REPORT 2 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-11)
National Drug Shortages
(Resolution 504-A-11)
(Reference Committee K)

EXECUTIVE SUMMARY

Objective. To review the historical involvement of the American Medical Association (AMA) in the drug shortage issue, examine recent trends on drug shortages, the explanations for such shortages, and potential solutions that have been advanced to help address this critical problem.

Methods. English-language reports were selected from a PubMed and Google Scholar search from 1999 to August 1, 2011 using the MeSH terms "pharmaceutical preparations," or "generics/economics," in combination with "supply/distribution," and using the text term "drug shortages." Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the U.S. Food and Drug Administration (FDA), American Society of Health-System Pharmacists (ASHP), the Institute for Safe Medication Practices, and from recent presentations on the topic at special organizational meetings at which the AMA was represented.

Results. Two major resources on current drug shortages are available, one maintained by FDA and the other by ASHP. The FDA applies a "medically necessary" filter to drugs appearing on their list. Such shortages have worsened appreciably over the last two years. Compared with 2005, twice as many drug shortages were identified in 2008, and in 2010 almost 180 shortages of medically necessary drugs were identified by the FDA, triple the amount from 2005. Sterile injectables comprise the most common type of shortage, with 74% of the shortages in 2010 involving such preparations, including many older off patent formulations and critical products for use in the acute care setting. The problem has continued to escalate with ASHP reporting more than 200 shortages as of September 15, 2011. The most prominent causes include manufacturing difficulties and regulatory compliance issues; corporate decision leading to product discontinuation; consolidation of the pharmaceutical industry; and raw, bulk, or active pharmaceutical ingredient shortage.

Conclusion. National drug shortages continue to increase, adversely affecting drug therapy and threatening patient care and safety. The existence of a shortage may compromise and delay treatment leading to progression of disease, adverse outcome, or therapeutic failure. With the increased use of less familiar alternative drugs, the potential for errors and preventable adverse drug events is increased. Additionally, costs to the healthcare system are increased both in terms of clinical hours that are diverted to managing drug shortages and increased acquisition costs of alternatives.

The current situation requires a comprehensive solution that includes an early warning system. The FDA, manufacturers, group purchasing organizations, distributors, hospitals, pharmacists, physicians, and other stakeholders should seek to establish more efficient and informative communications on drug product shortages, including timely and advanced warning about imminent shortages and future availability. Manufacturers and distributors should develop standards for allocating existing inventory in a fair and transparent process, and act to deter drug product shortages that may be caused or exacerbated by extremely large orders, hoarding, or "gray market" practices. In accordance with current AMA policy, federal law should be changed to

Action of the AMA House of Delegates 2011 Interim Meeting: Council on Science and Public Health Report 2 Recommendations Adopted as Amended in lieu of Resolutions 924 and 926 and Remainder of Report Filed.

require all manufacturers to provide prior notification to the FDA when any product is going to be discontinued or is anticipated to be in short supply.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 2-I-11

Subject: National Drug Shortages
(Resolution 504-A-11)

Presented by: Lee R. Morisy, MD, Chair

Referred to: Reference Committee K
(D. Robert McCaffree, MD, Chair)

Resolution 504-A-11, "National Drug Shortages," introduced by the Florida Delegation and referred by the House of Delegates asks:

> That our American Medical Association (AMA) evaluate the problem of pharmaceutical shortages in America and report on such shortages to the AMA House of Delegates by the 2012 Annual Meeting, to include but not limited to the role of government regulation, plaintiff lawsuits, pharmaceutical company decisions and any other relevant factors contributing to the pharmaceutical shortage; and
>
> That our AMA make recommendations, based on the findings of the AMA's evaluation of pharmaceutical shortages in America, on ways to prevent pharmaceutical shortages in this country.

Current AMA policy supports legislation that would require all manufacturers of Food and Drug Administration (FDA)-approved prescription drugs to provide public notice to the Agency of any anticipated voluntary or involuntary, permanent or temporary, discontinuation of such products. AMA policy also holds that when such termination or interruption is voluntary (and not due to circumstances beyond the control of the manufacturer), at least six months advance notice of termination or interruption should be required (Policy H-100.965, AMA Policy Database). Current policy also supports an ongoing role for the AMA in working with the federal government and other key stakeholders to develop and implement strategies that will prevent shortages of drugs, vaccines, and other medical products, and that will more effectively resolve shortages when they occur (Policy D-100.989).

This report reviews the historical involvement of the AMA in the drug shortage issue, examines recent trends on drug shortages, the explanations for such shortages, and potential solutions that have been advanced to help address this critical problem. Resources on drug shortages also are identified. In conducting research for this report, no evidence was uncovered that plaintiff lawsuits are, or have been, a significant contributor to the national drug shortage problem.

METHODS

English-language reports were selected from a PubMed and Google Scholar search from 1999 to August 1, 2011 using the MeSH terms "pharmaceutical preparations," or "generics/economics," in

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combination with "supply/distribution," and using the text term "drug shortages." Additional articles were identified by manual review of the references cited in these publications. Further information was obtained from the Internet sites of the U.S. Food and Drug Administration (FDA), American Society of Health-System Pharmacists (ASHP), the Institute for Safe Medication Practices (ISMP), and from recent presentations on the topic at special organizational meetings at which the AMA was represented.

BACKGROUND

The problem of prescription drug shortages initially gained prominence around the year 2000. The AMA first addressed this issue with a Board of Trustees Report at the 2001 Interim Meeting calling for the establishment of a Health and Human Services (HHS) Task Force to explore the causes of drug, diagnostic agent, and vaccine shortages and to identify appropriate solutions to these problems so that the health of the public is adequately protected (Policy D-100.993).[1] The AMA also previously urged the FDA to expand its list of "medically necessary products" (see below) and to more effectively monitor production, inventory, and planned cessation of such products. The AMA also recognizes the need to educate physicians on how to report potential drug and vaccine shortages to the FDA and to establish an effective means to communicate information about drug and vaccine shortages in a timely manner, including information about alternative therapies, to physicians.

The AMA and ASHP first addressed the occurrence of drug shortages nearly a decade ago by jointly convening a special meeting of key FDA officials and representatives of the pharmaceutical industry, drug distributors, group purchasing organizations, the American Hospital Association, the Institute of Medicine, and the Department of Veterans Affairs to examine drug product shortages and to make recommendations on how to address this problem.[2] Thirty-three potential solutions were promulgated comprising the categories of communication, manufacturing, distribution and inventory management, regulation and enforcement, economic incentives, and research and study. A summary of the provisional observations of this meeting and the potential solutions was published in November 2002.[3] Around this time, ASHP entered into an agreement with the University of Utah Drug Information Service to use shortage bulletins developed by the Service to maintain an electronic resource on drug shortages that could help address pharmacists' and other healthcare professionals' requests for information and guidance.

Subsequently (and comporting with existing AMA policy), the AMA and ASHP met with high-ranking FDA and HHS officials in 2003 to propose an HHS/FDA workshop, including all key stakeholders, to prioritize strategies for improving the market dynamics for prescription drugs in order to reduce shortages and improve the management of patients when shortages occur. The AMA and ASHP convened a follow-up meeting in March 2004 to discuss next steps; included in the discussion was a draft guidance developed by the Healthcare Distribution Management Association on "Ensuring Product Availability – A Recommended Voluntary Industry Guideline," which offered recommendations that could assist in mitigating year-end shortages.[4] Unfortunately, the proposed HHS/FDA workshop never took place, and the drug shortage problem has worsened, dramatically so over the last few years.

FEDERAL REGULATIONS PERTINENT TO DRUG SHORTAGES

Definitions

Drug discontinuation is a "situation in which a drug is no longer being commercially distributed by an FDA-regulated manufacturer whether or not a formal withdrawal request or notification has

been made to the FDA."[5] Formal notice to the FDA of the discontinuation of sole-source, medically necessary products is required under Section 506C of the Federal Food, Drug, and Cosmetic Act. The FDA defines medically necessary drugs "as products that are used to treat or prevent a serious disease or medical condition for which there is no other source or alternative therapy available in adequate quantity and that is judged to be an acceptable substitute." The FDA cannot force a manufacturer to produce a product and companies are not required to report plans to discontinue a product unless they are the sole manufacturer of a drug that is life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition (21 CFR 314.81) even though no legal penalty exists if the company chooses not to report the discontinuation.

According to the FDA, a drug shortage is "a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the user level."[5] Recommended procedures for notification, evaluation, and management of drug shortage situations including investigational and new drugs, biologics, and generic equivalents are available.[5] The ASHP defines a drug shortage as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent."[6]

DRUG SHORTAGE INFORMATION

Food and Drug Administration

Drug Shortages. The FDA drug shortages website provides information on shortages and limited distribution of medically necessary drugs.[7] It includes information about the specific drug, the reason for the shortage, and the manufacturer's anticipated date of availability. FDA also posts press releases and other notices of recalls from the firms involved. The drug shortage information on the FDA website is provided voluntarily by manufacturers. FDA cannot require firms to report the reason for a shortage, the anticipated duration of the shortage, or any other information about shortages. As of September 15, 2011 the FDA drug shortage site listed 71 drugs. A list of resolved drug shortages and drugs to be discontinued also is maintained on this site.

Biologic Shortages. A separate FDA website contains information on biologic shortages.[8] As of September 15, 2011, eight biologics were in short supply including immune globulin, black widow spider antivenin, hepatitis A & B, haemophilus, herpes zoster, and rubella vaccines.

American Society of Health-System Pharmacists

The ASHP maintains a Drug Product Shortages Management Resource Center on its website.[9] The "Drug Shortages Resource Center" is the most current, as well as the most comprehensive drug shortage information service. The Center maintains a current list of drug shortages, as well as resolved drug shortages and discontinued drugs. Each drug shortage monograph includes the product(s) affected, the reason(s) for the shortage (when known), and estimated resupply dates. ASHP evaluates the implications of the shortage for patient care and provides recommendations on alternative agents and management with supporting references and documentation. As of September 15, 2011 the Resource Center listed 209 different drug shortages. ASHP also has developed guidelines on managing drug product shortages in hospitals and health systems, including a detailed algorithm which may be used to improve the organizational response to drug shortages.[10]

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC) maintains a vaccine shortage webpage that contains the latest national information about vaccine supplies. The site provides guidance to healthcare providers who are facing vaccine shortages or delays only for vaccines that are included on the recommended childhood and adolescent immunization schedule.[11] As of August 1, the CDC's "Current Vaccine Shortages and Delays" website listed 5 vaccines in short supply.

CURRENT TRENDS IN DRUG SHORTAGES

Shortages of medically necessary drugs have worsened appreciably over the last two years. Compared with 2005, twice as many drug shortages were identified in 2008, and in 2010 almost 180 shortages of medically necessary drugs were identified by the FDA, triple the amount from 2005.[12] Sterile injectables comprise the most common type of pharmaceutical shortage, with 74% of the shortages in 2010 involving such preparations, including many older off patent formulations and critical use products in the acute care setting.

In 2010 many critical drugs (based on the FDA's medically necessary classification) were in short supply. Drug classes that experienced more than 10 shortages included central nervous system agents (28); antineoplastics (20); anti-infectives (19); electrolyte solutions (17); cardiovascular medications (14); autonomic nervous system drugs (13); eye, ear, nose and throat preparations (13); and hormone-based therapies (11).[12]

In 2010, the ASHP identified 211 drug shortages; the list maintained by ASHP includes all shortages and does not consider a "medically necessary" filter. Already in 2011 as noted above, ASHP has reported 209 drug shortages nationally through September 15, indicating substantial and continued worsening of the drug shortage problem.[13] Overall, the majority of drug shortages involve generic products.

GENERAL CAUSES OF SHORTAGES

Many root causes of shortages exist, virtually all of which are remote from AMA influence.[3,10,12-15] The lack of FDA authority to require notification of impending drug shortages or product discontinuation (except for sole-source manufacturers of medically necessary products) is a contributing factor. Shortages vary on a regional basis depending on the wholesaler, local competition, patient population, and general purchasing operations. Shortages can be the result of one or a combination of factors throughout the supply chain, including sources of raw materials, manufacturing issues, regulatory compliance, wholesaler or distributor behavior, prime vendors and group purchasing organization practices, and extended purchasing or hoarding involving end-user healthcare systems. The most common causes of national drug shortages include:

(1) Manufacturing difficulties and regulatory compliance issues.

Companies are required to conform to good manufacturing processes to stay in operation. These processes may change over time and, due to resource constraints, FDA inspections can be intermittent or sporadic. When a company is judged to be in noncompliance, remediation efforts can be lengthy, thereby creating shortages or eventually lead to a business decision to discontinue production because of the investment that would be required to bring the production facility into FDA compliance. When sole source manufacturing is in place, the stakes are heightened. In 2010, more than 40% of sterile injectable shortages were due to product quality issues, including the presence of particulates or impurities, microbial contamination, and stability concerns.[16] As noted

above, fewer firms are making sterile injectables. Generally, such products are not economically attractive, so when one firm has problems or discontinues a product, shortages almost always occur.

In some cases, recalls may precipitate a shortage and create immediate emergencies for clinical care. Changes in a product's formulation, reliance on a new raw material or source for the active ingredient, or switching to a new manufacturing site can substantially delay product availability, particularly for generic drugs. When such changes occur for generic products, the company must submit a new Abbreviated New Drug Application (ANDA) for review and approval by the FDA. ANDAs are required, of course, for new generics as well. Uncertainties about the review times for these applications can affect company planning at the manufacturing level. These factors are especially relevant given that the majority of drug shortages comprise generic products.

For controlled substances, annual quotas are established by the DEA for each manufacturer, which can interfere with efforts to increase production if, for example, another company making the same product experiences difficulties. In some cases, certain drugs that were approved prior to 1938 and have changed their labeling, or drugs that were initially approved between 1938 and 1962 based on safety assessments alone, may represent "unapproved drugs." When such a status is recognized and acted on by the FDA, this can create shortages or uncertainty in the market for these products (e.g., concentrated oral morphine solution).

(2) Corporate decisions leading to product discontinuation or decreased production.

Business decisions to discontinue a product or reallocate resources to other products can create shortages. Such decisions may be prompted by a lack of profitability or the specter of additional costs to re-establish good manufacturing practices in response to violations. Contemporary business models also may rely on tighter or "just-in-time" inventories of raw materials, excipients, and/or finished products. These practices, as well as existing contractural agreements with wholesalers and group purchasing organizations serving larger hospitals and healthcare systems, can create regional shortages. Overall, supply chains are more fragile, which places certain sites of care (e.g., ambulatory infusion centers, small or rural facilities) at greater risk of experiencing a shortage.

(3) Consolidation of the pharmaceutical industry.

Mergers and acquisitions in the pharmaceutical industry have been followed by a decline in the new drug pipeline. With the advent of the Prescription Drug User Fee Act in 1992 and a robust industry presence, an average of 31 drugs were approved annually in the 1990s (with a high water mark of 54 approved in 1996) compared with an average of 24 new drugs annually in the following decade. In fact, many of the companies that developed drugs in the mid-1990s no longer exist. Accordingly, only a few manufacturers of sterile injections exist. Additionally, the same production lines in one facility may be used for multiple items; reallocation of lines to produce more profitable (or new) drugs at the expense of older generics can cause shortages. Consolidation also has resulted in fewer suppliers and the migration of manufacturing to foreign sites.

(4) Raw, bulk material or active pharmaceutical ingredient shortage.

Shortages in raw materials or active pharmaceutical ingredients can affect multiple manufacturers leading to simultaneous manufacturing difficulties. Approximately 80% of such materials for prescription drug production come from outside the U.S.[10] Hostilities, political instability, disease

in farm animals, poor crop yields, or unstable storage or transport conditions can sometimes reduce available product.[10]

Overall Assessment of the Reasons for Drug Shortages

According to the Utah Drug Information Service, the reasons for overall drug shortages in 2010 were most often manufacturing/production issues and supply/demand factors.[12] Shortages due to the unavailability of raw materials or regulatory enforcement were infrequent. However, nearly half the time, reasons were not explained or identified. With respect to sterile injectable shortages in 2010, the FDA reports that 45% were due to product quality issues; 18% due to discontinuation; 17% due to delays or capacity issues; 8% due to raw material shortage; 5% due to loss of manufacturing site; 4% due to component problems/shortage; and 3% due to increased demand because of another drug shortage.[12]

IMPACTS OF DRUG SHORTAGES

The prevalence of drug shortages prompted U.S. hospitals to spend at least $200 million more a year on substitutes in 2010, according to a study of 228 hospitals, retail pharmacies, and other care facilities by Premier Healthcare Alliance, a purchasing agent for hospitals.[16] This estimate does not include added labor costs for managing shortages or ensuring safety and mitigating patient risk. Nearly 90% of the hospitals reported a drug shortage in the second half of 2010 that either: (1) caused a patient safety issue; (2) resulted in the delay or cancellation of a procedure; (3) required more expensive substitutes; or (4) resulted in a pharmacist having to compound a drug formulation. According to Premier, more than 240 drugs were in short supply or completely unavailable in 2010, and more than 400 generic drugs were back-ordered for five or more days.[16] According to the Premier analysis, the "annualized financial impact of drug shortages where generic equivalents are available exceeds $78 million," with the majority of the financial impact occurring within the acute care sector affecting principally infectious disease, surgery, and oncology.[16]

Three additional recent surveys confirm the substantial effects of drug shortages on patient safety and welfare, hospital costs, and resource utilization. A 2010 survey of more than 1,800 healthcare practitioners (two-thirds pharmacists) conducted by the Institute for Safe Medication Practices (ISMP) evaluated various difficulties associated with drug shortages.[15] Alarmingly, more than 80% of the time, drug shortages occurred without advance warning and information was lacking about the cause or expected duration of the shortage. Not surprisingly, physicians and other end users are often angered by these developments. Substantial resources are expended and significant costs (unspecified in this survey) are associated with developing a plan of action and obtaining suitable alternatives, which themselves may be lacking up to 70% of the time. Alternative medications may be less efficacious or also become depleted and in short supply. Additionally, because of unfamiliarity, the use of alternatives increases the probability of errors or adverse patient outcomes. Nearly two-thirds of the respondents in the ISMP survey reported patient outcomes had been adversely affected and near misses were more common. A number of such occurrences involving shortages of propofol, various neuromuscular blocking agents, morphine, epinephrine, heparin, fosphenytoin, several chemotherapy drugs, and various intravenous antibiotics have been detailed (See Table 1).[15]

A survey conducted by ASHP in collaboration with the University of Michigan Health System evaluated the personnel resources required to manage drug shortages in healthcare systems in the U.S.[17] On average, hospital pharmacists spend 9 hours per week gathering details, identifying alternatives, managing inventory, communicating information, and managing information or data systems related to drug shortages at an estimated annual labor cost of $216 million. Larger

institutions suffer more shortages. In 2010, 47% of institutions with ≥400 beds experienced more than 30 shortages. At the time this survey was administered, more than 80% of hospitals were in short supply of succinylcholine, dextrose 50% syringes, and epinephrine 1 mg/ml injection. One in ten hospitals were experiencing shortages of the anticancer drugs idarubicin and foscarnet, and 50% were experiencing a shortage of midazolam 1 mg/ml injection.

A survey of 820 non-federal, short-term acute care community hospitals conducted in June 2011 by the American Hospital Association revealed that 44% of hospitals experienced ≥21 drug shortages across various treatment categories.[18] The most common categories were surgery/anesthesia, emergency care, cardiovascular medicine, gastrointestinal/nutrition services, pain management, infectious disease, and oncology. Four out of five hospitals had to delay patient treatment, and more than half were not able to provide the patients with the recommended treatment in some cases. Accordingly, 75% of hospitals required rationing of drugs in short supply; virtually all hospitals reported increased drug acquisition costs as a result of drug shortages. The actual financial impact was not evaluated but the existence of a shortage forces the hospital to purchase excess inventory or a more expensive product or therapeutic alternate from outsourcing companies or a new distributor. In nearly half of the hospitals surveyed, drug shortages occurred daily. Generally, little or no advance warning of an impending drug shortage is forthcoming and substantive information often is lacking on the cause of the shortage and its expected duration. As one might expect, these continuing and serious shortages strain relationships among the medical staff, pharmacy, and hospital leadership.

Stockpiling and Gray Market Distributors

No hospital or healthcare facility wants to be in a position of experiencing a drug shortage. Accordingly, attempting to identify impending shortages and then stockpiling by submitting larger than regular orders occurs. Specialty licensed distributors or brokers that normally serve a very small niche may emerge and contribute to the so-called “gray-market” during times of shortages by acquiring available supplies and then redistributing/reselling the product at inflated prices (and sometimes via multiple steps) to end users who have been unable to procure the product through their normal suppliers.

SOLUTIONS

The Role of FDA and the Pharmaceutical Industry

Prompt notification from manufacturers is important for all shortage situations. Early notification increases the probability that the shortage issue can be prevented or resolved in a timely manner. Approximately 28 shortages were averted in 2010 because of early warnings to the FDA.[12] On the manufacturing side, companies must have an enduring commitment to quality and engage in redundancy/stockpiling of key manufacturing supplies and inventory. When manufacturing/quality problems are identified, the FDA should work with the company to expedite certain issues (e.g., new manufacturing site, production lines or manufacturer, changes in specifications, new raw material source or shortage, lengthen expiration dates). In some cases, discretion may be employed to address shortages of medically necessary drugs to mitigate significant risks to patients. If other firms also are manufacturing the product, they can be encouraged to increase production. Facilitation of importation from foreign sources also may be necessary on a temporary basis (e.g., propofol, foscarnet, ethiodol).

At an FDA-sponsored public hearing on drug shortages conducted on September 26th, 2011, agency staff revealed that 99 shortages had been averted already in 2011 because of early warnings

from manufacturers and collaborative efforts between the FDA and the manufacturer to resolve issues and maintain production capacity. These success stories demonstrate the importance of better communication and expedited solutions. In addition to the September 2011 public hearing, the agency is expected to release a report in the near future which provides further analysis of the drug shortage problem and recommendations with respect to its role in mitigating shortages.

Drug Shortage Summit

In an effort to better address the contemporary surge in drug shortages, ASHP, the American Society of Anesthesiologists, the American Society of Clinical Oncology, and the ISMP convened a drug shortages summit in November 2010.[14] A suite of 19 recommendations emerged involving regulatory and legislative factors, raw materials and manufacturing, business and market factors, and distribution. Many of these mirror the recommendations that surfaced nearly a decade ago when the AMA and ASHP convened the first summit. The recommendations for addressing drug shortages emanating from the November 2010 summit are available in Table 2.

Legislative Approaches

Two versions of the Preserving Access to Life Saving Medications Act (H.R. 2245 and S. 296) would address certain factors that contribute to drug shortages. Both versions would require all drug manufacturers to notify the FDA: (1) about manufacturing problems or anticipated shortages as soon they become aware of a problem; and (2) provide notification at least 6 months in advance when any drug is to be discontinued. Both bills also require the FDA to maintain a website listing drugs in shortage situations. The House version defines drug shortage as a "period of time when the total supply of such drug available at the user level will not meet the demand for such drug at the user level" and would establish civil monetary penalties for noncompliance. The Senate version would revise the FDA definition of "medically necessary" and attempt to develop a new, evidenced-based metric for predicting or identifying drugs that are vulnerable to a shortage.

SUMMARY

National drug shortages continue to increase, adversely affecting drug therapy and threatening patient care and safety. The existence of a shortage may compromise and delay treatment leading to progression of disease, adverse outcome, or therapeutic failure. With the increased use of less familiar alternative drugs, the potential for errors and preventable adverse drug events is increased. Additionally, costs to the healthcare system are increased both in terms of clinical hours that are diverted to managing drug shortages and increased acquisition costs of alternatives.

The current situation requires a comprehensive solution that includes an early warning system. Accordingly, the FDA, manufacturers, group purchasing organizations, distributors, hospitals, pharmacists, physicians, and other stakeholders should seek to establish more efficient and informative communications on drug product shortages, including timely and advanced warning about imminent shortages and future availability. Pharmacists, physicians, and other prescribers should be encouraged to report suspected drug shortages. Manufacturers and distributors should develop standards for allocating existing inventory in a fair and transparent process, and act to deter drug product shortages that may be caused or exacerbated by extremely large orders, hoarding, or "gray market" practices. In accordance with current AMA policy, federal law should be changed to develop a mechanism and framework for all manufacturers to report impending supply disruptions and discontinuation of drugs.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted in lieu of Resolution 504-A-11 and the remainder of the report be filed.

1. That our American Medical Association (AMA) support the recommendations of the 2010 Drug Shortage Summit convened by the American Society of Health System Pharmacists, American Society of Anesthesiologists, American Society of Clinical Oncologists and the Institute for Safe Medication Practices and work in a collaborative fashion with these and other stakeholders to implement these recommendations in an urgent fashion.~~.~~ (New HOD Policy)

2. That our AMA support drug shortage legislation such as H.R. 2245 and S. 296 that would require manufacturers, including those who share the market with others, to notify the FDA of any discontinuance, interruption, or adjustment in the manufacture of a drug that may result in a shortage. (Directive to Take Action)

3. That our AMA express appreciation to the President of the United States for issuing an Executive Order intended to assist in mitigationg ongoing drug shortages. (Directive to Take Action)

4. That our AMA advocate that the US Food and Drug Administration and/or Congress require drug manufacturers to establish a plan for continuity of supply of vital and life-sustaining medications and vaccines to avoid production shortages whenever possible. (Directive to Take Action)

5. That the Council on Science and Public Health report back at the 2012 Annual Meeting on efforts to mitigate drug shortages, including the evaluation of potential economic and regulatory factors that may contribute to drug shortages, especially with respect to oncologic drugs. (Directive to Take Action)

6. That our American Medical Association publicly declare the problem of unsafe and unverifiable medicines and medicine shortages a national public health emergency. (New HOD Policy)

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Table 1. Examples of Near Misses, Errors, and Adverse Outcomes Associated with Drug Shortages.[15]

Drug	Consequence
Propofol	• Wrong dosing rates used with dexmedetomidine or midazolam (alternative) leading to overdose. • A paralyzed, ventilated patient received no sedation because propofol was unavailable. • Difficulty extubating patients due to residual effects of lorazepam. • Unnecessary use of general anesthesia for procedures that would normally be accomplished with propofol. • Inadequate sedation with alternative agents led to agitation and self-extubation.
Neuromuscular Blockers	• Several patients given the wrong dose or infusion rate of alternative agent. • Early extubation due to shorter duration with alternative agent. • Cancellation of surgeries and procedures. • Patients developed rocuronium-induced pulmonary hypertension when preferred agents were unavailable.
Morphine	• Intravenous hydromorphone prescribed at the intended dose for morphine resulting in the death of two patients. • Misfilled an automated dispensing cabinet pocket for 2 mg morphine vials with 10 mg vials. • Administered 10 mg (10 mg/ml) instead of 1 mg (1 mg/mL); patient required naloxone and was transferred to critical care. • Increased incidence of drug diversion because pharmacy-prepared syringes of morphine and hydromorphone are less tamper-resistant than commercial forms.
Epinephrine	• Unable to keep up with the demand for epinephrine doses during a code (because each 1:1000 ampule needed to be diluted) patient died from 10-fold overdose of epinephrine when solution was administered undiluted. • Epinephrine with an intra-cardiac needle was needed but not available during a code; the cart had been stocked with epinephrine 1:10,000 prefilled syringes (no cardiac needle) from a compounding company.
Heparin	• Intravenous heparin was administered instead of magnesium during a code because the 10,000 U/ml heparin vials purchased to replace the 5,000 U/ml vials looked similar to magnesium vials. • Heparin bags prepared in the pharmacy look similar to other pharmacy admixtures; heparin was administered over 90 minutes instead of vancomycin, and azithromycin was administered instead of heparin. • Vials containing the wrong strength of heparin were stocked in automated dispensing cabinet leading to dosing errors.
Chemotherapy	• Cytarabine dosing error occurred when a pharmacist used a mixing protocol applicable to the usual 500 mg vials (50 mg/ml) not available but was actually using an alternative strength 1,000 mg vial. • Pre-diluted methotrexate was unavailable; a vial of drug power was reconstituted incorrectly so patient received too small a dose. • Intravenous etoposide was converted to oral dosing but the prescriber was not aware that the oral dose needed to be double the intravenous dose. • Several cases exist where chemotherapy treatments were delayed or had to be modified to less than optimal regimens due to shortages
Antibiotics	• A patient with a *Pseudomonas* infection sensitive only to amikacin died when the drug was unavailable. • Clinically significant delays in treating patients with *Pneumocystosis carinii* pneumonia due to Bactrim shortage. • A patient with viral meningitis had to be transported to another hospital because intravenous acyclovir was not available.

Table 2. Potential Solutions to Address National Drug Shortages.[14]

Regulatory and Legislative factors
1. Explore expanding FDA authority to require manufacturer notification of market withdrawals (e.g., notification required 9 to 12 months prior to planned market exit). 2. Evaluate the current FDA definition of medically necessary, including the established criteria and responsible party for making this determination, to assess the need for increased FDA statutory authority in this area. 3. Define and implement evidence-based and other criteria for identifying critical drug therapies that are vulnerable to drug shortages. Criteria might include factors such as availability of therapeutic alternatives, supply chain characteristics, and other elements that determine products' vulnerability for shortages. 4. Explore providing incentives (e.g., tax credits) to manufacturers that produce critical drug products or upgrade manufacturing plants to meet or exceed Good Manufacturing Practices (GMP) in exchange for guarantee of continued production of these therapies. 5. Require confidential notification of FDA when there is a single API or manufacturing source. Notification would also apply to informing FDA of an interruption in the supply of raw materials, API, or manufacturing processes. 6. Explore reauthorization of Prescription Drug User Fee Act (PDUFA) as a mechanism to establish a modified/reduced user fee program for generic drugs, which would provide FDA additional resources to support prioritization and expedited review of supplemental applications and ANDA. Intent of user fee program would be to provide more timely approval of applications and incentivize manufacturers to enter market based on increased ability to plan production schedules. 7. Establish an expedited approval pathway for those unapproved drugs (i.e., pre-1938 therapies) that are deemed critical therapies. In addition, reduce or eliminate the current NDA user fee that is required for these products. Incentives could also be considered. 8. Assess the need to establish or enhance use of existing processes to expedite approval of ANDA, supplemental applications (e.g., alternate source API), and new or altered production lines for drugs in short supply. In addition, advocate for additional FDA resources to minimize wait time for approval of these applications. 9. Evaluate processes for new product specifications (e.g., USP standards), including appropriateness of timeline for implementation. (Note: Invite USP to participate in these discussions). 10. Increase collaboration with industry, DEA, and FDA to establish a process that would more readily modify API quotas in response to drug shortages of controlled substances. 11. Establish improved processes to extend product stability for products in short supply. 12. Require manufacturing redundancies (e.g., multiple manufacturing sites for a sole product or multiple API sources, when available) as part of the FDA approval process. (This recommendation also listed under Raw Materials Sourcing and Manufacturing Factors as a voluntary action).
Raw Materials Sourcing and Manufacturing Factors
5. Require confidential notification of FDA when there is a single API or manufacturing source. Notification would also apply to informing FDA of an interruption in the supply of raw materials, API, or manufacturing processes 13. Encourage manufacturing redundancies (e.g., multiple manufacturing sites for a sole product or multiple API sources, when available). (This recommendation also listed under Regulatory/Legislative Factors as a proposed required action.) 14. Establish or improve mechanisms to communicate anticipated or actual manufacturing and inventory problems (e.g., standardize terminology for causes of shortages, eliminate causes being described as "reason unknown " or "not provided"). Some information may require privileged communication between FDA and manufacturers to avoid unintended consequences (e.g., hoarding, releasing business information that supports fair business competition). Other mechanisms should focus on improving communication and transparency among supply chain entities and health care providers. Ensuring that information on the reason for and anticipated duration of the shortage reaches frontline clinicians was considered key.

15. Maintain/improve adherence to GMP to avoid quality issues and recalls.

Business and Market Factors

16. Improve communication to, among, and from product manufacturers and FDA, including detailed information on reason and anticipated duration of shortage. Also enhance communication to supply chain entities and health care providers (e.g., Dear Provider letters).

17. Decrease barriers/disincentives to market entry (See recommendations under Regulatory/Legislative Factors).

Distribution factors

18. Enhance communication among manufacturers, health professional associations, and FDA to support product distribution.

19. Consider distribution options for products in short supply (with increased information exchange among supply chain members).