American Society of Anesthesiologists™

1061 American Lane | Schaumburg, IL 60173-4973 | (847) 825-5586
905 16th Street N.W. | Washington, D.C. 20006 | (202) 289-2222

January 11, 2019

Scott Gottlieb, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: [**Docket No. FDA-2018-N-3272**]; Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions; Public Meeting; Request for Comments

Dear Dr. Gottlieb:

On behalf of the 52,000 members of American Society of Anesthesiologists (ASA), I am writing in response to the above captioned Federal Register Notice and to provide feedback to the Inter-agency Drug Shortages Task Force as they work to develop recommendations to prevent and mitigate drug shortages. Through these comments, ASA will provide recommendations developed by a group of health care organizations and share information collected about physician anesthesiologists' experience with drug shortages.

In 2018, physician anesthesiologists and other health care providers experienced unprecedented drug shortages. Of particular concern to our members are shortages of local anesthetics and injectable opioids, both of which are critical to ensuring anesthesia is administered safely to patients under our care. ASA is pleased the Food and Drug Administration (FDA) recognizes the need to pursue enduring solutions to this public health concern. By responding to lawmakers concerns and forming the Task Force, as well as working with stakeholders, we believe additional actions to prevent and address shortages will be identified.

Historically, ASA has worked with a group of health care organizations to explore ongoing challenges related to drug shortages and identify solutions through periodic meetings. The FDA has been a gracious partner in our efforts and we appreciate the agency's ongoing involvement and attendance in these meetings. Most recently, ASA, along with the American Society of Health System Pharmacists (ASHP), American Hospital Association (AHA), American Society of Clinical Oncology (ASCO) and the Institute for Safe Medication Practices (ISMP), hosted such a meeting on September 20, 2018: "Drug Shortages as a Matter of National Security: Improving the Resilience of the Nation's Healthcare Critical Infrastructure." The discussion at this meeting was robust and the co-conveners were pleased the FDA could take part in the drug shortages summit. Following the meeting, we released 19 recommendations that provide suggestions for regulatory, legislative and marketplace solutions to stem drug shortages (see attachment for full list of recommendations). ASA will highlight some of these recommendations in detail below.

Recommendations to Address Drug Shortages
The 19 recommendations resulting from the September 2018 meeting are not necessarily the consensus of all the groups that attended the meeting, however, they were offered after the day's discussion as potential solutions. A few of ASA's priorities from these recommendations are highlighted here.

Key Regulatory Recommendations

Enhance communication
A large theme from the September meeting was enhancing communication with the entire drug supply chain, including health care providers during, or in advance of, a public health emergency or other event that may create a drug shortage. ASA supports enhancing communication as a key priority to address drug shortages.

As collected from ASA membership, it is clear that our physicians do not always know why there is a drug shortage, and this can perpetuate panic or confusion by providers (the collected information will be discussed in greater detail later). Enhanced communication is important to ensuring everyone in the health care community has the same information and receives that information at the same time. It is especially important that health care providers know what products will be impacted and the expected duration of the impact so that they can plan accordingly.

At the FDA stakeholder listening session in October, as well as the FDA public meeting in December 2018, communication was also highlighted as a top priority, mentioned by multiple parties and panelists presenting. ASA recommends that the FDA develop a notification system to alert all stakeholders simultaneously on drug shortages. We recognize that when all parties are notified at the same time, hoarding of inventory could become a concern. However, to prevent this from becoming an issue, manufacturers could put product on allocation to ensure that remaining supply is distributed equitably.

Streamline regulations
There are multiple competing interests within the regulatory environment that although well-intentioned, do not always accomplish the goals they aim to achieve. For example, manufacturers that have facilities throughout several different countries are faced with meeting the many different requirements of the international regulatory agencies. Manufacturers have stated that this is a challenge. If some of these regulations could be streamlined and aligned with one another, manufacturers might be incentivized to increase production. ASA recommends that the FDA work with other global regulatory bodies to see what might be accomplished to meet this goal. Moreover, this recommendation aligns with the FDA's initiative to harmonize international technical standards for approval of generic drugs.

Another area where there are regulatory burdens impacting drug shortages includes the regulations that govern 503(b) compounding pharmacies. These compounders have stated that it is entirely too costly to ramp up production for only a short time for the duration of a shortage.

ASA recommends that the FDA work with compounders to see how they might incentivize increased production and save on costs.

Key Legislative Recommendations

Assess risk of foreign sourced active pharmaceutical ingredients (API)
It is widely thought that many of the active pharmaceutical ingredients (APIs) that make up the drugs patients depend on come from foreign sources, such as China or India. However, there is a lack of knowledge about any specific details regarding where ingredients come from for certain products and whether this could put the U.S. at an unnecessary disadvantage. The U.S. needs to have the necessary knowledge about API to ensure the country is could procure the necessary ingredients for certain drugs if there is a foreign conflict and those ingredients cannot be obtained from the usual sources.

Relying predominantly on other countries for the necessary ingredients to manufacture crucial drugs could put the U.S. and its patients at risk. ASA recommends that legislation be enacted to require a risk assessment of foreign sourced APIs. The country would be better prepared from a national security standpoint if this was investigated; appropriate plans for ensuring the U.S. is not vulnerable can then be adopted.

GAO study to examine drug supply chain
ASA recommends that the Government Accountability Office (GAO) study drug shortages and the entire drug supply chain. GAO has examined drug shortages in the past and issued reports in 2014, 2015 and 2016. ASA believes it is time to revisit this issue and see if there are any new circumstances or events exacerbating drug shortages.

ASA is aware of groups or individuals that believe drug shortages are caused by Group Purchasing Organizations (GPOs), which negotiate purchasing contracts with drug manufacturers on behalf of hospitals and other health care providers. Yet, the Society is not aware of any independent and reliable data or information that supports this argument. Indeed, despite repeated requests for such data from those identifying GPOs as the cause of drug shortages, no data or information has been forthcoming. ASA enthusiastically supports research or study into GPOs and their impact or lack of impact on drug shortages, as well as other components of the drug supply chain.

In February 2014, GAO released its report, *Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability*, which makes recommendations to help combat drug shortages. The report identifies the trends and causes of drug shortages over the past several years, as well as recommendations for the FDA going forward. The report also addressed the topic of GPOs. Four of the 20 studies mentioned in the report suggested that the operating structure of GPOs results in fewer manufacturers producing generic drugs and this, in turn, contributes to a more fragile supply chain for these drugs. All of the representatives of the three GPOs that GAO contacted for the report, however, disagreed with the claim that GPOs are a cause of shortages. They emphasized that they have an incentive to avoid drug shortages and

ensure that the drug manufacturers with which GPOs contract, can meet GPOs' members' needs. All of the GPO representatives also noted that in recent years, GPOs have instituted strategies to avoid shortages. For example, one GPO representative told GAO that it typically tries to contract with two or more manufacturers for drugs that have a recent history of being in shortage.

To emphasize, the report from 2014 did not provide any concrete data or information to support the argument that GPOs are the cause of drug shortages. Therefore, it would be beneficial to all stakeholders to gather new information on these claims and have this issue resolved. ASA greatly appreciates consideration of this matter.

Key Legislative and Regulatory Recommendations

Ensure manufacturers have contingency/ redundancy plans for production
In September 2017, we saw the impact of a natural disaster on drug shortages when a major hurricane struck Puerto Rico, which houses significant drug manufacturing infrastructure. The result was a shortage of small volume parenteral solution (SVP) products due to production and supply problems on the island. SVP products include saline bags, which are the foundation of basic intravenous (IV) compounding for hundreds of drugs that need further dilution, such as antibiotics, chemotherapy drugs, and electrolytes. They are also frequently used to start IV lines or administer blood.

In addition, we observed the impact of how business decisions, such as mergers, impact drug shortages. The purchase of Hospira by Pfizer, for example, brings to light what can happen during manufacturer and production consolidation. The quality issues that are facing Pfizer in the McPherson plant has greatly impacted access to sterile injectables.

It's clear that manufacturers cannot always predict when a shortage will take place. Such shortages have negative impacts on patient safety and on access to care. Therefore, it is recommended that manufacturers establish contingency plans for a drug shortage, specifically when there are fewer than three manufacturers producing a drug. ASA recommends that incentives be developed for drug manufacturers to have contingency or redundant production plans for their pharmaceutical products, especially if these drugs are identified as "critical." These "back-up plans" should include prioritizing the most medically necessary products, qualifying third party suppliers across networks, and increasing production and inventory for API and finished goods.

Repackage medications (single-dose vials)
Inappropriately sized vials are problematic for physician anesthesiologists and other providers. First, it incentivizes physicians to purchase vials that contain a significant volume beyond a usual or maximum dose. It also results in limited resources and increased costs— contributing to waste and drug shortages. Physician anesthesiologists need prefilled syringes and appropriately sized vials that enable the appropriate dose for administration to a single patient. In turn, this can prevent waste and alleviate drug shortages.

In order to reduce waste and maximize hospital resources, ASA recommends that incentives be created to ensure appropriate-sized vials are available. We urge manufacturers and the FDA to work together to find ways to repackage pharmaceuticals according to the amount of medication commonly used (e.g. only a 30 mL vial of a drug is available when most common volume needed is 5 mL).

Key Market/Non-Legislative or Regulatory Recommendations

Standardize medications
During drug shortages, a big challenge that health care providers face is the need to constantly change the drug concentrations and formulations that are used, as well as the several updates to associated technology. ASA recommends that stakeholders work together to explore standardizing medications. This may entail standardizing medical concentration, containers, and sizes to stabilize pharmaceutical supply and reduce the probability of patient harm. Standardizing products can reduce the risk of adverse drug events when shortage products are substituted and standardizing the concentration of compounded products within organizations can also help provide a critical mass for industry to consider making previously unavailable products available.

ASA is in the process of developing policies around medication concentration standardization. The organization is exploring recommendations around national and local efforts, including which commonly used medications should be standardized. However, in developing these standardizations, ASA cautions federal agencies, manufacturers and other stakeholders to be vigilant and protect against further increasing any drug shortages.

Our organization has also worked with ASHP on their Standardize 4 Safety Initiative, which is an interprofessional effort to standardize medication concentrations in order to reduce errors and improve transitions of care. Working groups have developed proposed standard concentrations that can be adopted locally by individual hospitals and pharmacies.

ASA recognizes that finding a consensus among the multiple specialties regarding standardization is a difficult endeavor. The above-mentioned efforts are a great start but with the support of the Drug Shortages Task Force and a focus on mitigating shortages, ASA believes such a challenge might be more manageable. The Society welcomes the opportunity to explore future initiatives.

Ensure health care provider community can manage drug shortages
ASA recognizes communication as key importance to managing drug shortages. Although this was mentioned as a regulatory recommendation previously, the recommendation in this context now speaks to what can be done before there are shortages and what the community can do together. For example, ensuring hospital staff, health care providers and pharmacies are well equipped with the necessary tools and information can enable successful management of drug shortages. This might entail early notification of predictable medication shortages and medication substitutes, so staff can build the necessary information into communication efforts. For example, hospital and pharmacy teams preparing in advance and technology already

updated or built with the appropriate tools and resources to manage shortages. The medical and specialty organizations can also play a part by ensuring necessary information is built into educational efforts, including national guidelines and continuing education.

Drug Shortages Reported to ASA

As drug shortages grew at the end of 2017 and into 2018, ASA began to hear from members more frequently about problems they were facing with drug shortages in their own practices. To examine whether the drug shortages were really as far reaching and widespread as they seemed, ASA conducted an informal survey of its membership in March 2018. Through administration by an email communication, the organization received 2,272 responses. When asked if they were experiencing drug shortages on a consistent basis, 98.4% of the respondents indicated 'yes.' When asked if the recent drug shortages have affected how they provide patient care, 95.2% indicated 'yes.'

ASA continued to receive reports from concerned members about drug shortages leading up to summer 2018. Members shared their experiences with particular shortages, regularly relaying that bupivacaine or other local anesthetics were the problem and would also share stories about how shortages were impacting patient care. Then-President James Grant, M.D., M.B.A., FASA, wanted to provide ASA members and others with an outlet and a means to collect data on the drug shortages anesthesiologists face. In July, ASA launched a Drug Shortages Registry, where members and others can report shortages and share what they are doing in their practices. Now that the registry has been live for several months, ASA has begun to analyze the data and study if there are any trends. The Society is pleased to share this information with the FDA.

The data collected from the drug shortages registry demonstrates that local anesthetics continue to be the most prevalent shortages for physician anesthesiologists. Narcotics are also reported quite frequently (including fentanyl, hydromorphone, morphine and remifentanil). This is especially troubling as narcotics are a mainstay of physician anesthesiologists' armamentarium for pain control. Shortages of the medications meant to control patients' pain can truly compromise the standard of care and physicians' obligation to their patients. Other shortages reported include a few cardiovascular agents (atropine, hydralazine, dobutamine and labetalol). Finally, another commonly reported shortage is ketamine and some other anti-emetics, non-narcotic analgesics or sedatives. Attached is a complete list of the 53 drugs reported as shortages to the ASA registry from July-December in table format. While there were 357 unique entries over six months, the table includes just the drugs and the frequency for which each drug was reported. Highlighted in the table are the top five shortages reported, which are (in descending order): bupivacaine, lidocaine, hydromorphone (Dilaudid), fentanyl and ketamine.

ASA's Drug Shortages Registry also asks individuals reporting shortages to identify if they know why there is a shortage and what they are doing to accommodate or adjust for shortages. In the majority of instances, those reporting shortages did not know why there was a shortage. In fact, of the 357 unique entries, only 60 reported knowing why there was a shortage. Those that gave a reason for why they thought there was a shortage had varied responses. These answers demonstrate that more needs to be done to communicate with our members and other health

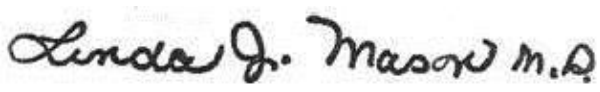
care providers about why there are certain drug shortages. For example, many still thought the shortages were due to facilities impacted by the hurricane (though these were actually associated with the quality issues at the Pfizer plant). Additionally, some individuals reported that the drug shortages were due to "backorders," which might indicate what their hospital pharmacies had communicated or be the result of information received second or thirdhand. Only a minority listed manufacturing or production problems at the factory as the cause for a shortage and even fewer mentioned manufacturer consolidation as a reason. Several other entries indicated "an issue with their supplier," which unfortunately doesn't provide an exact indication of why there is a shortage.

When individuals shared information about what their facility is doing to accommodate or adjust for shortages, the most common answer was "using drug substitutions." Other feedback indicated that many did not know what their facility was doing to accommodate or adjust for shortages. Some indicated that they were "doing nothing" or "conserving/rationing supply." A more troubling response to this question was "postponing surgery." Yet, only four entries provided this response. Though concerning that some shortages are impacting patients and affecting the health care they receive, ASA is glad this is not a more widely reported problem.

Overall, ASA's Drug Shortages Registry has provided valuable insight into what health care providers are experiencing in their practices. While we had hoped to identify regional or state-wide trends with shortages, the information reported did not indicate any clear patterns. The data did confirm that shortages of local anesthetics continue to be the biggest problem for physician anesthesiologists, as well as shortages of narcotics. Additionally, physician anesthesiologists continue to be innovative— performing workarounds, such as using drug substitutions, so that patient care is not impacted by drug shortages. ASA looks forward to continuing to share the information that we collect through the registry with the FDA.

ASA thanks you for your time and consideration of this important issue. As leaders in patient safety, physician anesthesiologists are ready and willing to work with the Task Force to address drug shortages and explore solutions that positively impact patient care. If we may be of assistance in anyway, please do not hesitate to contact Ashley Walton, J.D., ASA's Pain Medicine and Federal Affairs Manager at a.walton@asahq.org or by phone at (202) 289-2222.

Sincerely,



Linda Mason, M.D., FASA
President
American Society of Anesthesiologists

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Drug Shortages Reported to ASA Drug Shortages Registry, July-December 2018

Drug	Frequency Reported
Abciximab	1
Acetaminophen (IV) (Ofirmev)	2
Aminocaproic Acid Injection	5
Atropine	3
Bacteriostatic Sodium Chloride	1
Bupivacaine	83
Butorphanol	1
Calcium gluconate	1
Cefazolin	6
Ciproflox	1
Clindamycin	1
Dexamethasone	2
Dexmedetomidine	1
Diazepam	3
Diphenhydramine	1
Dobutamine	2
Dopamine	3
Edrophonium	2
Ephedrine	2
Epinephrine	2
Etomidate	1
Fentanyl	23
Glycopyrrolate	1
Hydralazine	16
Hydromorphone (Dilaudid)	31
IV Benadryl	2
Ketamine	20
Labetalol	10
Lactated ringers	2

Lidocaine	55
Magnesium	1
Mannitol	1
Mepivacaine	7
Midazolam	2
Mivacurium	2
Morphine	10
Ondansetron Hydrochloride Injection	14
Ophthalmic ointment - refresh/other lubricants	2
Phenylephrine	4
Potassium Hydrochloride Injection	3
Protamine	2
Remifentanil	9
Rocuronium	1
Ropivacaine	5
Scopolamine Patch	3
Sodium Bicarbonate Injection	1
Sterile Water	1
Succinylcholine	1
Sufentanil	1
Tromethamine	1
Valium	1
Vasopressin	1

Drug Shortages as a Matter of National Security: Improving the Resilience of the Nation's Healthcare Critical Infrastructure*

Recommendations from September 20, 2018 Summit:

Regulatory

1. Develop a list of critical drugs. Use the WHO Model Lists of Essential Medicines and other existing resources, as a starting point to define what a shortage is and develop a list of critical drugs needed 1) for emergency response and 2) for saving and preserving life. Using historical data and manufacturing input, address why these drugs have been on the shortage list. The critical list can be used to:
    a. Stabilize the availability of critical drugs by working with manufacturers and the Food and Drug Administration (FDA) to create redundant product in multiple locations in anticipation of natural disasters and other supply chain threats;
    b. Assess the quality of pharmaceutical manufacturers measured against the importance of drugs on the critical list.
    c. Work with the private sector for greater transparency surrounding the source of raw materials and manufacturing locations so providers can more easily assess pharmaceutical product quality. The FDA has proposed a star rating system for pharmaceutical manufacturers, which could increase transparency.

2. Create a multi-stakeholder advisory panel with the FDA to address key issues, such as the possibility of creating a stockpile of critical drugs, the logistics of warehousing such excess pharmaceutical inventory and where the excess inventory should be stored.

3. Enhance communication with the entire drug supply chain, including healthcare providers during, or in advance of, a public health emergency or other event that may create a drug shortage. FDA should provide the health care community with information simultaneously on the type of products that may be impacted and the expected duration of the impact. To prevent hoarding of inventory that could result from such communication, manufacturers could put product on allocation to ensure that remaining supply is distributed equitably.

4. Streamline regulations to incentivize increased manufacturing production.
    a. Compounding regulations: 503(b) outsourcers need incentives to make drugs in short supply; it's costly to ramp up for only a short duration.
    b. Global regulatory environment: there are multiple agencies internationally, all with competing requirements for manufacturers.
    c. Aligns with FDA's initiative to harmonize international technical standards for approval of generic drugs.

5. Engage CMS to discuss the practice of citing hospitals that use medications after the guaranteed stability period in product labeling. This may, for example, address a powder after it is solubilized, which can contribute to unnecessary medical waste.
    a. There are situations where evidence exists in the literature that stability goes well beyond the period of time listed in product labeling. However, CMS/TJC will cite a hospital even though the organization has evaluated this evidence and revised the date based on that. This warrants further discussion with CMS to see what might be needed to avoid or address drug shortage situations.

6. Encourage FDA to consider how reducing the number of unapproved (pre-1938 FD & C) drugs on the market might impact shortages.
    a. FDA has been assisting companies with finding opportunities to legally market older "grandfathered" products that are currently marketed without the required FDA approval. While the FDA approval process ensures that marketed drugs meet current FDA standards for safety, efficacy, quality, and labeling— there have been concerns that these efforts to bring widely used but unapproved drugs into compliance with current FDA requirements have resulted in drug shortages.

Legislative

1. Enact legislation that requires a notification requirement for medical product devices and equipment needed to administer medications, similar to the legislation enacted in 2012 that requires drug manufacturers to notify the Food and Drug Administration "of any changes in production that is reasonably likely to lead to reduction in supply" of a covered drug in the U.S.
    a. E.g. fluid containers to dilute medications for infusion

2. Enact legislation requiring a risk assessment of foreign source active pharmaceutical ingredients (APIs).
    a. Relying predominantly on other countries for the necessary ingredients to manufacture crucial drugs puts the U.S. at risk.

3. Require federal government authorities with jurisdiction over national security to conduct an analysis of domestic drug and medical device manufacturing capability and capacity for critical products to assess whether a threat to national security exists.

4. Require a GAO study to examine all aspects of the drug supply chain to see if there are any new issues exacerbating drug shortages.

Legislative and Regulatory

1. Develop incentives for drug manufacturers to have contingency or redundant production plans for their pharmaceutical products on the critical drug list. The back-up plan should include prioritizing the most medically necessary products, qualifying third party suppliers across their network, and increasing production and inventory for API and finished goods.

2. Investigate developing a system of paying suppliers to hold inventory, perhaps similar to the system employed by the DoD/Defense Logistics Agency. Consider partnering with the DoD to create contractual leverage with drug manufacturers for civilian hospitals.

3. Incentivize manufacturers and work with the FDA to repackage pharmaceuticals according to the amount of medication commonly used to reduce waste (E.g. only a 30 mL vial of a drug is available when most common volume needed is 5 mL).

4. Create an Office of Clinical Affairs within the Drug Enforcement Agency (DEA), so DEA personnel will be available to address the clinical side of medication shortages of controlled substances, rather than just the diversion enforcement aspect.

Market/Non-Legislative or Regulatory

1. Standardize medical concentration, containers, and sizes to stabilize pharmaceutical supply and reduce the probability of patient harm due to constantly needing to change concentrations and associated technology. Standardizing products reduces the risk of adverse drug events when shortage products are substituted. Standardizing the concentration of compounded products within organizations also helps provide a critical mass for industry to consider making previously unavailable products available.

2. Identify tools that address supply access, such as Pfizer's web access tool, which provides information about happenings at Pfizer's facilities, latest product updates and a Q&A forum.

3. Ensure hospital staff, health care providers and pharmacies have capacity to manage drug shortages.
    a. Ensure early notification of predictable medication shortages and medication substitutes so staff can build necessary information into communication efforts.
    b. Work with medical and specialty organizations to ensure necessary information is built into educational efforts, such as national guidelines and continuing education.

4. Examine how changes in United States Pharmacopeia (USP) standards for drugs with a solid historical safety record can affect supply, and whether these changes are necessary.
    a. Consult with USP representatives about pharmaceutical regulations that may lack an evidence base.

5. Request that electronic health record (EHR) vendors make changes to their systems to ease the burden of making drug product changes when a shortage occurs. An example would be some sort of tool that makes changes to various integrated technology databases at the same time (like EHR and smart pump drug libraries, or automated dispensing cabinets and pharmacy inventory systems).

*These are not consensus recommendations as they were offered after the day's discussion as potential policy and marketplace changes that help prevent and mitigate drug shortages. Attendees at the meeting do not necessarily endorse the recommendations brought forth.