

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

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)

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

3
4 That our American Medical Association (AMA) evaluate the problem of pharmaceutical
5 shortages in America and report on such shortages to the AMA House of Delegates by the
6 2012 Annual Meeting, to include but not limited to the role of government regulation, plaintiff
7 lawsuits, pharmaceutical company decisions and any other relevant factors contributing to the
8 pharmaceutical shortage; and

9
10 That our AMA make recommendations, based on the findings of the AMA’s evaluation of
11 pharmaceutical shortages in America, on ways to prevent pharmaceutical shortages in this
12 country.

13
14 Current AMA policy supports legislation that would require all manufacturers of Food and Drug
15 Administration (FDA)-approved prescription drugs to provide public notice to the Agency of any
16 anticipated voluntary or involuntary, permanent or temporary, discontinuation of such products.
17 AMA policy also holds that when such termination or interruption is voluntary (and not due to
18 circumstances beyond the control of the manufacturer), at least six months advance notice of
19 termination or interruption should be required (Policy H-100.965, AMA Policy Database). Current
20 policy also supports an ongoing role for the AMA in working with the federal government and
21 other key stakeholders to develop and implement strategies that will prevent shortages of drugs,
22 vaccines, and other medical products, and that will more effectively resolve shortages when they
23 occur (Policy D-100.989).

24
25 This report reviews the historical involvement of the AMA in the drug shortage issue, examines
26 recent trends on drug shortages, the explanations for such shortages, and potential solutions that
27 have been advanced to help address this critical problem. Resources on drug shortages also are
28 identified. In conducting research for this report, no evidence was uncovered that plaintiff lawsuits
29 are, or have been, a significant contributor to the national drug shortage problem.

30
31 **METHODS**

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

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

7 8 BACKGROUND

9
10 The problem of prescription drug shortages initially gained prominence around the year 2000. The
11 AMA first addressed this issue with a Board of Trustees Report at the 2001 Interim Meeting calling
12 for the establishment of a Health and Human Services (HHS) Task Force to explore the causes of
13 drug, diagnostic agent, and vaccine shortages and to identify appropriate solutions to these
14 problems so that the health of the public is adequately protected (Policy D-100.993).¹ The AMA
15 also previously urged the FDA to expand its list of “medically necessary products” (see below) and
16 to more effectively monitor production, inventory, and planned cessation of such products. The
17 AMA also recognizes the need to educate physicians on how to report potential drug and vaccine
18 shortages to the FDA and to establish an effective means to communicate information about drug
19 and vaccine shortages in a timely manner, including information about alternative therapies, to
20 physicians.

21
22 The AMA and ASHP first addressed the occurrence of drug shortages nearly a decade ago by
23 jointly convening a special meeting of key FDA officials and representatives of the pharmaceutical
24 industry, drug distributors, group purchasing organizations, the American Hospital Association, the
25 Institute of Medicine, and the Department of Veterans Affairs to examine drug product shortages
26 and to make recommendations on how to address this problem.² Thirty-three potential solutions
27 were promulgated comprising the categories of communication, manufacturing, distribution and
28 inventory management, regulation and enforcement, economic incentives, and research and study.
29 A summary of the provisional observations of this meeting and the potential solutions was
30 published in November 2002.³ Around this time, ASHP entered into an agreement with the
31 University of Utah Drug Information Service to use shortage bulletins developed by the Service to
32 maintain an electronic resource on drug shortages that could help address pharmacists’ and other
33 healthcare professionals’ requests for information and guidance.

34
35 Subsequently (and comporting with existing AMA policy), the AMA and ASHP met with high-
36 ranking FDA and HHS officials in 2003 to propose an HHS/FDA workshop, including all key
37 stakeholders, to prioritize strategies for improving the market dynamics for prescription drugs in
38 order to reduce shortages and improve the management of patients when shortages occur. The
39 AMA and ASHP convened a follow-up meeting in March 2004 to discuss next steps; included in
40 the discussion was a draft guidance developed by the Healthcare Distribution Management
41 Association on “Ensuring Product Availability – A Recommended Voluntary Industry Guideline,”
42 which offered recommendations that could assist in mitigating year-end shortages.⁴ Unfortunately,
43 the proposed HHS/FDA workshop never took place, and the drug shortage problem has worsened,
44 dramatically so over the last few years.

45 46 FEDERAL REGULATIONS PERTINENT TO DRUG SHORTAGES

47 48 *Definitions*

49
50 Drug discontinuation is a “situation in which a drug is no longer being commercially distributed by
51 an FDA-regulated manufacturer whether or not a formal withdrawal request or notification has

1 been made to the FDA.”⁵ Formal notice to the FDA of the discontinuation of sole-source,
 2 medically necessary products is required under Section 506C of the Federal Food, Drug, and
 3 Cosmetic Act. The FDA defines medically necessary drugs “as products that are used to treat or
 4 prevent a serious disease or medical condition for which there is no other source or alternative
 5 therapy available in adequate quantity and that is judged to be an acceptable substitute.” The FDA
 6 cannot force a manufacturer to produce a product and companies are not required to report plans to
 7 discontinue a product unless they are the sole manufacturer of a drug that is life-supporting, life-
 8 sustaining, or intended for use in the prevention of a debilitating disease or condition (21 CFR
 9 314.81) even though no legal penalty exists if the company chooses not to report the
 10 discontinuation.

11
 12 According to the FDA, a drug shortage is “a situation in which the total supply of all clinically
 13 interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected
 14 demand at the user level.”⁵ Recommended procedures for notification, evaluation, and management
 15 of drug shortage situations including investigational and new drugs, biologics, and generic
 16 equivalents are available.⁵ The ASHP defines a drug shortage as “a supply issue that affects how
 17 the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must
 18 use an alternative agent.”⁶

19
 20 **DRUG SHORTAGE INFORMATION**

21
 22 *Food and Drug Administration*

23
 24 Drug Shortages. The FDA drug shortages website provides information on shortages and limited
 25 distribution of medically necessary drugs.⁷ It includes information about the specific drug, the
 26 reason for the shortage, and the manufacturer’s anticipated date of availability. FDA also posts
 27 press releases and other notices of recalls from the firms involved. The drug shortage information
 28 on the FDA website is provided voluntarily by manufacturers. FDA cannot require firms to report
 29 the reason for a shortage, the anticipated duration of the shortage, or any other information about
 30 shortages. As of September 15, 2011 the FDA drug shortage site listed 71 drugs. A list of resolved
 31 drug shortages and drugs to be discontinued also is maintained on this site.

32
 33 Biologic Shortages. A separate FDA website contains information on biologic shortages.⁸ As of
 34 September 15, 2011, eight biologics were in short supply including immune globulin, black widow
 35 spider antivenin, hepatitis A & B, haemophilus, herpes zoster, and rubella vaccines.

36
 37 *American Society of Health-System Pharmacists*

38
 39 The ASHP maintains a Drug Product Shortages Management Resource Center on its website.⁹ The
 40 “Drug Shortages Resource Center” is the most current, as well as the most comprehensive drug
 41 shortage information service. The Center maintains a current list of drug shortages, as well as
 42 resolved drug shortages and discontinued drugs. Each drug shortage monograph includes the
 43 product(s) affected, the reason(s) for the shortage (when known), and estimated resupply dates.
 44 ASHP evaluates the implications of the shortage for patient care and provides recommendations on
 45 alternative agents and management with supporting references and documentation. As of
 46 September 15, 2011 the Resource Center listed 209 different drug shortages. ASHP also has
 47 developed guidelines on managing drug product shortages in hospitals and health systems,
 48 including a detailed algorithm which may be used to improve the organizational response to drug
 49 shortages.¹⁰

1 *Centers for Disease Control and Prevention*

2
3 The Centers for Disease Control and Prevention (CDC) maintains a vaccine shortage webpage that
4 contains the latest national information about vaccine supplies. The site provides guidance to
5 healthcare providers who are facing vaccine shortages or delays only for vaccines that are included
6 on the recommended childhood and adolescent immunization schedule.¹¹ As of August 1, the
7 CDC's "Current Vaccine Shortages and Delays" website listed 5 vaccines in short supply.

8
9 CURRENT TRENDS IN DRUG SHORTAGES

10
11 Shortages of medically necessary drugs have worsened appreciably over the last two years.
12 Compared with 2005, twice as many drug shortages were identified in 2008, and in 2010 almost
13 180 shortages of medically necessary drugs were identified by the FDA, triple the amount from
14 2005.¹² Sterile injectables comprise the most common type of pharmaceutical shortage, with 74%
15 of the shortages in 2010 involving such preparations, including many older off patent formulations
16 and critical use products in the acute care setting.

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

23
24 In 2010, the ASHP identified 211 drug shortages; the list maintained by ASHP includes all
25 shortages and does not consider a "medically necessary" filter. Already in 2011 as noted above,
26 ASHP has reported 209 drug shortages nationally through September 15, indicating substantial and
27 continued worsening of the drug shortage problem.¹³ Overall, the majority of drug shortages
28 involve generic products.

29
30 GENERAL CAUSES OF SHORTAGES

31
32 Many root causes of shortages exist, virtually all of which are remote from AMA influence.^{3,10,12-15}
33 The lack of FDA authority to require notification of impending drug shortages or product
34 discontinuation (except for sole-source manufacturers of medically necessary products) is a
35 contributing factor. Shortages vary on a regional basis depending on the wholesaler, local
36 competition, patient population, and general purchasing operations. Shortages can be the result of
37 one or a combination of factors throughout the supply chain, including sources of raw materials,
38 manufacturing issues, regulatory compliance, wholesaler or distributor behavior, prime vendors
39 and group purchasing organization practices, and extended purchasing or hoarding involving end-
40 user healthcare systems. The most common causes of national drug shortages include:

41
42 (1) Manufacturing difficulties and regulatory compliance issues.

43
44 Companies are required to conform to good manufacturing processes to stay in operation. These
45 processes may change over time and, due to resource constraints, FDA inspections can be
46 intermittent or sporadic. When a company is judged to be in noncompliance, remediation efforts
47 can be lengthy, thereby creating shortages or eventually lead to a business decision to discontinue
48 production because of the investment that would be required to bring the production facility into
49 FDA compliance. When sole source manufacturing is in place, the stakes are heightened. In 2010,
50 more than 40% of sterile injectable shortages were due to product quality issues, including the
51 presence of particulates or impurities, microbial contamination, and stability concerns.¹⁶ As noted

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

4
5 In some cases, recalls may precipitate a shortage and create immediate emergencies for clinical
6 care. Changes in a product's formulation, reliance on a new raw material or source for the active
7 ingredient, or switching to a new manufacturing site can substantially delay product availability,
8 particularly for generic drugs. When such changes occur for generic products, the company must
9 submit a new Abbreviated New Drug Application (ANDA) for review and approval by the FDA.
10 ANDAs are required, of course, for new generics as well. Uncertainties about the review times for
11 these applications can affect company planning at the manufacturing level. These factors are
12 especially relevant given that the majority of drug shortages comprise generic products.

13
14 For controlled substances, annual quotas are established by the DEA for each manufacturer, which
15 can interfere with efforts to increase production if, for example, another company making the same
16 product experiences difficulties. In some cases, certain drugs that were approved prior to 1938 and
17 have changed their labeling, or drugs that were initially approved between 1938 and 1962 based on
18 safety assessments alone, may represent "unapproved drugs." When such a status is recognized
19 and acted on by the FDA, this can create shortages or uncertainty in the market for these products
20 (e.g., concentrated oral morphine solution).

21
22 (2) Corporate decisions leading to product discontinuation or decreased production.

23
24 Business decisions to discontinue a product or reallocate resources to other products can create
25 shortages. Such decisions may be prompted by a lack of profitability or the specter of additional
26 costs to re-establish good manufacturing practices in response to violations. Contemporary
27 business models also may rely on tighter or "just-in-time" inventories of raw materials, excipients,
28 and/or finished products. These practices, as well as existing contractual agreements with
29 wholesalers and group purchasing organizations serving larger hospitals and healthcare systems,
30 can create regional shortages. Overall, supply chains are more fragile, which places certain sites of
31 care (e.g., ambulatory infusion centers, small or rural facilities) at greater risk of experiencing a
32 shortage.

33
34 (3) Consolidation of the pharmaceutical industry.

35
36 Mergers and acquisitions in the pharmaceutical industry have been followed by a decline in the
37 new drug pipeline. With the advent of the Prescription Drug User Fee Act in 1992 and a robust
38 industry presence, an average of 31 drugs were approved annually in the 1990s (with a high water
39 mark of 54 approved in 1996) compared with an average of 24 new drugs annually in the following
40 decade. In fact, many of the companies that developed drugs in the mid-1990s no longer exist.
41 Accordingly, only a few manufacturers of sterile injections exist. Additionally, the same
42 production lines in one facility may be used for multiple items; reallocation of lines to produce
43 more profitable (or new) drugs at the expense of older generics can cause shortages. Consolidation
44 also has resulted in fewer suppliers and the migration of manufacturing to foreign sites.

45
46 (4) Raw, bulk material or active pharmaceutical ingredient shortage.

47
48 Shortages in raw materials or active pharmaceutical ingredients can affect multiple manufacturers
49 leading to simultaneous manufacturing difficulties. Approximately 80% of such materials for
50 prescription drug production come from outside the U.S.¹⁰ Hostilities, political instability, disease

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

4 *Overall Assessment of the Reasons for Drug Shortages*

6 According to the Utah Drug Information Service, the reasons for overall drug shortages in 2010
7 were most often manufacturing/production issues and supply/demand factors.¹² Shortages due to
8 the unavailability of raw materials or regulatory enforcement were infrequent. However, nearly
9 half the time, reasons were not explained or identified. With respect to sterile injectable shortages
10 in 2010, the FDA reports that 45% were due to product quality issues; 18% due to discontinuation;
11 17% due to delays or capacity issues; 8% due to raw material shortage; 5% due to loss of
12 manufacturing site; 4% due to component problems/shortage; and 3% due to increased demand
13 because of another drug shortage.¹²

15 IMPACTS OF DRUG SHORTAGES

17 The prevalence of drug shortages prompted U.S. hospitals to spend at least \$200 million more a
18 year on substitutes in 2010, according to a study of 228 hospitals, retail pharmacies, and other care
19 facilities by Premier Healthcare Alliance, a purchasing agent for hospitals.¹⁶ This estimate does not
20 include added labor costs for managing shortages or ensuring safety and mitigating patient risk.
21 Nearly 90% of the hospitals reported a drug shortage in the second half of 2010 that either: (1)
22 caused a patient safety issue; (2) resulted in the delay or cancellation of a procedure; (3) required
23 more expensive substitutes; or (4) resulted in a pharmacist having to compound a drug formulation.
24 According to Premier, more than 240 drugs were in short supply or completely unavailable in
25 2010, and more than 400 generic drugs were back-ordered for five or more days.¹⁶ According to the
26 Premier analysis, the “annualized financial impact of drug shortages where generic equivalents are
27 available exceeds \$78 million,” with the majority of the financial impact occurring within the acute
28 care sector affecting principally infectious disease, surgery, and oncology.¹⁶

30 Three additional recent surveys confirm the substantial effects of drug shortages on patient safety
31 and welfare, hospital costs, and resource utilization. A 2010 survey of more than 1,800 healthcare
32 practitioners (two-thirds pharmacists) conducted by the Institute for Safe Medication Practices
33 (ISMP) evaluated various difficulties associated with drug shortages.¹⁵ Alarming, more than
34 80% of the time, drug shortages occurred without advance warning and information was lacking
35 about the cause or expected duration of the shortage. Not surprisingly, physicians and other end
36 users are often angered by these developments. Substantial resources are expended and significant
37 costs (unspecified in this survey) are associated with developing a plan of action and obtaining
38 suitable alternatives, which themselves may be lacking up to 70% of the time. Alternative
39 medications may be less efficacious or also become depleted and in short supply. Additionally,
40 because of unfamiliarity, the use of alternatives increases the probability of errors or adverse
41 patient outcomes. Nearly two-thirds of the respondents in the ISMP survey reported patient
42 outcomes had been adversely affected and near misses were more common. A number of such
43 occurrences involving shortages of propofol, various neuromuscular blocking agents, morphine,
44 epinephrine, heparin, fosphenytoin, several chemotherapy drugs, and various intravenous
45 antibiotics have been detailed (See Table 1).¹⁵

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

1 institutions suffer more shortages. In 2010, 47% of institutions with ≥ 400 beds experienced more
2 than 30 shortages. At the time this survey was administered, more than 80% of hospitals were in
3 short supply of succinylcholine, dextrose 50% syringes, and epinephrine 1 mg/ml injection. One in
4 ten hospitals were experiencing shortages of the anticancer drugs idarubicin and foscarnet, and
5 50% were experiencing a shortage of midazolam 1 mg/ml injection.

6
7 A survey of 820 non-federal, short-term acute care community hospitals conducted in June 2011 by
8 the American Hospital Association revealed that 44% of hospitals experienced ≥ 21 drug shortages
9 across various treatment categories.¹⁸ The most common categories were surgery/anesthesia,
10 emergency care, cardiovascular medicine, gastrointestinal/nutrition services, pain management,
11 infectious disease, and oncology. Four out of five hospitals had to delay patient treatment, and
12 more than half were not able to provide the patients with the recommended treatment in some
13 cases. Accordingly, 75% of hospitals required rationing of drugs in short supply; virtually all
14 hospitals reported increased drug acquisition costs as a result of drug shortages. The actual
15 financial impact was not evaluated but the existence of a shortage forces the hospital to purchase
16 excess inventory or a more expensive product or therapeutic alternate from outsourcing companies
17 or a new distributor. In nearly half of the hospitals surveyed, drug shortages occurred daily.
18 Generally, little or no advance warning of an impending drug shortage is forthcoming and
19 substantive information often is lacking on the cause of the shortage and its expected duration. As
20 one might expect, these continuing and serious shortages strain relationships among the medical
21 staff, pharmacy, and hospital leadership.

22 23 *Stockpiling and Gray Market Distributors*

24
25 No hospital or healthcare facility wants to be in a position of experiencing a drug shortage.
26 Accordingly, attempting to identify impending shortages and then stockpiling by submitting larger
27 than regular orders occurs. Specialty licensed distributors or brokers that normally serve a very
28 small niche may emerge and contribute to the so-called “gray-market” during times of shortages by
29 acquiring available supplies and then redistributing/reselling the product at inflated prices (and
30 sometimes via multiple steps) to end users who have been unable to procure the product through
31 their normal suppliers.

32 33 SOLUTIONS

34 35 *The Role of FDA and the Pharmaceutical Industry*

36
37 Prompt notification from manufacturers is important for all shortage situations. Early notification
38 increases the probability that the shortage issue can be prevented or resolved in a timely manner.
39 Approximately 28 shortages were averted in 2010 because of early warnings to the FDA.¹² On the
40 manufacturing side, companies must have an enduring commitment to quality and engage in
41 redundancy/stockpiling of key manufacturing supplies and inventory. When manufacturing/quality
42 problems are identified, the FDA should work with the company to expedite certain issues (e.g.,
43 new manufacturing site, production lines or manufacturer, changes in specifications, new raw
44 material source or shortage, lengthen expiration dates). In some cases, discretion may be employed
45 to address shortages of medically necessary drugs to mitigate significant risks to patients. If other
46 firms also are manufacturing the product, they can be encouraged to increase production.
47 Facilitation of importation from foreign sources also may be necessary on a temporary basis (e.g.,
48 propofol, foscarnet, ethiodol).

49
50 At an FDA-sponsored public hearing on drug shortages conducted on September 26th, 2011,
51 agency staff revealed that 99 shortages had been averted already in 2011 because of early warnings

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

6 7 *Drug Shortage Summit*

8
9 In an effort to better address the contemporary surge in drug shortages, ASHP, the American
10 Society of Anesthesiologists, the American Society of Clinical Oncology, and the ISMP convened
11 a drug shortages summit in November 2010.¹⁴ A suite of 19 recommendations emerged involving
12 regulatory and legislative factors, raw materials and manufacturing, business and market factors,
13 and distribution. Many of these mirror the recommendations that surfaced nearly a decade ago
14 when the AMA and ASHP convened the first summit. The recommendations for addressing drug
15 shortages emanating from the November 2010 summit are available in Table 2.

16 17 *Legislative Approaches*

18
19 Two versions of the Preserving Access to Life Saving Medications Act (H.R. 2245 and S. 296)
20 would address certain factors that contribute to drug shortages. Both versions would require all
21 drug manufacturers to notify the FDA: (1) about manufacturing problems or anticipated shortages
22 as soon they become aware of a problem; and (2) provide notification at least 6 months in advance
23 when any drug is to be discontinued. Both bills also require the FDA to maintain a website listing
24 drugs in shortage situations. The House version defines drug shortage as a “period of time when
25 the total supply of such drug available at the user level will not meet the demand for such drug at
26 the user level” and would establish civil monetary penalties for noncompliance. The Senate
27 version would revise the FDA definition of “medically necessary” and attempt to develop a new,
28 evidenced-based metric for predicting or identifying drugs that are vulnerable to a shortage.

29 30 SUMMARY

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

38
39 The current situation requires a comprehensive solution that includes an early warning system.
40 Accordingly, the FDA, manufacturers, group purchasing organizations, distributors, hospitals,
41 pharmacists, physicians, and other stakeholders should seek to establish more efficient and
42 informative communications on drug product shortages, including timely and advanced warning
43 about imminent shortages and future availability. Pharmacists, physicians, and other prescribers
44 should be encouraged to report suspected drug shortages. Manufacturers and distributors should
45 develop standards for allocating existing inventory in a fair and transparent process, and act to
46 deter drug product shortages that may be caused or exacerbated by extremely large orders,
47 hoarding, or “gray market” practices. In accordance with current AMA policy, federal law should
48 be changed to develop a mechanism and framework for all manufacturers to report impending
49 supply disruptions and discontinuation of drugs.

1 RECOMMENDATIONS

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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 mitigating 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)

Fiscal note: \$1000

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

Drug	Consequence
Propofol	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • A patient with a <i>Pseudomonas</i> infection sensitive only to amikacin died when the drug was unavailable. • Clinically significant delays in treating patients with <i>Pneumocystosis carinii</i> 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
<ol style="list-style-type: none"> 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
<ol style="list-style-type: none"> 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).