingency plans for a drug shortage, specifically when there are fewer than 3 manufacturers producing a drug.

4. FDA should establish incentives to encourage manufacturers to produce drugs in shortage.

When a drug is in shortage, it is often difficult to find a manufacturer willing to increase or begin production of the drug. Therefore, FDA should explore incentive options to encourage other manufacturers to begin producing drugs that are in shortage. Incentives should also be considered for outsourcing facilities that compound drugs, as provided under Section 503B of the Food, Drug, and Cosmetic Act.

5. FDA should provide more information on the quality of outsourcing facilities' compounding.

Although 503B outsourcing facilities registered with FDA are able to compound drugs that are in shortage, it is difficult for pharmacies to evaluate the quality of a 503B facility. This is especially true for an outsourcing facility that has received FDA Form 483, indicating that the company has a problem with quality. The recommendation is for FDA to not only include more disclosure on its website regarding why FDA Form 483 was issued but also ensure the timely removal of the form when the issue has been resolved.

6. Reconsider the purchasing process of 0.9% sodium chloride injection.

As this product is

used more widely than most drugs, the group discussed unbundling 0.9% sodium chloride injection from the purchasing of other supplies. Additionally, the group proposes that an authoritative body such as FTC look into the purchasing process to determine if it is stifling competition.

7. Manufacturers need to be more transparent. Title X of FDASIA could be strengthened to require more transparency. The recommendation is for manufacturers to disclose to FDA the location of production, including situations in which a contract manufacturer is used. Further, there may be situations, such as the hurricane in Puerto Rico, where FDA could release the names of products produced at certain locations to allow clinicians to make patient care plans in advance. In these situations, allocated purchasing could also be employed as a means to prevent hoarding.

8. Examine drug shortages as a national security initiative. When a drug is in shortage, it affects all forms of medical care, from public and private hospitals to the U.S. military and Veterans Affairs medical centers. The group recommends that HHS and DHS identify ways that they can support manufacturers and the healthcare provider community in preparing and responding to future disasters and other supply disruptions in order to improve supply chain resilience. As part of these efforts, the group recommends exploring funding opportunities to support the continued flow of products needed during emergency situations.

9. Request EHR vendors to make changes to their systems to ease the burden of making drug product changes. In recent years, changes have been implemented across the healthcare system to improve patient safety, such as establishing more standardized practices. However, when

a shortage occurs, countless hours and staff time are required to make a change to the EHR system. The group recommends a statement be crafted requesting that EHR vendors make changes to their systems to make it easier to switch products.

10. FDA should establish a quality manufacturing initiative. FDA should establish a manufacturing rating system in which higher-quality manufacturing receives a higher rating. FDA should consider incentives for manufacturers to participate in the program. The rating system should include factors such as whether the company has a contingency plan for interruptions or disasters and whether the company has a plan for redundancy in production.

11. FTC should include the potential risk for drug shortages in its review of drug company merger proposals. The number of drug companies making products that are widely used in hospitals and other healthcare settings is declining, particularly companies that produce generic sterile injectable products. This is partly due to continued consolidation among drug companies. The group recommends that among the factors that FTC examines in reviewing drug company mergers and acquisitions, it also consider the potential risk for drug shortages.

Conclusion

The drug shortages roundtable discussion largely focused on (1) examining drug shortages over the past 5 years and assessing what has worked in terms of preventing and mitigating shortages as well as what could be improved and (2) whether there have been notable changes in the causes of drug shortages, the trends in the types of shortages, or the marketplace dynamics that affect supply. In addition, the meeting provided an opportunity to hear from new potential stakeholders within the Office of the ASPR on

how the healthcare community can plan for future disasters and threats to critical infrastructure in order to minimize their impact on the drug supply.

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References

1. Food and Drug Administration Safety and Innovation Act. Pub. L. No. 112-144, § 1001, 126 Stat. 993, 1099 (2012) (codified at 21 U.S.C § 356c).
2. U.S. General Accounting Office. Drug shortages: certain factors are strongly associated with this persistent public health challenge (2016). HYPERLINK “http://www.gao.gov/products/GAO-16-595” www.gao.gov/products/GAO-16-595 (accessed 2018 Mar 9).
3. Institute for Safe Medication Practices. Drug shortages continue to compromise patient care (January 11, 2018). HYPERLINK “http://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=1185” www.ismp.org/newsletters/acutecare/showarticle.aspx?id=1185 (accessed 2018 Mar 9).
4. Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587 (2013) (codified as amended at 21 U.S.C. 301 et seq.).

Meeting Attendees

- American Hospital Association
- American Medical Association
- American Society of Anesthesiologists
- American Society of Clinical Oncology
- American Society of Health-System Pharmacists
- American Society of Parenteral and Enteral Nutrition
- Institute for Safe Medication Practices
- Pew Charitable Trusts
- Society of Critical Care Medicine
- University of Utah Drug Information Services

Public Sector Meeting Attendees

- Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response
- Food and Drug Administration