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Division of Dockets Management (HFA 305)
Food and Drug Administration
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To Whom It May Concern:

The American Association of Nurse Anesthetists (AANA) welcomes the opportunity to submit comments regarding the experience of Certified Registered Nurse Anesthetists (CRNAs) with drug shortages. The AANA shares the U.S. Food and Drug Administration’s (FDA’s) concern about the persistence and severity of drug shortages and is committed to working in collaboration with the FDA, other healthcare associations, and industry to mitigate and resolve this complex problem that undermines patient safety.

**Background of AANA and CRNAs**

The AANA is the professional association representing nearly 53,000 Certified Registered Nurse Anesthetists (CRNAs) and student registered nurse anesthetists in the United States. Nearly 90 percent of the nation’s nurse anesthetists are members of the AANA. CRNAs are advanced practice registered nurses who personally administer more than 45 million anesthetics to patients each year in the United States. CRNAs provide anesthesia for every type of surgery and procedure across a patient’s life and in some states are the sole anesthesia providers in nearly 100 percent of rural hospitals, affording these medical facilities obstetrical, surgical, trauma stabilization, and pain management capabilities. CRNAs work in every setting in which anesthesia is delivered including hospital surgical suites and obstetrical delivery rooms, ambulatory surgical centers, pain management facilities, the offices of dentists, podiatrists, and specialty surgeons, and U.S. military, Public Health Services, and Department of Veterans Affairs healthcare facilities.

**Comments and Recommendations**

The AANA submits comments and recommendations in response to the following questions posed:

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

**Anesthesia and pain drug shortages.** Anesthesia-related drug shortages, persistent since 2007, have profoundly affected the delivery of quality anesthesia care in the United States, resulting in crisis conditions at many facilities. Generally, drug shortages lead to: increased risk of morbidity and
mortality; delays or cancellations in care; rationing of specific medications and prioritizing patients to receive limited supplies; providing alternative medications that may be less effective; transfer of patients to facilities that have the drugs available; and increased length of hospitalizations.\(^1\)

Anesthesia medications and pain medications are two of the most common classes of drugs affected by shortages, with 85 and 81 percent affected respectively. Examples of drug shortages affecting CRNAs and other anesthesia professionals include benzocaine, hydralazine IV, ipratropium/Atrovent oral inhaler, magnesium IV, ciprofloxacin, diltiazem/Cardizem IV, potassium chloride IV, calcium IV, ondansetron/Zofran IV, ketamine IV, IV opioids (fentanyl, hydromorphone, morphine), propofol (in 2010), lidocaine, bupivacaine, and lorazepam.

The opioid shortage leads to drug rationing and less effective care. The opioid shortage, beginning in the summer 2017, has led to hospitals rationing supplies and reserving them for patients with pain not addressed with non-opioid drugs. For example, opioid shortage rationing has resulted in cancer patients receiving less potent drugs.

New medication protocols increase medication error risks. Due to shortages, facilities and clinicians, including anesthesia professionals, must revise well-understood and established medication protocols and implement new practices that are less familiar, potentially increasing the risk of patient harm stemming from inexperience with technique, variability in patient response, and interaction with other drugs. Medication errors are more likely to occur when a pharmacy must change how a product is ordered, prepared, packaged or dispensed. Often, clinicians must abruptly alter clinical practice with little or no notice for planning and communication. Medication errors include errors of omission, wrong dose dispensed/administered, wrong frequency, wrong route, and wrong indications. Substituting drugs often requires using less familiar drugs with different concentrations and potencies, which increases the risk of medication error.

Substitutions increase side effects, complications, and mortality rate. A study exploring change in clinical practice after the propofol shortage showed that 80 percent of surgical patients received propofol before the shortage. During the shortage, 81 percent of patients received etomidate instead. Etomidate use increased by 600 percent. Although the study did not find increased mortality, it was unknown if this substitution led to adrenal insufficiency or death due to suppression of adrenal steroidogenesis.\(^2\)

Neff, et al examined the use of inhaled agents instead of propofol during the propofol shortage. In the patients that received inhaled agents, the authors found twice the incidence of postanesthesia nausea and vomiting (PONV), greater need for rescue antiemetics, and longer patient stay durations.

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In addition, more patients reported PONV at home (14 percent versus seven percent) and two patients required an unplanned admission or return to the hospital.³

A study of the norepinephrine shortage from July 1, 2008 to June 30, 2013 found increased hospital mortality for patients with septic shock by 3.7 percent with phenylephrine the most commonly used substitution vasopressor.⁴

The replacement of hydromorphone with morphine has resulted in increased side effects. Hydromorphone is commonly used due to fast onset and fewer side effects. Replacing it with morphine leads to increased histamine release and nausea and vomiting. Even morphine is in shortage now, so older drugs, such as meperidine which had been removed from many formularies years ago, are being used.

*The shortage of resuscitation medications, atropine and lidocaine, has led to keeping expired medications in anesthesia carts as a back-up because of a lack of alternatives.* CRNAs are worried that these expired drugs will not be effective or might cause complications, yet they fear the consequences if they do not have these drugs at all.

**Drug omissions due to the drug shortage negatively impact patient care and the patient experience.** CRNAs report that the lidocaine shortage has resulted in patients who receive propofol feeling a burn on induction, leading to patient agitation and stress at precisely the time they should be relaxed and without stress as they undergo sedation or anesthesia. Lidocaine has value in reducing airway irritability.

**Drug substitutions and protocol alteration affects the education of student registered nurse anesthetists.** Student registered nurse anesthetists learn evidence-based practice, incorporating the medications that are best suited for the clinical technique or scenario, during the didactic portion of their nurse anesthesia programs. When they enter their clinical practice rotations, however, due to drug shortages and limited supplies of current or most-widely used medications, students are asked to apply unfamiliar alternatives. This scenario applies to all clinicians in training, including nursing students and medical residents. The persistence of shortages raises concerns about how students are educated and the variability they see when moving from didactic to clinical education. There is value in collaboration between educators, academic institutions and clinical sites to communicate and educate on shortages, their impact, and alternatives for clinical practice.

**How anesthesia professionals mitigate the effects of drug shortages.** In August 2018, the *AANA Journal* article, *Considerations for Management of Bupivacaine Formulation Shortage Affecting Obstetric Anesthesia Services*, addressed interprofessional methods to mitigate anesthesia-related drug shortages. Although this article was precipitated by the bupivacaine shortage, the article’s considerations apply to facility management of all anesthesia-related drug shortages. Recommendations include establishing an interprofessional team to: (1) develop a drug supply

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management policy and procedure outlining how drug shortages will be identified, communicated, and addressed; (2) monitor drug availability and proactively identify and address an anticipated or sudden drug shortage; and (3) educate staff on new practice changes (e.g., selecting and using alternative drug(s) or techniques) and quality improvement data regarding practice changes.

Additional considerations describe safe drug preparation practices, including seeking medications from the facility or compounding pharmacy, and engaging in alternative analgesia and anesthesia strategies, including multimodal obstetric analgesia and, for the bupivacaine shortage, the strategies outlined in the Society for Obstetric Anesthesia and Perinatology (SOAP) Advisory in Response to Shortages for Local Anesthetics in North America.

Do drug shortages affect patients disproportionately by geographic region, age, disease or condition, socioeconomic status, or other factors? Are there specific times of year or classes of drugs that see episodic, more frequent or more severe shortages? If so, why does this happen? Do the adverse consequences of shortages affect providers disproportionately by, for example, geographic region, clinical area, or other characteristics?

Anesthesia professionals face shortages of critical injectables daily regardless of the size of the facility or the location or region where they work. CRNAs report that there are more medications on backorder than they have seen in the past. Generally, CRNAs receive little or no notice of shortages. For example, Pfizer/Hospira has had many emergency drugs on back order, including epinephrine, lidocaine, and atropine. As a result, the FDA has approved extensions of expiration dates. As discussed above, facilities and clinicians ration medications, administer alternative medications, or omit medications that are not available.

For example, a CRNA who administers anesthesia in a urology outpatient clinic reported that after Hurricane Maria, shortages impacted her practice every day. Her clinic faced shortages before the hurricane, but the shortages worsened after the hurricane. For several weeks, they were unable to acquire hydrocodone. Fentanyl was also in short supply. Consequently, they used narcotics sparingly in the operating room (OR); only patients who absolutely needed fentanyl in the postanesthesia care unit (PACU) could have it. This likely resulted in inadequate pain control upon patient awakening and subsequent delay of discharge because post-operative pain was acutely managed in the PACU instead of proactively managed in the OR by CRNAs.

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?

CRNAs report that, to address a backorder, drugs may be purchased from an outside pharmacy that sells them for two to four times the cost. In response to the persistence of these shortages, facilities are increasing stock of necessary drugs, purchasing more expensive brands where necessary, using alternative suppliers or outsourcers, and using the secondary market, all of which substantially increase costs. In addition, extra resources (e.g., personnel, staff time) are necessary to respond to shortages, including communicating with and educating staff on substitutions and alternatives and revising electronic health records and protocols.
What policies could the Federal Government adopt, and what strategies could it implement, that would reduce the likelihood, severity, and duration of shortages? Would additional authorities be necessary or helpful?

The AANA believes the following strategies are helpful and necessary to reduce the likelihood, severity, and duration of shortages. As these alternatives are considered, unintended consequences must also be evaluated:

1. Establish a list of "essential medicines" for use in preventing and mitigating shortages.
2. Modify regulatory policy to help prevent elimination of manufacturers that create a single medication (e.g., neostigmine), which results in significant shortage and increased cost.\(^5\)
3. Provide financial incentives, such as reimbursement policies for additional payments for drugs in/at risk of shortage.
4. Establish ongoing communication between FDA and drug manufacturers to identify potential supply issues early and take steps to prevent or mitigate potential shortages.
5. Identify and inspect foreign sources/manufacturers of medications to decrease the impact of US drug shortages (e.g., during the IV saline solution shortage, the FDA allowed temporary importation of IV fluids from Baxter facilities in Ireland, Australia, Mexico and Canada and from B. Braun in Germany).

Our general recommendations are described below.

**Expanding Supply**

While the AANA will not recite the well-researched economic root causes for this persistent and complex problem (e.g., market practices that lead to market consolidation), we believe the FDA should continue to focus on expanding supply through support of increased number of manufacturers and locating and expediting approval of additional supply sources for each drug. As the FDA cannot force manufacturers to make products, incentives must be considered for increasing the supply of critical drugs, especially generic drugs that may have a low profit margin and continue to remain in shortage.

Few manufacturers and raw material suppliers cannot fulfill the needs of all healthcare professionals and their patients. Increasing competition among manufacturers and suppliers and incentivizing market entry or staying in the market are economic necessities for strengthening the drug supply infrastructure. Quality problems in manufacturing and raw materials are consistent themes in drug shortages, as are disruptions in the supply chain caused by natural disasters. Hurricane Maria alone affected 80 manufacturing facilities that produced seven of the top 10 drugs globally manufactured. Ninety products, including IV normal saline, were affected. These disasters are unlikely to decrease. The U.S. needs to be prepared for these disruptions in the critical drug supply chain.

**Targeting Critical Drugs**

Regulatory action, such as the compilation of a list of high-priority, critical and life-saving drugs for targeted action, is essential to mitigating the impact of drug shortages on those who will suffer most.

The AANA welcomes the opportunity to collaborate in development of this list with the FDA and other stakeholders. These drugs should be continuously monitored. Mitigation plans should be developed in advance of shortages and strategically implemented. Advance notice should be widely distributed and measures to reduce or eliminate hoarding should be developed. Targeted action could include incentivizing manufacturers to create contingency production plans and redundant supply chains.

*Increasing Transparency*

Increasing transparency to identify manufacturers and suppliers, their quality, and anticipated shortages is also necessary to help prevent and mitigate shortages. For example, increased transparency regarding how public health emergencies may affect or are affecting drug shortages is key to allowing healthcare providers to prepare in the safest way possible. The AANA agrees with other stakeholders, such as the American Society of Anesthesiologists and the American Hospital Association, that increased and timely communication from the FDA during a public health crisis (e.g., recent hurricanes) regarding the types of drugs affected and the duration of the anticipated impact will help healthcare facilities and providers evaluate their inventories in preparation for the shortage. Similarly, manufacturers also need to increase transparency regarding impending shortages so that facilities and providers can plan, prepare, and review other options.

Facilities and healthcare professionals that ultimately administer drugs to their patients may lack access to timely basic information, which leads to asymmetric power in the marketplace. Providing and streamlining information about manufacturers of critical drugs will help improve transparency. Such information should include identification of suppliers, manufacturing locations, quality issues and metrics, drug shortage responses, and raw supply sources and locations.

Group purchasing organizations (GPOs) may also be a structural factor, as they represent many hospitals and buy most drugs and supplies used in healthcare facilities. GPOs may enter into exclusive contracts with suppliers in exchange for discounted prices. This may limit competition and the market. Currently, there is very little transparency about GPO practices. To understand how these practices contribute to the economic drivers of the shortage, consider action to increase transparency regarding GPO contracting practices including available doses in the supply chain and facilities.

*Improving Release Date Accuracy*

Drug release dates are also problematic. Some release dates have a year-long range, making it difficult to plan. Requiring more realistic release dates would help facilities and providers prepare and plan their inventories.

*Enhancing FDA Authority*

This crisis is sufficiently urgent, threatening the quality of patient care in this country, that the FDA should seek all authority it needs after evaluating the effectiveness and unintended consequences associated with each option. The 2012 FDA Safety and Innovation Act has not dramatically reduced
the severity and duration of many anesthesia-related shortages or improved the confidence in safe drug supply.

Such enhanced FDA action could include increased FDA staffing, resources, and budget for monitoring and expediting inspecting both manufacturing and compounding facilities.

**Collaborating with Affected Stakeholders**

All stakeholders, including the AANA, must be involved in collaboratives to address the problem and potential solutions. Information exchange among industry, regulatory agencies, GPOs, healthcare facilities and professionals, academic institutions that educate healthcare professionals, and patients is necessary for transparency and effective crisis resolution and prevention of future shortages.

**Summary**

The AANA requests inclusion on stakeholder task forces or advisory panels whenever there is a question related to anesthesia services to address key issues presented by drug shortages. As drug shortages severely impact CRNAs and the patients they serve, CRNAs must have a voice on any panel that seeks to understand how these shortages affect daily care and potential solutions.

The AANA looks forward to collaborating with the FDA and our healthcare colleagues to contribute our knowledge, expertise, and dedication to solving this problem. Thank you for the opportunity to comment and partner with the FDA on this important issue. Please do not hesitate to contact Lynn Reede, DNP, MBA, CRNA, FNAP, Chief Clinical Officer, at (847) 655-1136 or lreede@aana.com for questions, comments, and outreach for future meetings on this topic.

Sincerely,

Garry Brydges, DNP, MBA, ACNP-BC, CRNA, FAAN
AANA President

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