CALIFORNIA HOSPITAL ASSOCIATION

Providing Leadership in Health Policy and Advocacy

November 13, 2018

Scott Gottlieb, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

SUBJECT: Docket No. FDA-2018-N-3272, Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions; Public Meeting; Request for Comments; Federal Register (Vol. 83, No. 175), September 10, 2018

Dear Commissioner Gottlieb:

The California Hospital Association (CHA), representing more than 400 hospitals and health systems, appreciates the opportunity to provide the Food and Drug Administration (FDA) input on the continuing impact of drug shortages within our hospitals. **CHA believes strongly that these continued drug shortages are negatively impacting the quality of patient care. We are very supportive of the FDA's efforts to convene stakeholders on November 27 for a public meeting to identify root causes of drug shortages and find enduring solutions. We offer the following comments and recommendations for consideration and discussion during this meeting.** We hope that providing our initial thoughts and recommendations in advance of the January comment deadline will inform this important dialogue. Moreover, it is critical that the FDA continue to work with congressional leaders, in partnership with all stakeholders, to advance and implement policy recommendations that address this public health crisis.

CHA offers the following comments for your consideration and discussion on November 27.

The California Drug Shortage Experience

Due to current drug shortages, California hospitals continue to experience extensive, widespread operational challenges as well as compromised medication administration safety and reliability. Common and routine drug shortages hospitals have experienced for many years were recently made more acute by the shortage of intravenous (IV) fluid bags after Hurricane Maria in Puerto Rico, as well as the ongoing — and escalating — opioid drug shortage, resulting in part from drug manufacturing quotas imposed by the Drug Enforcement Administration (DEA). **These two events have compromised years of medication safety improvement measures taken by hospitals.**

499 So. Capitol Street SW, Suite 410, Washington, DC 20003 • *Telephone:* 202.488.3740 • *Facsimile:* 202.488.4418
1215 K Street, Suite 800, Sacramento, CA 95814 • *Telephone:* 916.443.7401 • *Facsimile:* 916.552.7596 • www.calhospital.org
Corporate Members: Hospital Council of Northern and Central California, Hospital Association of Southern California, and Hospital Association of San Diego and Imperial Counties

Two influential reports from the Institute of Medicine — *To Err is Human: Building a Safer Health System*, published in 1999, and *Preventing Medication Errors: Quality Chasm Series*, published in 2006 — generated a national agenda for reducing medication errors and accelerated performance improvement activities. **Unfortunately, gains made in recent years have been severely compromised — and in some cases, lost entirely — due to current IV and opioid shortages.**

To Err is Human: Building a Safer Health System identified medication errors as the most common type of error in health care, and attributed several thousand deaths annually to medication-related events. At the urging of the Senate Finance Committee, the United States Congress directed the Centers for Medicare & Medicaid Services (CMS) to contract with the IOM in developing a study that would inform a national agenda for reducing medication errors. That study — *Preventing Medication Errors: Quality Chasm Series* — found that, on average, a hospital patient is subject to at least one medication error per day. Further, the report approximated that 380,000-450,000 preventable adverse drug events occur in hospitals annually. The report also estimated hospital costs for each adverse drug event —an average of $5,857 per event, for an annual cost of $2.3 billion in 1993 dollars. Adjusted for inflation, that cost would have been $3.5 billion in 2006. **In light of the current shortages, CHA is concerned that these numbers have more than likely increased exponentially, particularly given the latest drug shortage events that compromise patient care.**

Based on the recommendations from the IOM studies, California hospitals have invested billions of dollars in technology, labor and performance improvement activities to provide the safest medication administration systems available. In addition, California is one of a few states that require, as part of hospital licensure, facilities to submit extensive Medication Error Reduction Plans that include implementation of technology proven to reduce errors. The California Department of Public Health approves the submitted plans, and each hospital must review and approve the plan annually. Hospitals are surveyed on their plans every three years; penalties are assessed for non-compliance.

Through this extensive and resource-intensive process, California hospitals have meticulously implemented up-to-date information systems, such as electronic prescribing and monitoring technology, automated point-of-care reference information monitoring, comprehensive medication reconciliation and decision support systems. In addition, hospitals have implemented advanced medication administration systems, such as smart IV pumps, and bar code administration systems. **These activities have resulted in marked improvements in the medication administration process through standardization, increased provider and consumer knowledge, and system alerts for near-miss events. Even routine drug shortages have been successfully managed through proactive practices. While routine drug shortages are not new to hospitals and remain a concern, the current shortages affect the medication use process in a profoundly different manner.**

Drug Shortage Impact on Patients and Health Care Providers

Today, medication errors occur at all steps of the medication use process — from procuring the drug itself to prescribing, dispensing and administering it, and monitoring the patient's response. Because routine drug shortages have been occurring since approximately 2000, hospitals have strategically developed backup systems to obtain drug replacements and prevent the drug shortage from affecting the medication administration steps after procurement. **However, the latest drug shortage events have exacerbated existing shortages and are affecting every step of the process — complicating even the simplest or most common medication administration processes.**

For example, hospitals are currently experiencing a shortage of IV bicarbonate, a drug commonly used to treat emergency patients suffering from acidosis. It is stocked on all emergency code carts in every hospital and is packaged in a unique, injectable cartridge so that it may be quickly administered to the patient without requiring it to be diluted or reconstituted. The shortage of this drug and its characteristic packaging, and lack of a perfect replacement "look-alike," forces hospitals to use other substitutes in different types of vials and ampules. In some incidences, another suitable substitution may not be available, requiring the pharmacist to switch to a different dilution or vial than the standard. This requires providers to determine a new drug dosage, note new packaging, educate staff and manipulate doses manually, setting into motion a cascade of potential errors across all steps of the medication administration process. Most concerning, these added steps delay patient care, particularly in emergency situations.

California hospitals report daily frustrations in providing safe, timely and efficient pharmaceutical administration — even after years of meticulous medication safety improvements. These issues have led to deleterious instances of unsafe practices, compromised care and potentially harmful errors and adverse events. While "routine" drug shortages have gone on for years, the recent IV fluid shortage and opioid shortages continue at a disturbing rate. We are alarmed by their impact, which threatens our ability to administer medication in a safe, highly reliable, patient-centric and fiscally responsible manner.

California-Specific Data

In an effort to support the FDA's request for information and additional comments, CHA collaborated with our partners at CHPSO — one of the first, and the largest, patient safety organizations in the nation — in reviewing data from its event reporting database. We also solicited input from pharmacy experts across the state — including California hospital and health system pharmacists, pharmacy staff, nurses, quality improvement directors and direct patient care staff who practice in various hospital settings, like infection control or medical/surgical units, to provide additional examples and qualitative information that add context to this reporting.

Drugs Involved and Frequency of Shortages

Medication shortages were reported across all hospital settings. The highest reported shortages impact emergency care, anesthesia care, critical care, pain management, antibiotic treatment, cardiovascular

care, oncological care and obstetrics/gynecology. The most frequently reported drug shortages include sodium bicarbonate, IV hydralazine, calcium gluconate, lidocaine and IV morphine.

Many of these unavailable drugs are essential to patient care. If they are unavailable and a substitute is used, a ripple effect is felt throughout the medication use process — resulting in increasingly complicated adverse drug reactions.

Errors in the Medication Use Process and Harm Examples

When a provider works with a patient safety organization (PSO) like CHPSO, many long-recognized impediments to successful improvement projects — most notably, provider fear of increased liability — can be overcome. The PSO law provides confidentiality and privilege protections to hospitals when certain requirements are met, eliminating that fear and encouraging reporting to improve performance. In turn, the PSO is able to aggregate confidentially reported data and disseminate it so that others may learn from these events and take action to prevent future events.

Hospitals that are actively engaged with CHPSO report numerous errors, throughout the medication use process, associated with drug shortages. An overview of the most frequently reported errors is provided in the table below.

Most Frequently Cited Errors
1. Pharmacists dispensing medication in vials to patient care units that need to be prepared and administered by front line staff via IV push. Previously, these medications were available in premixed containers or mixed in small volume containers. This is a particular concern for standardized code cart medications that staff know to be in a particular place, in a particular container, with a particular dose.
2. Nurses administering IV push medications rapidly, due to a lack of IV bags with the appropriate volume; smaller volume bags increase the change of rapid infusion, particularly for medications that should be administered more slowly via a syringe pump
3. Nurses or front-line staff diluting or reconstituting medications in saline flush syringes on patient care units due to shortages of normal saline
4. Nurses compounding products that were previously available as premixed solutions or injectables in the pharmacy or operating room
5. Pharmacists providing medications in concentrations that differ from that typically used for direct injectables, or for compounding products according to standardized formulas that are then no longer accurate
6. Nurses and front-line staff receiving different sizes or concentrations of drugs, resulting in extreme waste — particularly with respect to opioid dosages

Despite staff education, continuous performance improvement activities and routine monitoring, errors still occur. Many are a direct result of the drug shortages and the operational challenges hospitals and

health systems face on a daily basis in managing this crisis. Specific examples of medication errors and their impact on patient care and outcomes are detailed below.

Procurement: Errors occur throughout the procurement process, stemming primarily from backorders, inappropriate product allocations and shipping delays. Further errors can occur when providers receive incorrect information from credible resources. For example, a national, credible resource recommended — during the IV bag shortage — that providers give an antibiotic as IV push; this inaccurate information led to patient harm. Patient harm can also result when the product ordered and the product supplied are not **exactly** the same — for instance, ordering Ropivacaine but receiving Ropivacaine 0.2%, which is the same concentration but requires a different volume to be infused in the pump. Providers reported to CHPSO the following specific instances of procurement errors:

- Suppliers did not have IV bicarbonate. As a result, a patient receiving a high dose methotrexate infusion suffered renal failure.
- Suppliers did not have D50 in omnicell, rapid response box and ED cart, nor did they have D10 or 250 ml bags with D10. As a result, providers were unable to procure a drug to assist a hypoglycemic patient.
- Suppliers did not have hyaluronate antidote for vincristine; the patient in this case hemorrhaged.
- A hospital did not have Acyclovir available for a patient with HSV meningitis, causing delay and temporary harm.
- A hospital experienced a shortage of cefepime, resulting in a 24–hour delay in antibiotic treatment for a neutrogenic patient.

Storage/Space: Errors related to storage issues strain the drug supply chain, diverting items from patients in critical need. These often stem from a lack of space, particularly for refrigerated products; inappropriate labels for storage; and hoarding or stockpiling of extra supplies. Specific examples providers reported to CHPSO include:

- The routinely used Ropivacaine infusion was previously intended to be stored at room temperature, but the available product, in a different dosage, is refrigerated. This change resulted in a patient's epidural being paused while the new product was located, because the computer system did not specify "refrigerated" as with other refrigerated medications.
- A lack of storage space led a provider to stack heparin bags side-by-side, leading to a Pyxis machine misfill.
- A cath lab code cart that is normally stocked with two vials of IV bicarbonate had only one available due to shortage. The patient in this instance needed two, resulting in patient code.

Prescribing: Prescribing errors often result from a computer physician order entry (CPOE) system that is not updated, wrong formulation, confusion as to whether a product is preservative-free, substitutions by provider or pharmacy, whether order sets are available, and mistakes in order review and processing. Providers reported to CHPSO the following specific examples:

- Due to a shortage of Labetalol, a different prescription was needed, which resulted in delayed care during an obstetric hypertension crisis.
- Due to a nationwide shortage of .5mg/ml preservative-free morphine, a hospital could only obtain the 2mg/ml preservative-free morphine. This caused dosage confusion between .5mg of the normal dose and 2mg of the non-normal dose.

Preparation and Compounding: Providers experience errors during preparation and compounding due to changes in dose or concentrations, forcing front-line staff to prepare unfamiliar medications; receipt of products in different sizes or concentrations that may require diluting by front-line staff, resulting in more waste if the package is larger than the usual product; and front-line staff's unfamiliarity with alternative medications. For example, errors can occur if a received product is more concentrated or a larger volume than the product the provider typically receives. Specific examples reported to CHPSO include:

- Calcium Chloride, a substitute medication, was improperly diluted and administered in a peripheral line. This led to extravasation and severe patient harm.
- Providers were forced to substitute hydromorphone 1mg/ml vials with hydromorphone 2mg/ml vials in the automated dispensing cabinet. As a result, several patients received double the ordered dose.
- A patient undergoing chemotherapy needed IV bicarbonate but — due to shortages — did not receive the necessary dose. This delay resulted in the patient's increased pH level, increased acidosis and subsequent patient harm.
- Because premixed vials were unavailable in the hospital, staff were forced to compound epinephrine and bupivacaine in a much smaller dose at a 10-fold higher concentration, causing temporary patient harm.

Dispensing: Medication errors related to dispensing procedures typically result from confusion over actual stock versus actual need — especially when providers do not know how long the shortage will last — and confusion, particularly by front-line staff, over drug substitution names. Errors can also occur when code cart stock looks different, or when extra steps must be taken for controlled substance accountability and witnessing of waste for each dose administered. Specific examples reported to CHPSO include:

- A standard dosage of epinephrine was unavailable in a code cart, so a different vial dosage was mistakenly dispensed in a critical case, resulting in patient harm.
- Gentamycin was inaccurately substituted during an erythromycin ointment shortage, causing redness and blistering around the patient's eyes.
- A hospital experienced a shortage of pre-filled duramorph syringes, and staff substituted a different concentration of morphine. In this case, the patient suffered respiratory distress.

Administration: The administration of medications presents its own opportunities for error, usually related to drug compatibility, pump issues, drug library issues, scannable barcode issues, or fast and hard stop overrides. Providers reported to CHPSO the following specific examples:

- Staff provided the wrong dose of sodium acetate, which was substituted during a shortage of sodium bicarbonate, resulting in the patient's renal failure.
- Due to a shortage of routine epinephrine code cart vials, staff were forced to compound a different epinephrine dose during code, causing patient harm.

Other Important Considerations

Interdepartmental Tensions and Process Issues

Drug shortages often require rapid changes in the entire medication safety process — changes that may not reach all staff in a timely manner. Delays in emergency care or with routine standard drug concentrations necessitate that staff perform unfamiliar diluting activities. Unfamiliar substitution containers, particularly in code carts, require staff to dilute or reconstitute, further delaying patient care. Overall frustration with drug shortages, and their resultant process breakdowns, foster interdepartmental tension in hospitals.

Breaches in Drug Purchasing or Allocation Policies

Due to drug shortages, most hospitals report breaches in their drug purchasing or allocation policies. These breaches can include using drugs from emergency carts for non-emergency care, stockpiling excessive amounts of drugs, using override technology on automated drug cabinets despite restrictions, using single dose vials as multiple-dose vials and purchasing sterile products compounded from non-sterile ingredients.

Costs of Drug Shortages

A 2013 survey[1] estimated hospital costs due to shortages at $100,000 each quarter. More than 25 percent of the 1,516 hospital pharmacy directors surveyed reported adding at least one full-time equivalent staff member to manage drug shortages. One large health system reported an annual cost of $5.3 million in drug costs and $570,000 in labor costs, for a total of $5.87 million per year.

Actions to Address Drug Shortages

California hospitals and health systems are committed to reducing drug shortages' impact on patient care and ensuring that patients receive needed treatment. To accomplish those goals, providers have taken innumerable resource-intensive actions, including:

- **Securing and Maintaining Products:** Hospitals report stockpiling drugs, outsourcing drugs, using alternative drugs, and implementing conservation or minimal usage procedures. For critically important drugs, hospitals add backup inventory and purchase excess inventory

[1] Effects On Patient Care Caused by Drug Shortages: A Survey. McLaughlin, M, Thomson, K, et. al, *Journal of Managed Care Pharmacy*, 2013, Nov-Dec;19(9);783-8

from wholesalers; in some cases, they may purchase a more expensive brand, a generic product or a therapeutic alternative. Often, smaller hospitals rely on borrowing or purchasing drugs from another health system. Almost all providers purchase necessary drugs in different concentrations. As noted above, this can lead to operational challenges resulting in preventable errors.

- **Limiting or Extending Drug Use:** Almost all hospitals are rationing or restricting drugs that are in short supply. To do this, they establish criteria, restrict access via override technology on automated dispensing cabinets and provide re-established kits for emergency drug use. Many providers report that they use these drugs outside of their specific labeling to help extend their use — such as keeping expired products, without FDA-extended dating, in code carts. These workarounds result in the unintended consequences of drug shortages — jeopardized patient care.
- **Increasing Communication and Education Processes:** All hospitals are devoting limitless resources to keeping staff — particularly medical staff — informed of drug shortages. Most have deployed drug shortage staff to proactively plan, evaluate and develop communication strategies. These increased costs to the health care system could be avoided with improved policies to address this critical shortage.

Hospitals refine these stopgaps every day to ensure they continue to provide high-quality care. However, this is unsustainable given the increasing frequency of drug shortages. We must work together to address the fundamental causes of these issues. CHA supports recommendations advocated by the American Hospital Association and others, and calls on the FDA to work with Congress to address the gaps in policy that lead to these adverse outcomes.

We urge Congress to:

- **Require manufacturers to provide the FDA with more information on shortages' causes and their expected duration.** Congress should strengthen Title X of the Food and Drug Administration Safety and Innovation Act to include disclosure of the problem causing the interruption and an expected timeline to address it.
- **Require manufacturers to establish contingency plans or redundancies.** Congress should require that manufacturers establish contingency plans to be used in the event of a shortage, specifically when there are fewer than three manufacturers producing a drug.
- **Require manufacturers to be more transparent.** Congress should require manufacturers to disclose to the FDA the production location, including in situations where a contract manufacturer is used.
- **Examine drug shortages as a national security initiative.** Congress should require the U.S. Department of Health and Human Services and the Department of Homeland Security to identify ways that they can support manufacturers and the health care provider community in preparing for and responding to future disasters and other supply disruptions.

- **Ask the Federal Trade Commission (FTC) to include, in its review of drug company merger proposals, the potential risk for drug shortages.** Congress could request that the FTC consider the potential risk for drug shortages when reviewing drug company mergers and acquisitions.

CHA's member hospitals and health systems are committed to utilizing the safest, most reliable medication practices. Unfortunately, we have reached a current tipping point as a result of these shortages, and our ability to provide that level of care is severely affected. While we appreciate the work that many state and government organizations are doing to remedy the situation, we need immediate intervention.

CHA appreciates the opportunity to provide the FDA with our comments and looks forward to participating in the stakeholder discussion on November 27. If you have any questions, please contact me at akeefe@calhospital.org or (202) 488-4688, or my colleague BJ Bartleson, CHA vice president, nursing and clinical services, at bjbartleson@calhospital.org or (916) 552-7537.

Sincerely,

/s/
Alyssa Keefe
Vice President, Federal Regulatory Affairs