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January 10, 2019

Dr. Scott Gottlieb
Commissioner
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA-2018-N-3272

Re: Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions; Public Meeting; Request for Comments

Dear Dr. Gottlieb:

On behalf of nearly 38,000 members, the American College of Emergency Physicians (ACEP) appreciates the opportunity to respond to this request for comments on identifying the root causes of drug shortages and developing policies and strategies that may help to prevent or mitigate them. ACEP is deeply grateful for your continued efforts, including the establishment of an interagency task force that is looking into this issue. We have actively participated in the Task Force's public listening sessions and look forward to our continued engagement with the Food and Drug Administration (FDA) and other stakeholders. Our comments below specifically address how drug shortages are affecting emergency physicians and the patients we serve.

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Drug Shortages Impact on Health Care Providers

What economic impacts (including increased inventory management costs, substitution of more expensive drugs for drugs in shortage, and increased liability from adverse events) have health care providers, including veterinarians, experienced because of drug shortages?

The ongoing shortage of life-saving medicines is one of the greatest problems that emergency physicians deal with on a day to day basis. A report from the Government Accountability Office (GAO) from 2014 found that both new shortages and ongoing shortages have increased each year since 2007.[1] As part of the report, the GAO conducted interviews with providers who stated that the shortages led to "delays in or rationing of care, difficulties finding alternative drugs, the risk associated with medication errors, higher costs, reduced time for patient care, and hoarding or stockpiling of drugs in shortage. During a shortage, providers may have to cancel or delay procedures, which can have detrimental health effects on patients. Providers may

[1] United States Government Accountability Office, "Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability," February 2014, https://www.gao.gov/products/GAO-14-194

also have to ration care by prioritizing the patients who have a greater need for the drug."[2] The GAO concluded that the immediate cause of drug shortages was manufacturer production issues related to quality problems, as well as other potential underlying causes specific to the generic sterile injectable product market.[3]

Shortages of commonly-used but essential medications remain an acute problem throughout the health care system, but these shortages tend to disproportionately affect emergency medicine (both hospital and pre-hospital) due to its reliance upon generic medications for rapid sequence intubation, seizures, antidotes, resuscitation, as well as analgesics, antiemetics, and anticoagulants. One study conducted in 2015 found that half of all reported drug shortages from 2002 to 2014 involved acute care drugs used in the emergency department (ED) and that these shortages are increasingly frequent and prolonged.[4] As of June 2017, there are 69 preparations of 28 emergency care medications that are in shortage, including most forms of adenosine, atropine, bicarbonate, calcium, dextrose, dopamine, epinephrine, fentanyl, furosemide, labetalol, magnesium, lorazepam, and paralytic agents.[5] By July of 2018, these shortages peaked at 170 emergency medication preparations and 50 intravenous fluid preparations that were not available. More than 110 drugs for emergency care remain in shortage as of December 2018.

In May 2018, ACEP surveyed its members and found that 9 out of 10 emergency physicians have experienced a drug shortage in the last month. The plurality of the respondents stated that they had experienced shortages with 6 to 10 medicines and nearly 70 percent found that drug shortages in their ED have significantly increased over the last year. Finally, almost all respondents claimed that they had to use an alternative to a medication that was unavailable because of a supply shortage and had to take time away from patients (at a computer, consulting, or coordinating with other experts, etc.) to explore the viability of alternative treatments or medications.[6]

Not only are these shortages severe, but they are also persistent. Drug shortages can last for several months or longer and constitute a significant risk to patients. Patients need access at all times to medications that are used to treat life-threatening conditions. While there is a mostly predictable demand for essential emergency medications, the supply is becoming increasingly unpredictable, and we see every day the impact this has. Not having access to critical life-saving medications and drugs such as local anesthetics, injectable opioids for the treatment of severe acute pain and trauma, anti-nausea drugs, and even sterile IV fluids is disastrous and potentially devastating in terms of patient outcomes. In the ED the difference between life and death, or traumatic pain and relief, can be a matter of minutes and seconds. Patients can't afford delays. There should never be a shortage of essential and life-saving, but simple products such as saline, sodium bicarbonate, and epinephrine.

With respect to the economic impact of drug shortages, the ongoing price increases of certain essential medications also present a major challenge to the budgets of emergency providers, such as emergency medical services (EMS) organizations. For example, a drug that is critically needed for emergency care is naloxone, the rescue medicine for patients that have overdosed on opiates. This frequently-used medication has been employed as a first-line response for opioid overdose treatment for nearly fifty years but has only recently become prohibitively expensive,

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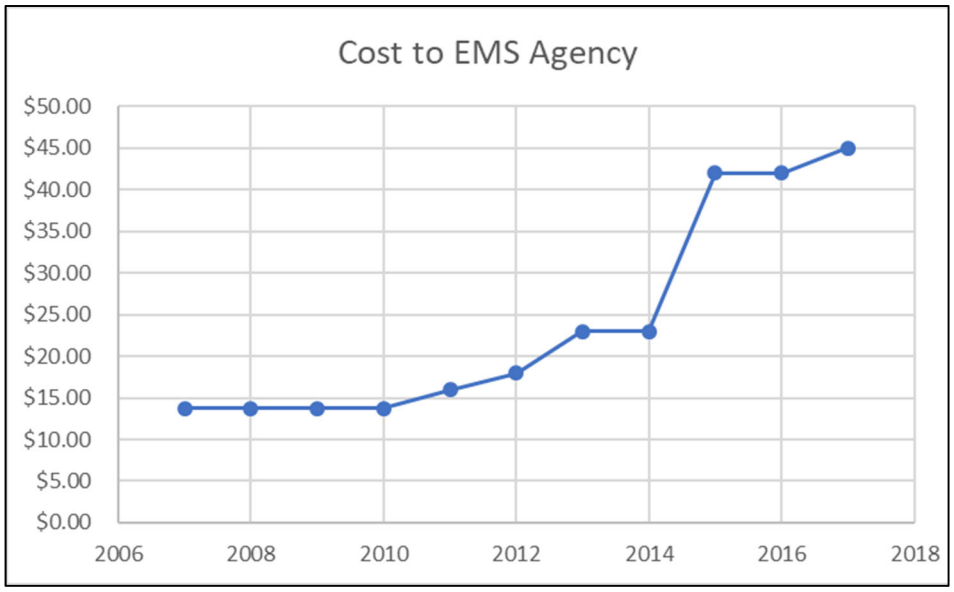
[2] Ibid.
[3] Ibid.
[4] *National Shortages of Drugs Used in the Emergency Department*, 2002-2014, Chen, S.I. et al. Annals of Emergency Medicine , Volume 66 , Issue 4 , S64
[5] ACEP Now, "Emergency Departments Need Plan to Deal with Drug Shortages," Augustine, James J., 2017, August 15, https://www.acepnow.com/article/emergency-departments-need-plan-deal-drug-shortages/?singlepage=1&theme=print-friendly
[6]ACEP New Release, "Most Emergency Physicians Report Hospitals Lack Critical Medicines; Not "Fully Prepared" for Disasters, Mass Casualty Incidents," May 22, 2018, http://newsroom.acep.org/2018-05-22-Most-Emergency-Physicians-Report-Hospitals-Lack-Critical-Medicines-Not-Fully-Prepared-for-Disasters-Mass-Casualty-Incidents

especially at the higher doses now needed to treat many patients with opioid-use disorders. A number of factors may contribute to this particular increase – higher overall rates of opioid overdoses, increased awareness of naloxone as an overdose reversal agent, or even recent state and federal policies enacted to promote co-prescribing of naloxone. Found below is the price history of that medicine over the last ten years from a single emergency provider that has used the same medication supplier for all the years of study:

Naloxone Injection 2mg/2ml Stock number 4750



The combination of limited supply, increasing demand, and rapidly rising prices have a significant impact on emergency patient care. Not only are drug shortages expensive on the front end for providers, but there are serious downstream costs and consequences for patients, as shortages can also increase the risk for errors or contribute to delays in care. Each day in EDs throughout the country there are multiple conversations around what medicines might or might not be available for care. Having to constantly find alternatives to drugs causes emergency providers to take longer to respond to an emergency, and furthermore, staff has to be trained and re-trained on what drugs to use in particular cases, and new processes and protocols have to be created each time a new medication shortage is announced. Overall, there is tremendous frustration for emergency providers, inconvenience and risk for patients, and much higher costs for care.

Drug Shortages' Impact on Patients

What clinical impacts have patients experienced: e.g., adverse events, treatment delays, accelerated disease progression, or worsened outcomes due to patients' to using less effective or less safe alternatives?

Drug shortages seriously jeopardize the safety of our patients. In many cases, medication substitutions often have side effects, are less effective, or do not work at all. In the ACEP study referenced above, more than a third of respondents stated that patient outcomes had been negatively affected (including direct patient harm) by drug shortages. For example, emergency physicians have noted that the shortage of cardiac drugs has had a profound impact on patients. The medicine diltiazem is unique in its ability to help the patient restore their normal heart rhythm in the ED, ensuring the patient can be released home safely. When this medication is unavailable in hospitals, patients often are given less effective medicines, and then require admission to the hospital for a lengthier process of rhythm conversion. The patient stress under these circumstances can be severe, potentially exacerbating

their condition and resulting in less than optimal long-term health outcomes. Further, limitations on repackaging and the need to recalculate the concentration of drugs in shortage may frequently lead to medication errors through dispensing too much or too little of a needed drug, severely impacting patient care.

Identifying the Root Causes and Drivers of Drug Shortages

What factors affect the likelihood, severity, and duration of shortages? Are these factors mostly related to raw materials, management, and resilience of production facilities, or other factors such as contracting or market structure? Do they differ for various drugs?

Reasons for drug shortages cited by the GAO, the FDA, and the Pew Agency for Charitable Trusts, among others, include greater scrutiny and regulatory oversight on the manufacturing process and quality controls, as well as additional factors such as consolidation of manufacturers (especially for generic injectables), low profit margins, shortages of raw materials, absences of redundancy in the supply chain, increased demand, and discontinuations. A 2017 Pew Report on drug shortages for example found that while quality factors are one of the most significant driving factors, it is not the only issue leading to shortages, and that other key factors are market withdrawals, supply chain design, purchaser-manufacturer incentives, limited market insights into future demands, and managing regulatory expectations.[7]

A GAO report published in 2016 also found that two factors were strongly associated with shortages of sterile injectable anti-infective and cardiovascular drugs – a decline in the number of suppliers, and failure of at least one establishment making a drug to comply with manufacturing standards resulting in an FDA warning letter.[8] According to the GAO, this suggests that "…shortages may be triggered by supply disruptions." The GAO report also indicates that a third factor (drugs with sales of a generic version) is associated with shortages, in that low-profit margins for generic drugs mean that "…manufacturers are less likely to increase production, making the market vulnerable to shortages."

Our health care system also recently witnessed how shortcomings in the resiliency of the drug supply chain contribute to the overall drug shortage issue, as shortages are made worse by both man-made and natural disasters. Drug shortages are exacerbated after large-scale events both because of the need for supplies to react to the disaster, as well as the impact, and disruptions disasters can pose to the supply chain and manufacturing of certain drugs, requiring the need to find temporary alternatives to alleviate potentially short-term shortages. The overall effect on our nation's hospitals from Hurricane Maria highlight just how fragile our current system is. Hurricane Maria severely damaged much of Puerto Rico's drug manufacturing industry, and for months after the hurricane hit, hospitals around the country have faced drug shortages, including injectable opioids, because they have no alternatives to acquire certain vital medications. Over time, the FDA has narrowed the list of drugs that are in short supply due to the hurricane, but the recovery effort is still ongoing, and much work still needs to be done to get hospital drug supply levels up to where they should be. However, while supply levels may eventually return to normal, it remains unclear whether the supply chain is resilient enough to mitigate the effects of similar disasters in the future.

[7] The Pew Charitable Trusts, "Drug Shortages An exploration of the relationship between U.S. market forces and sterile injectable pharmaceutical products: Interviews with 10 pharmaceutical companies," January 2017, https://www.pewtrusts.org/-/media/assets/2017/01/drug_shortages.pdf.

[8] United States Government Accountability Office, "Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge," July 2016, https://www.gao.gov/assets/680/678281.pdf.

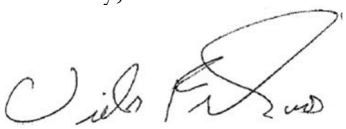
Identifying Strategies for Preventing or Mitigating Drug Shortages

What policies could the Federal Government adopt, and what strategies could it implement, that would reduce the likelihood, severity, and duration of shortages?

As the Federal Government attempts to address this issue, ACEP believes that there are three overarching objectives that agencies must focus upon. These objectives are (1) routine measurement in the way of inventory surveillance, (2) broadly applied transparency as related to manufacturing and distribution practices to ensure adequate competition (including how existing federal laws may affect transparency and competition), (3) flexibility in terms of granting authority to adjust protocols to fit the needs of real-time circumstances, and 4) comprehensive strategies to increase the manufacturing of generic drugs in shortage, especially sterile injectables (such as developing regulatory or process incentives to accelerate the development of new manufacturing sites). Given that there are numerous stakeholders directly involved with the process of drug and medical supply production, distribution, and utilization, we must be strategic and intentional about determining aligned incentives and cooperative initiatives that focus on providing quality patient care.

ACEP appreciates the opportunity to share our comments. We remain hopeful that we can begin to identify the necessary steps to ensure stable, predictable supplies of emergency medications for both every-day operation and disaster preparedness and response. If you have any questions, please contact Jeffrey Davis, ACEP's Director of Regulatory Affairs at jdavis@acep.org.

Sincerely,



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