

Advertising Supplement

UPDATE ON  
**Critical Perioperative  
Drug Shortages**

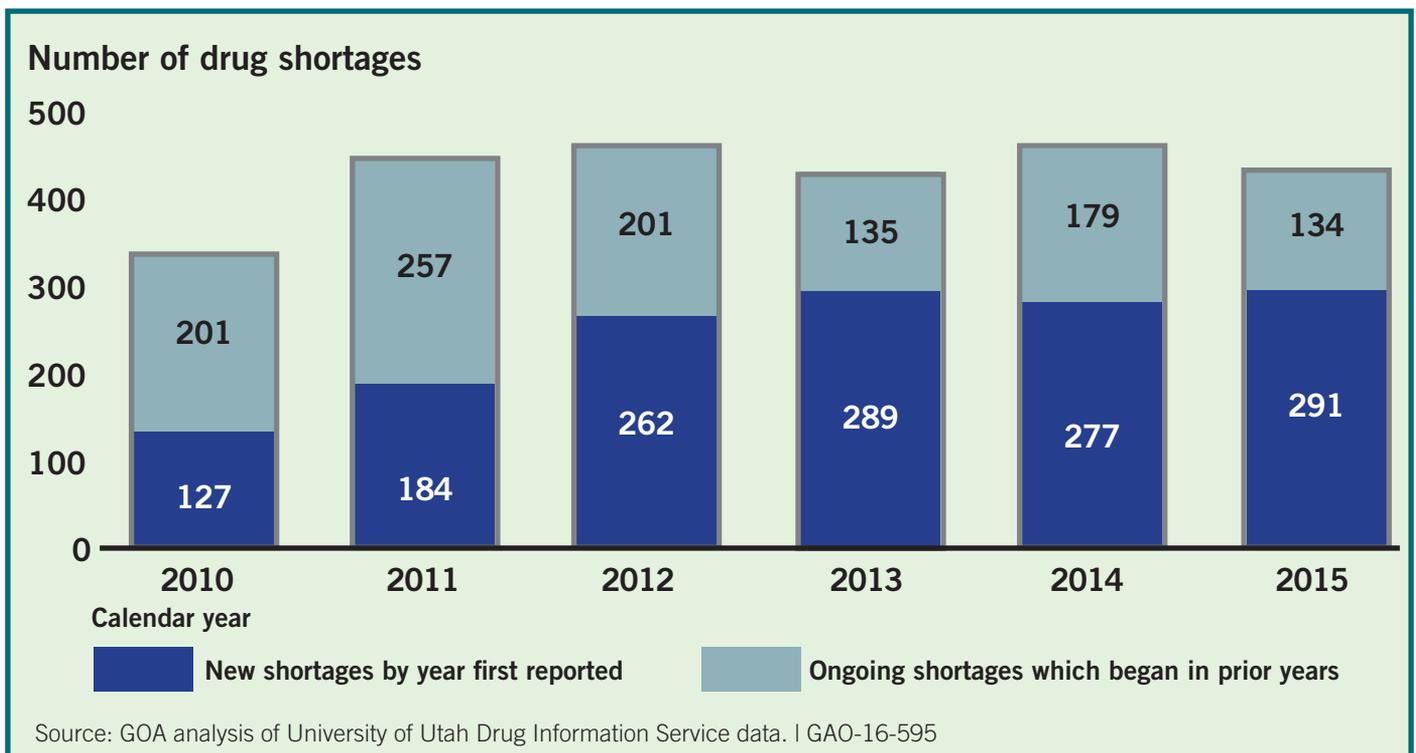
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# UPDATE ON Critical Perioperative Drug Shortages

**A**t the 2018 annual meeting of the American Society of Anesthesiologists (ASA), Edward R. Mariano, MD, MAS, Chief of Anesthesiology and Perioperative Care Service and Associate Chief of Staff for Inpatient Surgical Services, VA Palo Alto Health Care System; Professor of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, and Val Jensen, RPh, Associate Director, CDER Drug Shortage Staff, US Food and Drug Administration (FDA), discussed the impact of ongoing shortages in local anesthetics and intravenous pain medications on the perioperative process, current strategies to avoid compromising patient care, and potential long-term solutions. They shared a national perspective on how ASA, FDA, and the pharmaceutical industry are working together to mitigate these issues.



## Introduction

Hospitals across the country continue to report medication shortages—often receiving little to no advance warning themselves—as a consequence of various business, economic, and regulatory issues, supply chain vulnerabilities, and natural disasters that disrupt drug manufacturing and delivery. Challenges in acquiring raw materials, closure of manufacturing facilities for remediation of quality issues, and loss of manufacturing infrastructure in natural disasters such as Hurricane Maria in Puerto Rico in 2017 have contributed to recent significant shortages in a number of drugs.

Unfortunately, drug shortages are not new—an analysis by the US Government Accountability Office (GAO) revealed consistently high numbers of both new and ongoing shortages since 2010.

Though the number of new drug shortages per year has decreased from a peak in 2011, shortages of drugs for which there are no good alternatives, such as generic injectables, have been difficult to resolve. Shortages in local anesthetics used for regional blocks in surgical procedures and intravenous (IV) pain medications for the management of surgical pain continue to challenge anesthesiologists and directly affect the safety and care of patients. In this respect, addressing the crisis of drug shortages is an ethical imperative. Shortages in anesthetics and IV analgesics may lead to suboptimal pain control or sedation during procedures, increased side effects from use of alternatives, an increased risk of medication errors (as practitioners make substitutions for commonly used medications in response to fluctuations in drug availability), and even postponement or cancellation of procedures. In the latter case, patients not only do not receive timely care, but also may require changes in perioperative pain control, in particular, extended use of opioids.

### Most commonly reported anesthetic and analgesic medication shortages, 2018

- Fentanyl Citrate (Sublimaze®) Injection
- Hydromorphone Hydrochloride Injection, USP
- Methadone Hydrochloride Injection
- Morphine Sulfate Injection, USP
- Remifentanyl (Ultiva®) Lyophilized Powder for Solution Injection
- Bupivacaine
- Lidocaine
- Ropivacaine
- Ketamine

## Strategies to maintain patient safety and care

To avoid procedure delays and ensure adequate periprocedural pain management, clinicians have relied on prioritizing the use of available medications and using safe alternatives when possible. Other short-term approaches to drug shortages include collecting up-to-date supply information from the pharmacy (through daily calls, emails, or a centralized

dashboard) and avoiding medication waste by asking the pharmacy to split large multi-dose vials into multiple single-dose syringes.

Each of these strategies was reflected in a recent statement released by the Society of Obstetric Anesthesia and Perinatology (SOAP) in response to shortages in hyperbaric spinal bupivacaine used for anesthesia in cesarean deliveries and other local anesthetics used for labor analgesia. SOAP recommended that institutions check their current inventory of hyperbaric spinal bupivacaine, estimate whether the available supply meets anticipated needs, determine whether multiple single dose syringes can be prepared from multi-dose vials to minimize waste, and consider preservative-free drug substitutions when possible. SOAP also suggested that institutions prioritize use of existing hyperbaric spinal bupivacaine for use in obstetric emergencies over all other scheduled surgical procedures.

### **Transparency and communication to mitigate the effects of drug shortages**

Work to raise awareness of the drug shortage issue and advocate for solutions is being undertaken by many professional societies. ASA recently shared with the FDA the results of its recent survey of 2500 ASA members, 95% of whom reported that drug shortages—most commonly fentanyl, hydromorphone, morphine, and bupivacaine—are significantly impacting patient care. Several organizations have joined the ASA, such as the American Society of Health System Pharmacists (ASHP) and American Hospital Association, among many others, to draft recommendations for mitigating drug shortages and call for greater transparency regarding expected shortages and improvements in drug manufacturing infrastructure.

In his presentation, Dr. Mariano stressed the importance of engaging in open discussions about the drug shortage issue with colleagues, regulatory agencies, legislators, and patients. Patients in particular may not be aware of anesthetic drug shortages or the effect that shortages may have on outcomes of their scheduled procedures or perioperative pain management. Dr. Mariano recommended that anesthesiologists warn patients undergoing elective surgeries about how drug shortages may affect anesthetic and analgesic choices both during and after surgery. He also encouraged consistent reporting of drug shortages to the ASA and routinely checking the FDA Drug Shortages database. The University of Utah pharmacy service also tracks drug shortages for ASHP and makes the list available on their website.

## Mitigation of drug shortages on a national scale – the role of FDA

Longer-term solutions to preventing drug shortages will require improvements in the supply chain and pharmaceutical manufacturing infrastructure. Captain Jensen described the efforts of the Drug Shortage Staff (DSS) at FDA, which is working closely with suppliers, facilities, and the pharmaceutical industry to address the drug shortage issue. The DSS is facilitating both temporary and long-term strategies to address shortages, coordinating timely and comprehensive risk/benefit decisions, and distributing information to stakeholders, with the goal of maintaining drug availability and minimizing risk to patients.

Captain Jensen described how Hurricane Maria destroyed Puerto Rico's pharmaceutical manufacturing infrastructure, exacerbating the drug shortages already being experienced across the US. For example, IV fluid shortages, which began in 2014, were worsened after extensive damage to a Baxter facility during the storm. FDA helped arrange temporary imports from B. Braun and Baxter sites to help resolve these shortages; however, additional capacity for the US market was needed to avoid further shortages. While the overall situation continues to improve, the experience with Hurricane Maria underscored the importance of having clear backup plans in place and working closely with FDA on both short-term and longer-term plans to help lessen the impact of shortages on patients and the health care system as a whole.

Captain Jensen also relayed the experience of one large manufacturer, Pfizer, which reported shortages of emergency syringes and critical drugs, including injectable opioids, resulting from a combination of manufacturing, distribution, and third-party supplier delays, as well as ongoing remediation efforts at one of their facilities. FDA coordinated the efforts of Pfizer and other manufacturers to mitigate the shortage. Approaches included the release of instructions to inspect and withdraw contents with a filter needle before use. Expiration dating was extended for multiple Pfizer products listed on the FDA drug shortage website based on data Pfizer provided to FDA. In addition, FDA expedited review of related applications addressing drug shortages, including new approvals from Westward and Fresenius Kabi, and a temporary import for hydromorphone was initiated by Pfizer.

## Encouraging industry to anticipate and communicate shortages

While FDA is able to advise, assist, and expedite solutions when a drug shortage arises, it is up to the manufacturer to report a problem that may lead to a drug shortage. Under Section 506C of the FD&C Act (2012), manufacturers are required to notify the FDA of “a change in production that is reasonably likely to lead to a reduction in the supply” of a covered drug in the US. This should occur “at least 6 months in advance of...but in no case later than 5 business days after the...interruption in manufacturing occurs.” The FDA asks manufacturers to notify FDA of any change in manufacturing that may lead to a reduction in supply of a product before—not as, or after—they are unable to fill orders or unable to meet expected demand. Changes that may impact drug supply could include plans for facility upgrade or remediation, manufacturing issues, raw material batch failures, particulate issues, or sterility issues. Early notifications of anticipated supply issues by manufacturers has already made a difference: from 2016 to 2017, the number of prevented drug shortages increased from 115 to 145. FDA continues to work closely with manufacturers to identify and address problems in order to prevent future drug shortages.

Though manufacturers are required to notify FDA of supply disruptions, delays, discontinuations, and manufacturing changes that may lead to a drug shortage, FDA cannot require companies to manufacture a drug, increase production, or change how much and to whom a drug is distributed. FDA is looking at ways to encourage manufacturers to develop clear Drug Shortage Plans that identify risks to their supply chain, include better inventories of finished product and raw materials and components, and outline procedures for handling issues that may lead to a shortage. Overall, there is a need for greater capacity for the manufacture of critical drugs, and FDA is recommending redundancy in manufacturing and suppliers, with additional “warm” lines and components and supplies for critical drugs that are at the ready if needed. Finally, better notification procedures must be put in place; some companies and manufacturers still do not provide more than the minimum amount of information or provide information at the last possible minute.

## Looking ahead

In July 2018, FDA Commissioner Gottlieb announced the formation of a new FDA Task Force that would identify long-term solutions for shortages, including potential incentives for quality and increased capacity for manufacturing critical drugs. On November 27, the Task Force hosted a public meeting “Identifying the Root Causes of Drug Shortages and Finding

Enduring Solutions,” to hear directly from all stakeholders—from health care providers and manufacturers to members of the public. Other stakeholder engagement is planned, with the goal of identifying policy changes and other steps that could be implemented to address the causes of drug shortages.

## Conclusions

Shortages of local anesthetics and IV pain management medications continue to pose significant challenges for anesthesiologists that ultimately affect patient care and safety. Several short-term approaches may help mitigate the health risks associated with drug shortages, including monitoring supply, anticipating use, prioritizing use, reducing waste, improving communication, and using safe alternatives. Long-term, larger-scale solutions are urgently needed to anticipate and prevent drug shortages and reduce their impact on the US health care system and patient care—these solutions will require cooperation between federal agencies, suppliers, manufacturers, and industry to improve transparency and communication around anticipated shortages and to strengthen the supply chain and manufacturing infrastructure so that it will be able to withstand external factors that affect drug availability.

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