

REPORT 7 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-12)
Drug Shortages Update
(Reference Committee E)

EXECUTIVE SUMMARY

Objective. To evaluate and summarize existing data on national drug shortages and proposed remedies since the last Council report in November 2011.

Methods. English-language reports were selected from a PubMed and Google Scholar search from September 2011 to May 23, 2012 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 General Accounting Office, American Society of Anesthesiologists, the Generic Pharmaceutical Association, and from recent presentations on the topic at special organizational meetings at which the AMA was represented.

Results. Drug shortages continue to represent a national concern, with sterile injectables comprising the most common type of shortage. The ASHP Drug Shortage Resource Center reported more than 220 shortages as of May 23, 2012. The most prominent causes continue to be 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. According to the FDA, they have been able to mitigate more than 125 potential drug shortages since October 2011 through a combination of early warnings from manufacturers and the creation of expedited solutions. Ongoing negotiations over the 2012 Prescription Drug User Fee Act have afforded a platform to create some legislative and regulatory solutions to the drug shortage problem.

Conclusion. National drug shortages continue to threaten patient care and safety. The existence of a shortage may compromise and delay treatment leading to progression of disease, adverse outcome, or therapeutic failure. The current situation requires a comprehensive solution, including expansion of notification requirements for all manufacturers, expedited review of new manufacturing capacity, and expansion of supply and maintenance of product quality in sectors with high capacity utilization. The AMA supports a requirement for the Secretary of HHS to establish a task force to enhance the FDA response to shortages, study the problem, and create a strategic plan to address shortages. The AMA is particularly supportive of provisions that require the FDA to consult and collaborate with impacted stakeholders. In the meantime, based on the demonstrated success of advance notification, FDA and the industry should continue to work on collaborative solutions to individual shortage problems until legislative solutions emerge.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 7-A-12

Subject: Drug Shortages Update

Presented by: Lee R. Morisy, MD, Chair

Referred to: Reference Committee E
(Frederick R. Ridge, Jr., MD, Chair)

1 Council on Science and Public Health Report 2-I-11 reviewed the historical involvement of the
2 American Medical Association (AMA) in the drug shortage issue, examined recent trends on drug
3 shortages, the explanations for such shortages, and potential solutions that have been advanced to
4 help address this critical problem.¹ The report recommended that the AMA support a suite of 21
5 recommendations to address the drug shortage issue emanating from a 2010 drug shortages summit
6 convened by the American Society of Health System Pharmacists (ASHP), American Society of
7 Anesthesiologists, American Society of Clinical Oncologists, and the Institute for Safe Medication
8 Practices.² In addition, the House of Delegates directed CSAPH (Policy H-100.956, AMA Policy
9 Database) to report back at the 2012 Annual Meeting on efforts to mitigate drug shortages,
10 including the evaluation of potential economic and regulatory factors that may contribute to drug
11 shortages, especially with respect to oncology drugs.

12

13 Because existing drug shortages created a public health emergency and legislative action may not
14 take place until Congress considers the Prescription Drug Users Fee Act Reauthorization (PDUFA)
15 later this year, the Administration issued an executive order on October 31, 2011 that instructed the
16 FDA to increase staff in its drug shortage program office, expand efforts to speed review of drug
17 applications and approve replacement manufacturing sites, investigate and penalize price gouging
18 for products in short supply, and urge manufacturers to voluntarily notify the agency of impending
19 shortages.³ The Administration also released two new reports on the underlying causes of
20 shortages and the FDA's role in preventing them.^{4,5} Subsequently, both the General Accountability
21 Office (GAO) and IMS released reports analyzing drug shortages.^{6,7} These various analyses
22 reinforced the findings of CSAPH Report 2-I-11 on the general causes of drug shortages, citing
23 manufacturing problems, business decisions, disruption in the supply of active ingredients,
24 unexpected increases in demand, industry consolidation, unstable supply chains, manufacturing
25 capacity constraints, and lean inventory systems as primary contributing variables.⁴⁻⁷

26

27 Accordingly, this report reviews our current understanding of drug shortages and various
28 regulatory initiatives and legislative proposals intended to prevent or mitigate drug shortages; most
29 of the latter are part of the ongoing legislative process related to passage of PDUFA. The AMA
30 has been extensively involved in this process. At the time of this writing, PDUFA negotiations
31 remained ongoing. For further information on current federal regulations, comprehensive sources
32 of information on existing drug shortages, and the general causes of drug shortages, see CSAPH
33 Report 2-I-11.

1 CURRENT DRUG SHORTAGE INFORMATION

2
3 As of May 23, 2012, the Drug Shortages Management Resource Center maintained by ASHP
4 identified 226 existing drug shortages.⁸ The Food and Drug Administration drug shortages website
5 identified 122 existing shortages of “medically necessary drugs.”⁹ Existing and new drug shortages
6 continue to be problematic. Manufacturing issues and the discontinuation or suspension of
7 production are the most commonly cited reasons, followed by increased demand.⁸ Manufacturing
8 problems may result from temporary shut down in order to maintain or upgrade a production line
9 or the entire facility, or may be related to temporary manufacturing suspension of a specific drug to
10 evaluate or resolve a manufacturing problem.

11
12 In April 2011, the ASA re-surveyed its members on drug shortages.¹⁰ More than 90% of
13 respondents reported they are currently experiencing a shortage of at least one anesthesia drug.
14 Virtually all respondents (>98%) reported they have experienced a shortage of at least one
15 anesthesia drug in the last year, most commonly propofol (89%), succinylcholine (80%), and
16 thiopental (60%). Because respondents had to use alternative drugs or change procedures in some
17 way, nearly half of their patients reportedly experienced less optimal outcomes (e.g., post-operative
18 nausea and vomiting) and longer operating room or recovery times. Additionally, some surgical
19 cases were postponed or even cancelled.

20
21 On a positive note, the FDA reported that 42 new shortages of medically necessary drugs had been
22 reported through April 2012 compared with 90 at the same time last year.¹¹ This reduction has
23 been attributed to more extensive early notification of potential problems by manufacturers and
24 expedited solutions (see below).

25
26 ANALYSES OF THE DRUG SHORTAGE PROBLEM

27
28 Four new reviews and comprehensive analyses of drug shortages have been released since the
29 previous Council report was drafted. The Office of Science and Data Policy within the Assistant
30 Secretary for Planning and Evaluation (ASPE) conducted an analysis of the underlying factors
31 leading to periods of shortages in the prescriptions drug market, particularly those that have
32 contributed to the current shortages in the areas of sterile injectable oncology drugs.⁵ A companion
33 report from the FDA reviewed the agency’s approach to medical product shortages.⁴ The GAO
34 reviewed trends in drug shortages, described FDA’s response, and evaluated the FDA’s ability to
35 protect public health; a detailed analysis of 15 selected drug shortages of anti-infective, oncologic,
36 and anesthesia drugs was included in the GAO report.⁶ The IMS Institute for Healthcare
37 Informatics also examined in some detail factors associated with products experiencing shortages,
38 suppliers, and volume volatility.⁷ Although these reports took somewhat different approaches,
39 several important facts and realities emerged. The next five sections are based on the findings in
40 these reports. Specific findings and conclusions vary somewhat depending on the time period
41 studied.

42
43 *Overview of Demand Issues*

44
45 As medically necessary products, few or no substitutes are available to physicians and hospitals
46 that can buffer shifts in consumption over time. Services for consumers in the prescription drug
47 market are accomplished through health insurance contracts that pre-establish payment rates and
48 both consumers and hospital/physician demand for prescription medication are not very responsive
49 to the average wholesale price paid to manufacturers for the drug. Thus, sterile injectable products
50 used for acute, medically necessary indications are characterized by very low price responsiveness

1 on the demand (and supply) side. This condition increases the likelihood of a shortage in the
2 presence of demand changes that are not anticipated by manufacturers.

3

4 *Overview of Supply Issues*

5

6 On the supply side, production line processes for sterile injectables are complex. Generic
7 companies operate a limited number of facilities each containing multiple production lines.
8 However, cytotoxic oncologic drugs (and certain antibiotics) require specific equipment and
9 regulatory approvals limited to that class. These special containment controls can limit a
10 manufacturer's transfer of production of these drugs to other lines. Furthermore, these drugs have
11 a limited shelf life so that holding excess inventory can be very expensive. Therefore,
12 manufacturers of these products cannot respond simply to supply chain disruptions.

13

14 *Purchasing and Pricing*

15

16 Most sterile injectable drugs are purchased by hospitals (and in some cases physicians) through
17 group purchasing organizations (GPOs), which negotiate prices with manufacturers. Drug delivery
18 is accomplished by wholesalers who purchase inventory at the wholesale acquisition price with
19 manufacturers issuing a "chargeback" if the acquisition price exceeds the GPO's negotiated price.
20 Hospitals also may source their products outside of this structure. GPO contracts typically have
21 price adjustment clauses as well as "failure to supply" penalties. The latter usually do not apply
22 when the product is not available, are otherwise of limited duration, and have been characterized by
23 "erosion" of their impact.⁵ Pricing flexibility by suppliers may be constrained by long-term
24 purchase contracts, although in many cases companies have multiple contracts staggered
25 throughout the year, which provides some ability to adjust pricing to market conditions.⁵

26

27 The Medicare Prescription Drug, Improvement, and Modernization Act, enacted in 2003,
28 substantially reduced payment rates for chemotherapy drugs administered on an outpatient basis
29 starting in January 2005. Currently, in Medicare, injectable drugs are covered under Part B, which
30 pays physicians the average sale price (ASP) plus 6% to cover the cost of administering the drugs.
31 Increases are limited to maximum of 6% every six months. Although some proposals have
32 suggested that this formula contributes to drug shortages, no consensus exists that raising the ASP
33 formula (or changing the metric to use average wholesale prices instead) would lessen drug
34 shortages because of other complexities in the drug distribution chain. Reimbursement cost,
35 whatever it may be, is not the price that is paid to the manufacturers. A disconnect exists between
36 money paid to purchasers, GPOs, and manufacturers. The HHS report concluded that increased
37 production capacity for generic sterile injectable drugs is the single most important solution to the
38 drug shortage crisis while maintaining that payments to manufacturers are not the primary
39 problem.⁵

40

41 *Some Relevant Drug Shortage Findings⁴⁻⁷*

- 42
- 43 • The number of drug shortages has increased each year from 2006-2011, and sterile injectables
44 make up a disproportionate share of the drugs in shortage. Impacted patients therefore are
45 mostly acute care and/or cancer patients being treated in hospitals and in out-patient facilities.
 - 46 • About half of the sterile injectable market is branded and half is generic, but the latter fraction
47 is increasing. Overall, current shortages (~75-80%) of sterile injectables are concentrated in
48 the generics industry.
 - 49 • Two-thirds of drugs on the shortage list are used in oncology, infectious diseases,
50 cardiovascular diseases, pain management, and central nervous system disorders. Half were
51 marketed before 1990 but 25% have been introduced since 2000; 6.5% were controlled

1 substances. For the oncology products, an estimated 550,000 cancer patients may be affected
2 annually.

3 • Overall (brand and generic) production of sterile injectables has increased. From 2006-2011,
4 the supply of sterile injectable oncology drugs increased 14% overall and 20% within
5 Medicare, but generic volume increased disproportionately by 30%.

6 • Drugs that were in short supply sometime in 2008 or beyond experienced a declining volume
7 of sales from 2006-2008; those that were not in short supply experienced an increase (11%) in
8 sales volume over the entire period. Similarly, drugs that eventually experienced a shortage
9 demonstrated a mean 27% drop in price, while prices of drugs that did not develop a shortage
10 were steady or slightly increased.

11 • More than 80% of the market for generic sterile injectables is supported by seven
12 manufacturers in the U.S.; for oncologic products, typically 3 or fewer companies comprise the
13 market and more than 50% of the drugs have two or fewer suppliers.

14 • During 2006-2011, the number of new generic manufacturer-drug combinations in the sterile
15 injectable market increased every year, outnumbering the number of exits from the market.

16 • After remaining relatively constant from 2000-2007 (varying between 62 to 79 annually except
17 for 2003), the overall number of new generic injectable approvals surged in 2008 (135) and
18 2009 (103), creating a much larger portfolio of possible drugs for manufacturing sites.

19 • Among drug shortages occurring from 2009 through June 2011, 59% involved more than one
20 manufacturer.

21

22 In summary, the volume of injectable chemotherapy drugs used has increased and the number of
23 products available for generic manufacturing has increased dramatically. The process itself
24 remains complex and subject to Good Manufacturing Practice regulations, precluding early entry
25 into the marketplace, and financial incentives are lacking for investing in excess capacity.
26 Contrary to some belief, consolidation of manufacturing among sterile injectable companies has
27 not occurred, but current capacity is limited. A limited ability to benefit from failure-to-supply
28 clauses and low price elasticity prompts manufacturers to limit reserve inventory.

29

30 *Supplies and Volume of Sales over Time*

31

32 Based on their proprietary drug supply chain data, IMS examined the problem of drug shortages
33 (168 drugs) on the FDA list as of October 7, 2011 including supplies and volume and sales of these
34 drugs over time.⁷ The overall supply of drugs experiencing shortages has increased or been stable
35 over the past five years, but not in a uniform fashion. In aggregate, injectable volume has grown
36 4% over the past five years for drugs on the FDA shortage list, and dollar sales have trended
37 upward. Although the supply has been stable, the contribution of individual suppliers may change
38 from month-to month. A “high volatility with unusually sharp swings in supply” has been
39 especially pronounced in the past year.⁷ A segment of the drugs on the shortage list exhibits
40 declining sales in 2010-2011 compared with the base period of 2006-2009; a smaller percentage is
41 stable; and about 20% are experiencing growing volume sales (over 3-fold since 2006). For those
42 in the declining category, monthly supply has fallen an average of 47% over the five-year period.
43 The average annual price per standard unit varies significantly across these three segments but not
44 in a consistent way.

45

46 Although a number of firms produce sterile injectables (~80), the production of any given molecule
47 is commonly concentrated among a very small number of manufacturers. The top three generic
48 injectable manufacturers account for 71% of the market by volume and most sterile injectables
49 have one manufacturer that produces at least 90% of the drug; 60% of sterile injectables in 2010
50 were virtually sole sourced (90% or more of market share by one manufacturer). Two-thirds of the

1 drugs in short supply are produced by three or fewer companies. Fifty-six products were provided
2 by sole source manufacturers and 51% of products with shortages have two or fewer suppliers.
3 Only 1% of products have two of the top producers accounting for less than 50% market share by
4 volume. Substantial market concentration increases the vulnerability of the supply system to
5 shortages, and the number of companies supplying these products has fluctuated over the last five
6 years. Several current oncology shortages can be traced to just three cytotoxic lines operated by
7 two separate manufacturers.⁷

8
9 The IMS report recommended that FDA create an early warning system for drug shortages that
10 would include systematic risk identification, continuous long-term demand forecasting, creation of
11 a supply volatility index as signal for problems, and comprehensive predictive modeling.⁷

12
13 STAKEHOLDER RESPONSES

14
15 *Food and Drug Administration*

16
17 On December 19, 2011, the FDA issued an interim final rule modifying the definitions of
18 “discontinuance” and “sole manufacturer” {§ 314.81(b)(3)(iii)}.¹² Under Section 506C of the
19 FD&C Act, a sole manufacturer of a prescription drug product that is “life-supporting, life
20 sustaining, or intended for use in the prevention of a debilitating disease or condition” is required
21 by statute to notify the Agency of a discontinuance of that drug product at least six months prior to
22 discontinuing manufacture of the product. The interim final rule modifies the term
23 “discontinuance” and clarifies the term “sole manufacturer” with respect to notification of
24 discontinuance requirements. The broader reporting resulting from these changes will enable FDA
25 to improve its collection and distribution of drug shortage information to physician and patient
26 organizations and to work with manufacturers and other stakeholders to respond to potential drug
27 shortages.

28
29 Under this interim final rule, the FDA is now defining “discontinuance” to “include both
30 permanent and temporary interruptions in the manufacturing of a drug product, if the interruption
31 could lead to a disruption in supply of the product.” For example, delays in acquiring active
32 pharmaceutical ingredients (APIs) or inactive ingredients that lead to an interruption in
33 manufacturing or a suspension in production for maintenance or other routine services that exceeds
34 expected durations would trigger a “discontinuance” reporting requirement under the new
35 definition. These types of temporary discontinuances must be reported only if the discontinuance
36 reasonably could be expected to lead to a disruption in supply of the product. A planned
37 maintenance period would not necessarily be reported to the FDA if it is not expected to impact
38 production and does not exceed scheduled down-time.

39
40 “Sole manufacturers” now include any companies who are the “only entity currently manufacturing
41 a drug product of a specific strength, dosage form, or route of administration for sale in the United
42 States, whether the product is manufactured by the applicant or for the applicant under contract
43 with one or more different entities.” A manufacturer will be considered a “sole manufacturer even
44 if other manufacturers hold an approved new drug application (NDA) or abbreviated new drug
45 application (ANDA) for the same product, if the other applicants are no longer manufacturing (or
46 have never manufactured) the product for sale in the United States.” The definition of sole
47 manufacturer is linked to the specific strength, dosage form, and route of administration, because
48 these characteristics may be critical for the targeted needs of particular patients. Manufacturers are
49 responsible for determining whether their particular situation falls within the mandatory reporting
50 requirement.

1 Guidance for Industry

2
3 The FDA subsequently published a Guidance for Industry in February 2012 reflecting the above
4 amendments to the implementing regulations of the interim final rule.¹³ This document provides:
5 (1) guidance to industry on requirements for mandatory notification to the FDA of discontinuances;
6 (2) additional explanation of the voluntary notification processes; and, (3) advice on advance
7 planning strategies that might be considered to prevent or mitigate product shortages.

8
9 *FDA Actions to Mitigate or Prevent Drug Shortages*

10
11 The FDA's response to drug shortages is managed by the Drug Shortage Program within the Center
12 for Drug Evaluation and Research. The FDA can take certain actions to help alleviate or prevent a
13 shortage from occurring in the first place. Analysis of the Agency's response to 127 shortages of
14 medically necessary drugs that occurred in 2010-2011 revealed that the FDA asked other
15 companies to boost production (31%), exercised regulatory discretion (28%), expedited review of
16 other sources (26%), and occasionally exercised discretion on importation, or a sole source
17 manufacturer to boost production.⁷

18
19 The FDA may exercise regulatory discretion to allow the continued marketing of a product with
20 labeling errors for misbranded products or quality issues, assuming an interim solution to the
21 quality problem (e.g., filtering of impurities or particulates) can be identified. In some cases, the
22 FDA may work to accomplish importation of drugs that are approved for use in foreign countries,
23 but not the U.S. Two recent examples of regulatory discretion assisted in relieving two high profile
24 drug shortages. The FDA approved the temporary importation of an unapproved liposomal
25 doxorubicin drug product, and expedited the approval of a new manufacturer for preservative-free
26 methotrexate and convinced other manufacturers to increase the supply of this product as well.

27
28 For these strategies to work, there must be enhanced communication between FDA and
29 manufacturers, and the industry must give early notice of potential problems. FDA Commissioner
30 Margaret Hamburg, MD recently revealed that since President Obama's October 31, 2011
31 directive, the FDA had prevented 128 new drug shortages, prompted by a six-fold increase in
32 voluntary reports from manufacturers.¹¹ Shortages were prevented by expediting the review of new
33 manufacturing sites, new suppliers and specification changes, exercising regulatory flexibility and
34 discretion, and asking other firms to ramp up production. According to the GAO analysis, the FDA
35 was able to mitigate 90% of potential shortages that it learned about in advance in the first half of
36 2011.⁶

37
38 In addition to increased staffing, improved communication, voluntary reporting, and expedited
39 action, the FDA has proposed implementing and maintaining a database that can analyze the
40 characteristics of drug shortages. The GAO report noted that the Agency needs to implement a
41 systematic approach to managing its complex workload and to maintain data in a manner that
42 enhances its ability to understand trends in shortages and the effectiveness of interventions related
43 to preventing or mitigating the effects of shortages.⁶

44
45 *Generic Manufacturers*

46
47 Several generic manufacturers of sterile injectables (e.g., APP Pharmaceuticals, Hospira, Bedford
48 Laboratories, Teva) are building new plants and expanding facilities to help them better respond
49 when manufacturing lines are shut down.¹⁴

1 The Generic Pharmaceutical Association (GPhA) also announced a proposal, known as the
2 Accelerated Recovery Initiative (ARI) to address sterile injectable drug shortages, although not all
3 prominent generic drug manufacturers have endorsed the plan.¹⁵ It would involve voluntary
4 communication between an independent third party and stakeholders involved in the manufacturing
5 and distribution of generic injectable medications currently in shortage and be designed to use real-
6 time supply and distribution information to give stakeholders, especially manufacturers,
7 wholesalers, distributors, GPOs and the FDA a clear picture of current conditions and a plan to
8 expand the production and supply of critical drugs in short supply. Specific elements of this
9 initiative include:

- 10
- 11 • Use of an independent third party to gather current and future supply information from
12 stakeholders for products identified as meeting the critical criteria;
 - 13 • That information be used to determine current and potential supply gaps, with a focus on
14 those products where a shortage is expected to last longer than 90 days; and
 - 15 • A high-level dedicated drug shortage management team be formed within the FDA with
16 the ability to quickly respond to critical shortages and work with the current drug shortage
17 staff.

18

19 Implementation of this voluntary initiative would require Federal Trade Commission and HHS
20 approval. In April 2012, GPhA selected IMS Health to act as the proposed independent third party
21 to collect production and release schedule information in a voluntary manner from manufacturers
22 and work with industry and FDA to mitigate shortages.

23

24 LEGISLATIVE APPROACHES

25

26 The Council on Legislation (COL) recommended to the Board of Trustees (BOT) that our AMA
27 support the "Preserving Access to Life-Saving Medications Act," a bipartisan bill (H.R. 2245) to
28 reduce shortages of drugs and biologicals introduced by Representatives Diana DeGette (D-CO)
29 and Tom Rooney (R-FL). H.R. 2245 would establish an early warning system to help prevent
30 sudden shortages of medication by requiring manufacturers of all prescriptions, including drugs
31 and biologics, to notify FDA of any discontinuance or interruption in the product of a drug at least
32 six months in advance, or in the event of unforeseen or unplanned circumstances, as soon as
33 possible. Also, the bill would require the FDA to develop criteria for drugs vulnerable to a
34 shortage. Thereafter, the AMA expressed support for a nearly identical Senate bill, S. 296,
35 "Preserving Access to Life-Saving Medications Act" after concerns with that bill were addressed
36 by the sponsor, Senator Amy Klobuchar (D-MN).

37

38 More recently, the COL recommended that the BOT not support H.R. 3839, the "Drug Shortage
39 Prevention Act," introduced by John Carney (D-DE) and Larry Bucshon (R-IN) until AMA
40 concerns and questions about a key provision were resolved. This provision directs the FDA to
41 provide advance notice to wholesale distributors prior to informing the public that there is a
42 shortage without any specific obligation on the part of distributors to prevent hoarding or gray
43 market stratagems.

44

45 None of these bills address possible changes to reimbursement or other financial incentives that
46 have been mentioned in some quarters as contributing factors. Payment reforms have generally not
47 been viewed as a key solution. Other economic incentives being discussed include tax credits for
48 research and development or creating manufacturing redundancy.

49

50 Both the House and Senate are actively engaged in drafting legislative proposals related to drug
51 shortages as part of the PDUFA authorizations. On the House side, many provisions of the Carney

1 and DeGette bills have been incorporated into legislative drafts that are being widely circulated,
2 lacking controversial provisions including the requirement that the FDA provide wholesale
3 distributors advance notice of actual shortages prior to public disclosure. The AMA strongly
4 supports the efforts of the Senate to address the crisis of drug shortages and met with the Senate
5 Health, Education, Labor, and Pensions (HELP) Committee majority staff to underscore the
6 concern of AMA members and to emphasize our support for the requirement that manufacturers
7 provide the FDA advance notice of anticipated or actual shortages. The Senate PDUFA bill (S.
8 3187) as amended provides that manufacturers of drugs that are: life-supporting; life-sustaining;
9 intended for use in the prevention of a debilitating disease or condition; a sterile injectable product;
10 or used in emergency medical care or during surgery, shall notify the FDA of permanent
11 discontinuation or temporary interruption in manufacturing 6 months in advance or as soon as
12 practicable. The Secretary also may include biological and biosimilar manufacturers in the
13 reporting requirement through rule-making. The foregoing is a vast improvement over the status
14 quo and the AMA believes that most prescription drugs would meet one of these criteria.^{15,16} The
15 current version does not include any enforcement authority, such as civil monetary penalties, but it
16 does direct the FDA to report when manufacturers fail to report as required by law. It also creates
17 positive incentives for reporting because manufacturers will be eligible for expedited consideration.
18

19 The S. 3187 section on drug shortages also would authorize the Secretary of HHS to expedite
20 facility inspections and review of supplements and applications that could help mitigate or prevent
21 a “shortage,” as defined in this title. It also would require the Secretary to establish a task force to
22 enhance the Secretary’s response to shortages and create a strategic plan to address stated aspects
23 of shortages. The AMA is particularly supportive of provisions that require the FDA to consult and
24 collaborate with impacted stakeholders. In addition, the AMA supports the preparation of a report
25 studying market factors contributing to drug shortages and stockpiling.^{15,16}

26 **DISCUSSION**

27 Several solutions and approaches for addressing the drug shortage problem have been recently
28 advanced by the FDA, GAO, IMS, and HHS (see Table). Just-in-time manufacturing and
29 inventory practices leave little margin for error. The “current class-wide shortages in the sterile
30 injectable drug industry appear to be a consequence of a substantial expansion in the scope and
31 volume of products produced by the industry that has occurred over a short period of time without
32 a corresponding expansion in manufacturing capacity.”⁵ However, lower profits available for the
33 manufacture of generic drugs have led to lower levels of redundancy in manufacturing for these
34 products.

35 The structure of the sterile injectable market, the recent expansion in volume and scope, and the
36 consequent very high level of capacity utilization, means that small disruptions to supply – such as
37 may occur because of quality problems – and which might otherwise be absorbed through
38 diversion of capacity, can lead to cascading and persistent shortages. Quality problems are linked
39 with a majority (more than 50%) of sterile injectable shortages.

40 The most robust solution is to expedite review of new manufacturing capacity and expand supply
41 and maintenance of product quality in sectors with high capacity utilization. More extensive and
42 complete analysis is required on the potential economic causes of drug shortages and what would
43 constitute appropriate and effective incentives. In the meantime, based on the demonstrated
44 success of early notification, FDA and the industry should continue to work on collaborative
45 solutions to individual shortage problems until legislative solutions emerge.

1 RECOMMENDATIONS
2

3 The Council on Science and Public Health recommends that the following statements be adopted
4 and the remainder of the report be filed.

5
6 That Policy H-100.956 National Drug Shortages be amended by insertion and deletion to read as
7 follows:

8
9 1. Our AMA supports the recommendations of the 2010 Drug Shortage Summit convened by the
10 American Society of Health System Pharmacists, American Society of Anesthesiologists,
11 American Society of Clinical Oncology and the Institute for Safe Medication Practices and
12 work in a collaborative fashion with these and other stakeholders to implement these
13 recommendations in an urgent fashion.

14
15 2. Our AMA supports requiring all manufacturers of Food and Drug Administration approved
16 drugs and, including FDA approved drugs with recognized off-label uses, to give the agency
17 advance notice (within at least 6 months prior or otherwise as soon as practicable) of
18 anticipated voluntary or involuntary, permanent or temporary, discontinuance of manufacture
19 or marketing of such a product.~~drug shortage legislation such as H.R. 2245 and S. 296 that~~
20 ~~would require manufacturers, including those who share the market with others, to notify the~~
21 ~~FDA of any discontinuance, interruption, or adjustment in the manufacture of a drug that may~~
22 ~~result in a shortage.~~

23
24 3. Our AMA supports authorizing the Secretary of Health and Human Services to expedite
25 facility inspections, and the review of manufacturing changes, drug applications and
26 supplements that would help mitigate or prevent a drug shortage.

27
28 34. Our AMA will express appreciation to the President of the United States for issuing an
29 Executive Order intended to assist in mitigating ongoing drug shortages supports the creation
30 of a task force to enhance the HHS Secretary's response to preventing and mitigating drug
31 shortages and to create a strategic plan to: (a) enhance interagency coordination; (b) address
32 drug shortage possibilities when initiating regulatory actions (including the removal of
33 unapproved drug products from the market); (c) communicate with stakeholders; and (d)
34 consider the impact of drug shortages on research and clinical trials. address ongoing aspects of
35 drug shortages.

36
37 45. Our AMA will advocate that the U.S. Food and Drug Administration and/or Congress require
38 drug manufacturers to establish a plan for continuity of supply of vital and life-sustaining
39 medications and vaccines to avoid production shortages whenever possible. This plan should
40 include establishing the necessary resiliency and redundancy in manufacturing capability to
41 minimize disruptions of supplies in foreseeable circumstances including the possibility of a
42 disaster affecting a plant.

43
44 56. The Council on Science and Public Health will continue to evaluate the drug shortage issue and
45 keep the HOD informed about AMA efforts to address this problem report back on progress
46 made in addressing drug shortages at the 2012 Interim Meeting of the House of Delegates. will
47 report back report back at the 2012 Annual Meeting on efforts to mitigate drug shortages,
48 including the evaluation of potential economic and regulatory factors that may contribute to
49 drug shortages, especially with respect to oncologic drugs.

- 1 67. Our AMA publicly declares the problem of unsafe and unverifiable medicines and medicine
2 shortages a national public health emergency. (CSAPH Rep. 2, I-11). Our AMA urges the
3 development of a comprehensive federal independent report on the root causes of drug
4 shortages. Such an analysis should include consider federal actions, the number of
5 manufacturers, economic factors, including federal reimbursement practices, as well as
6 contracting practices by market participants on competition, access to drugs, and pricing.
7
- 8 8. Our AMA urges that procedures be put in place: (1) for the FDA to monitor the availability of
9 Schedule II controlled substances; (2) for the FDA to identify the existence of a shortage that is
10 caused or exacerbated by existing production quotas; and (3) for expedited DEA review of
11 requests to increase aggregate and individual production quotas for such substances.
12
- 13 9. Our AMA urges regulatory relief designed to improve the availability of prescription drugs by
14 ensuring that such products are not removed from the market due to compliance issues unless
15 such removal is clearly required for significant and obvious safety reasons.
16
- 17 10. Our AMA urges Congress to amend the 2003 Medicare Modernization Act to allow for more
18 reasonable payment rates for prescription drugs.

Fiscal Note: \$2,500

REFERENCES

1. Council on Science and Public Health Report 2. National drug shortages. American Medical Association. House of Delegates. November, 2011. New Orleans, LA.
2. Drug Shortages Summit Summary Report. November 5, 2010.
<http://www.ashp.org/drugshortages/summitreport>. Accessed March 16, 2012.
3. The White House. Executive Order 13588 -- Reducing Prescription Drug Shortages. October 31, 2011.
4. U.S. Food and Drug Administration. A review of FDA's approach to medical product shortages. October 31, 2011.
5. ASPE Issue Brief. Economic analysis of the cause of drug shortages. Office of Science and Data Policy, Assistant Secretary for Planning and Evaluation.
6. U.S. Government Accountability Office. Drug shortages. FDA's ability to respond should be strengthened. November 2011. GAO 2-116.
7. IMS Institute for Health Informatics. Drug shortages: a closer look at products, suppliers and volume volatility. November 2011.
8. American Society of Health-System Pharmacists. Drug Shortages Resource Center.
<http://www.ashp.org/shortages>. Accessed March 17, 2012.
9. Food and Drug Administration. Current drug shortages
<http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm>. Accessed March 17, 2012.
10. American Society of Anesthesiologists. Drug shortages survey. April 2012.
<http://www.asahq.org/For-Members/Advocacy/Federal-Legislative-and-Regulatory-Activities/Drug-Shortages.aspx#Drug Shortages Survey>. Accessed May 23, 2012.
11. Hamburg M. Six-month check-up: FDA's work on drug shortages.
<http://blogs.fda.gov/fdavoice/index.php/2012/05/six-month-check-up-fdas-work-on-drug-shortages/>. Accessed May 23, 2012.
12. Food and Drug Administration. 21 CFR Part 314 [Docket No. FDA-2011-N-0898]. Applications for Food and Drug Administration Approval To Market a New Drug; Revision of Postmarketing Reporting Requirements—Discontinuance. Interim Final Rule. Federal Register, Volume 76, No. 243. Pages 7853-78540.
13. U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry. Notification to FDA of issues that may result in a prescription drug or biological product shortage. February 2012.
14. Generic manufacturers increase capacity to combat shortages. Inside HealthPolicy.com. October 12, 2011.

15. Generic Pharmaceutical Association. GPhA Reveals the Accelerated Recovery Initiative: An Unprecedented Multi-Stakeholder Proposal to Address Drug Shortages. Press release. December 15, 2011. www.gphaonline.org/media/press-releases/2011/gpha-reveals-accelerated-recovery-initiative-unprecedented-multi-stakehold. Accessed March 17, 2012.
16. Drug shortages legislation 2nd draft comments to Senate HELP Committee Chair and Ranking Member. April 24, 2012 <http://www.ama-assn.org/resources/doc/washington/drug-shortages-ama-comments-help-24april2012.pdf>. Accessed May 23, 2012.
17. Drug shortages. ASHP-generated sign-on letter to E&C Committee and Senate HELP. <http://www.ama-assn.org/resources/doc/washington/drug-shortages-sign-on-letter-16march2012.pdf>. Accessed May 23, 2012.

Table. Recent Recommendations to Address Drug Shortages

| <i>IMS Recommendations</i> | |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Risk Identification | Systematically identify the high-risk sectors of the generics market. Identify all the low-cost, technically challenging and critical medicines – whether or not they are currently on shortage lists. |
| Demand Forecasting: | Continuously forecast the long-term demand for low-cost, technically challenging and critical medicines. Adjust forecasts based on such factors as demand trends, new medications, changes in clinical guidelines, practice patterns, care delivery changes and needs of clinical trials. |
| Volatility Index | A quantitative measure to systematically track and report month-to-month changes in the volume of drugs supplied to hospitals, clinics and retail pharmacies. |
| Predictive Modeling: | With the wealth of data available, predictive modeling techniques could be applied to anticipate shortages or supply disruptions for critically important medications at the national and regional levels. As data accumulate and measures are improved, the model can tightly focus interventions on those specific parts of the market and supply chain genuinely needing attention. |
| <i>GAO Recommendations</i> | |
| Drug Shortage Program | Assess the resources allocated to the Drug Shortage Program to determine whether reallocation is needed to improve the agency's response to drug shortages. |
| Informatics | Develop an information system that will enable the Drug Shortage Program to manage its daily workload in a systematic manner, track data about drug shortages—including their causes and FDA's response—and share information across FDA offices regarding drugs that are in short supply. |
| Strategic Planning | Ensure that FDA's strategic plan articulates goals and priorities for maintaining the availability of all medically necessary drugs—including generic drugs. |
| Performance Metrics | Develop results-oriented performance metrics to assess and quantify the implementation of the agency's goals and FDA's response to drug shortages. |
| <i>FDA Recommendations</i> | |
| Manufacturer Communication | Write a letter to drug manufacturers reminding them of their current legal obligations to notify FDA in advance of the discontinuation of certain drugs and urging them to voluntarily notify FDA of other potential disruptions to the supply of drugs that are not currently required, as soon as they become aware of them. |
| Guidance | Develop guidance and regulations that clarify and enhance the information on potential drug shortages that is submitted by industry. |
| Staffing | Provide additional staffing resources for FDA's efforts to prevent and mitigate shortages. |
| Legislation | Support legislation that requires early notification by manufacturers for drug shortages and provides new authority to FDA to enforce these requirements. |
| Informatics | Implement and maintain a database that can analyze the characteristics of drug shortages. |

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|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Preventing Shortages | Identify factors that contribute to success or failure in preventing drug shortages and continue exploring new approaches to preventing drug shortages under existing authorities. |
| Quality | Identify the quality issues in manufacturing practices that have contributed to severe drug shortages and develop approaches to addressing them. |
| Manufacturing Redundancy | Encourage product manufacturers to develop and maintain a plan for back up manufacturing and sources of Active Pharmaceutical Ingredients and other essential product components. |
| Early Warning | Explore development of a sentinel reporting network (e.g., major healthcare systems, wholesalers, physician specialty societies) to facilitate early warning of drug shortages. |
| Wholesalers | Encourage wholesalers to develop and publicize their procedures for distributing medical products in shortage. |
| Public Notification | Continue to maximize public disclosure of information regarding medical product shortages in FDA's possession, within the bounds of what must remain confidential. |
| Communication | Continue improving communication between FDA's field investigators and the Center for Drug Evaluation and Research's Office of Compliance and Drug Shortage Program staff. |
| Website | Improve the Drug Shortage Program's web site as a communications tool for health-care providers and other members of the public. |
| Probability Forecasting | Explore the feasibility of developing a model based on available data on drug shortages, manufacturer characteristics, and market factors with the goal of assessing the probability of future shortages. |
| <i>ASPE Recommendations</i> | |
| Regulatory Responses | Policymakers must balance the short-run benefits of tailoring regulatory responses to specific situations against the risk of strategic behavior and consequent reductions in competition in the long run. |
| Expedited Review | Steps that both expedite expansion of supply and maintain product quality in sectors with high capacity utilization could reduce the risk of shortages not only in the current situation, but in the future as well. To facilitate this, FDA can expedite review of new manufacturing capacity in this area and we understand that FDA is committed to doing this. |
| Purchase Agreements | Private organizations that purchase drugs and vaccines (including GPOs and insurers), can help to alleviate future shortages by strengthening the failure-to-supply requirements in their contracts in exchange for increases in price. Such contract changes are likely to lead manufacturers to invest in extra capacity of both production lines and API. |