

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 8-A-13

Subject: National Drug Shortages: Update

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Referred to: Reference Committee E
(Lawrence K. Monahan, MD, Chair)

1 INTRODUCTION

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3 Policy H-100.956, "National Drug Shortages," directs the Council on Science and Public
4 Health to continue to evaluate the drug shortage issue and report back at the 2013 Annual
5 Meeting of the House of Delegates on progress made in addressing drug shortages. This report
6 accomplishes that task.

7

8 METHODS

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10 English-language reports were selected from a PubMed and Google Scholar search from 2011
11 to April 15, 2013, using the MeSH terms "pharmaceutical preparations," or
12 "generics/economics," in combination with "supply/distribution," and using the text term
13 "drug shortages." Additional articles were identified by manual review of the references cited
14 in these publications. Further information was obtained from the Internet sites of the U.S. Food
15 and Drug Administration (FDA), American Society of Health-System Pharmacists (ASHP),
16 the Generic Pharmaceutical Association (GPhA), and from recent presentations on the topic at
17 special organizational meetings at which the AMA was represented.

18

19 CURRENT DRUG SHORTAGES

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21 Data on drug shortages come from various points across the supply chain.¹ Title X of the Food
22 and Drug Administration Safety and Innovation Act of 2012 (P.L. 112-144; FDASIA) includes
23 an "early notification clause" that instructs manufacturers of drugs that are "life-supporting,
24 life-sustaining, and intended for use in the prevention or treatment of a debilitating disease or
25 condition, including those used in emergency medical care or surgery" to notify the Food and
26 Drug Administration (FDA) 6 months in advance (or as soon as possible) if manufacturing is
27 going to be interrupted or discontinued.² Accordingly, the industry supplies voluntary
28 information on inventory/production data and supply interruptions. If the product is a
29 controlled substance, the FDA notifies the Drug Enforcement Administration in an effort to
30 adjust nationwide production quotas if necessary. Failure to notify is not subject to an
31 enforcement penalty, but companies that do not comply will be publicly identified in an annual
32 report. At this point, the voluntary notification approach is working according to FDA staff.

33

34 Wholesalers also may voluntarily submit information on inventory/supply interruptions.
35 Additionally, information on drug shortages is derived from hospital reports or less commonly

1 from individual practitioners or the public. Sometimes, sales and market share data indicating
2 a developing shortage are available to FDA from IMS Health.
3 Other features of Title X include: (1) enabling FDA to expedite review of a new or abbreviated
4 drug application to mitigate a potential drug shortage; (2) requiring FDA to form a dedicated
5 task force (see below); (3) requiring FDA to maintain a drug shortages list; (4) permitting
6 hospitals to repack medication in short supply (except controlled substances) into smaller
7 volume doses for use within a specific health system, defined as a collection of hospitals that
8 are owned and operated by the same entity and share access to databases with drug order
9 information. Title X also requires the Government Accountability Office to conduct an
10 extensive review of the myriad underlying causes of drug shortages and to recommend
11 solutions to alleviate drug shortages; AMA staff provided input to the GAO for this report.
12 Finally, the FDA also must provide an annual report to Congress that includes, among other
13 things, a list of actions taken by the agency to mitigate drug shortages, and the number and
14 description of the instances where FDA has used regulatory flexibility to prevent or alleviate
15 shortages.

16 17 *Trends in Shortages*

18
19 As previously discussed, the FDA tracks and focuses on shortages of “medically necessary”
20 drugs.³ A medically necessary drug product is one that is “used to treat or prevent a serious
21 disease or medical condition for which there is no other alternative drug, available in adequate
22 supply, that is judged by medical staff to be an adequate substitute.” The drug shortage
23 resource center maintained by the American Society of Health-System Pharmacists (ASHP)
24 tracks a somewhat broader array of drug and biological product shortages based largely on
25 reports from hospital pharmacists. In some cases these are local or regional shortages.

26
27 The FDA successfully prevented 282 shortages in 2012, a substantial increase from the 195
28 shortages FDA prevented in 2011.^{4,5} One hundred seventeen new shortages of medically
29 necessary drugs occurred in 2012, significantly fewer than the 251 shortages that were
30 recorded in 2011.⁵ FDA believes that the early notification requirement of FDASIA is one
31 important contributing factor in this trend. As of April 19, 2013, the FDA identified a total of
32 125 shortages of medically necessary products, a number that is comparable to the situation in
33 August 2012.⁴ In contrast, the ASHP drug shortages resource center identified more than 230
34 drug shortages as of April 19, 2013, a number that is about 5% higher than the number of
35 shortages catalogued by ASHP in August 2012.⁶ New shortages appear to be decreasing, but it
36 is taking longer to resolve existing shortages.

37 38 *Reasons for Drug Shortages*

39
40 Solutions to the drug shortage crisis require understanding the causes. Approximately one-
41 third of the shortages in 2012 were triggered by findings emanating from an FDA inspection,
42 while more than one-half were related to self-reported findings or causes.⁵ In 2012, shortages
43 of medically necessary drugs were evenly divided between “quality” and “delays/capacity”
44 issues together accounting for 54% of such shortages. Product discontinuations (13%) and
45 problems with the raw materials for active pharmaceutical ingredients (9%) accounted for 22%
46 of shortages. In some cases, shortages resulted from manufacturing failures for one drug that
47 increased demand for another drug and companies producing the latter were unable to meet
48 demand (3%). The causes of 20% of drug shortages in 2012 were not identified or reported.⁵

49 50 Sterile Injectables

1 Sterile injectables continued to comprise the vast majority of shortages (72%) in 2012.⁵
2 Intravenous nutrition products, electrolytes, emergency medicines, anesthesia, and cancer
3 drugs have been most affected recently. Shortages of sterile injectables are directly linked with
4 the state of the industry as just five manufacturers supply the majority of the market for these
5 products.¹

6
7 Most facilities producing generic sterile injectables are based in the United States because of
8 high transportation costs associated with liquids that require climate control. Many are aging
9 with inefficient processing lines and facility layouts prone to mechanical problems requiring
10 manual interventions and thus are at higher risk for contamination. This high market
11 concentration can turn a single production line disruption into a drug shortage.

12
13 Sterile injectables require a highly specialized manufacturing process. Production is often
14 committed to specific production lines within those facilities because of the drug's chemical
15 properties, potential for cross contamination, and end product characteristics (e.g., vial size or
16 whether a syringe is filled rather than a vial); and little or no redundant manufacturing
17 capability is in place. If a production line dedicated to a cytotoxic chemotherapy drug becomes
18 disabled or must be taken out of production, a ripple effect for shortages of other
19 chemotherapy drugs produced in that facility can occur.⁷ Other manufacturing lines may
20 produce multiple products in a continuous fashion (24/7) with little or no margin for error.
21 When new generic product opportunities become available as occurred in 2008-2011 when
22 several blockbuster drugs went off patent, trade-offs in production sometimes become
23 necessary.

24
25 The best solution for this set of circumstances is upgraded and expanded manufacturing
26 capacity. Given the current manufacturing environment, this can only be accomplished by
27 having manufacturers go through this process in a way that is responsive to any required
28 remediation, accomplishes upgrades to existing production lines, and incorporates construction
29 of entirely new facilities while simultaneously manufacturing an array of finished products.
30 While new and upgraded capacity is being established, manufacturing conditions that will
31 allow for more stable supplies of sterile injectables are still at least a few years away.

32 33 CURRENT ACTIVITIES

34 35 *FDA Drug Shortage Program*

36
37 The FDA's drug shortage program resides with the Center for Drug Evaluation and Research.
38 Eleven full-time staff work to help prevent and resolve acute shortages by working in a
39 collaborative fashion with others in the FDA, other government agencies, manufacturers, and
40 the public. The FDA also is collaborating on more widespread system solutions by working
41 with various stakeholders including the Generic Pharmaceutical Association (GPhA), the
42 Pharmaceutical Research Manufacturers of America, and the Biotechnology Industry
43 Organization.

44
45 The FDA's primary "toolbox" for mitigating drug shortages includes:

- 46 • the use of regulatory discretion that allows for the continued manufacture of a
47 medically necessary product when minor, low risk issues are identified, or the
48 application of additional safety controls (i.e., extra testing at plant, 3rd party oversight
49 of production, special instructions for safe use);
- 50 • requesting other manufacturers to increase production;
- 51 • expedited review of company proposals and applications; and,

- 1 • temporary importation from unapproved sources.

2 *FDA Task Force on Drug Shortages*

3
4 Consistent with AMA Policy H-100.956, FDASIA required the FDA to form an internal drug
5 shortages task force to develop and implement a strategic plan for preventing and mitigating
6 drug shortages.² As part of this process, the FDA issued a notice and request for comments to
7 assist the agency in developing and implementing this plan; the AMA submitted formal
8 comments on the proposal.

9
10 The strategic plan must include:

- 11 • plans for enhanced interagency and intra-agency coordination;
- 12 • plans for ensuring that drug shortages are considered when the Secretary initiates a
13 regulatory action that could precipitate a drug shortage or exacerbate an existing drug
14 shortage;
- 15 • plans for effective communication with outside stakeholders, including whom the
16 Secretary should alert about potential or actual drug shortages, how the
17 communication should occur, and what types of information should be shared;
- 18 • plans for considering the impact of drug shortages on research and clinical trials; and,
- 19 • an examination of whether to establish a “qualified manufacturing partner program,”
20 as described in section 506D(a)(1)(C) of the FD&C Act.

21
22 In its request for public comment, the FDA solicited input⁸ on several topics, including:
23 (1) how to encourage high quality manufacturing and expansion of capacity; (2) incentives that
24 federal agencies, including the FDA, could offer to help prevent shortages; (3) how to best use
25 existing tools or consider other actions that the FDA can take under its existing authority to
26 address impending shortages; (4) tools the FDA should be using to manage communications to
27 help alleviate potential or actual shortages, including the current public shortage Web site; (5)
28 the impact of drug and biological shortages on research and clinical trials and what FDA can
29 do to mitigate such impacts; and, (6) other actions or activities the FDA should consider
30 including in the strategic plan to help prevent or mitigate shortages.

31
32 The strategic plan is scheduled to be completed by July 2013; a final rule implementing the
33 plan is due by January 2014.

34
35 *Generic Pharmaceutical Association*

36
37 Given that the bulk of drug shortages involve generic sterile injectables, the GPhA proposed
38 an innovative voluntary approach to identify shortages and craft a unified response addressing
39 shortages from the production side. Under the Accelerated Recovery Initiative (ARI), generic
40 companies will share manufacturing information about drugs in short supply with FDA
41 through a third-party (IMS Health); as of April 19, 2013, five companies had agreed to
42 participate. ARI seeks to provide FDA with information that GPhA believes will enable
43 agency staff to more efficiently and effectively accelerate the recovery of critical drugs in
44 short supply. ARI is predicated on voluntary, confidential communication between IMS Health
45 and pharmaceutical companies involved in the manufacturing of generic injectable drugs in
46 shortage, a process which has been given the go-ahead by the Federal Trade Commission. A
47 pilot version of this program is reportedly near launch. FDA and GPhA are currently working
48 to identify four to eight products (all sterile injectables) that have at least two manufacturers
49 who could cooperate in meeting market production needs. In addition, a multi-stakeholder
50 approach involving participation from wholesalers, distributors, group purchasing

1 organizations and the FDA will provide information that will be critical in assuring a focus on
2 real-time decisions.

3
4 *Medicare Part B Pricing*

5
6 The basis for reimbursement for products covered under Medicare Part B changed under the
7 Medicare Modernization Act of 2003 from Average Wholesale Price to Average Sales Price
8 (ASP). Some have postulated that lower reimbursement to providers in turn puts more price
9 pressure on generic manufacturers. One element of the “Patient Access to Drugs in Shortage
10 Act” (as introduced) would change the Medicare reimbursement rate for sterile generic
11 injectable products with 3 or fewer active manufacturers from ASP + 6% to the Wholesale
12 Acquisition Cost (WAC) in order to achieve market price stability. However, the ASP
13 reimbursement formula may be targeted during the federal budgeting process to an even lower
14 percentage. ASP is the weighted average of all non-federal sales to wholesalers net of
15 chargebacks, discounts, rebates, and other benefits tied to the purchase of the drug product,
16 whether it is paid to the wholesaler or the retailer. WAC is developed by manufacturers using
17 algorithms to account for expected demand for the product, future competition for the product
18 and project marketing costs. The WAC is the baseline price at which wholesale distributors
19 purchase products.

20
21 In any event, it is not the manufacturers who are being reimbursed. However, the prices that
22 Group Purchasing Organizations try to negotiate for pharmaceutical products are under
23 constant downward pressure from hospital members, who must adjust to declining revenues
24 and reimbursement rates. The overall impact of these dynamics on shortages is unclear, and
25 disagreement persists on whether the change in Medicare reimbursement is a driving force in
26 drug shortages, especially in the case of chemotherapy drugs. Trends in shortages of drugs
27 affected by the Medicare Part B formula are similar to the pattern among drugs that should not
28 be affected by it.⁹ The GAO report is expected to more closely examine this issue, along with
29 other economic variables.

30
31 COMMENT

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33 Drug shortages continue to be a significant problem for hospitals, ambulatory care centers,
34 physicians and their patients. Some improvement in the number of new shortages affecting
35 “medically necessary drugs” is apparent although the overall number of shortages remains
36 elevated. The majority of drug shortages are due to manufacturing quality issues, often related
37 to aging infrastructure or production equipment. High market concentration of manufacturers
38 and limited spare production capacity contribute to scenarios promoting drug shortages.
39 Although the exercise of regulatory discretion by the FDA has been beneficial in mitigating
40 individual drug shortages, this approach will not be as effective as company-based
41 improvements in infrastructure, processes, and manufacturing lines. It also may paradoxically
42 delay necessary upgrades if companies are able to temporarily cope from incident to incident
43 with the help of dedicated FDA assistance.

44
45 Some new efforts are underway. The upcoming GAO report is designed to shed more light on
46 the real world causes of drug shortages, including market driven and economic variables, and
47 to recommend solutions in light of root cause analysis. A more comprehensive and dedicated
48 strategic plan for mitigating and resolving drug shortages will be forthcoming from the FDA.
49 The GPhA’s voluntary Accelerated Recovery Initiative shows promise for crafting real time,
50 market-based solutions for a limited number of high profile, sterile injectables. The issue of
51 incentives for manufacturers to upgrade facilities and expand production capacity, or to enter

1 the market in the first place, is worth considering. Additionally, creation of a qualified
2 manufacturing partner program is worth evaluating. The latter, perhaps modeled after the
3 Biomedical Advanced Research and Development Authority, which coordinates the
4 development and provides end-stage funding for products to be stored in a national stockpile
5 and used as medical countermeasures, may have the potential to introduce redundancy and
6 bolster supplies for a limited list of products. However, several barriers exist to this approach
7 including the sheer number of shortages, lack of excess production capacity, and no suitable
8 funding infrastructure for this type of approach.

9
10 In the meantime, additional resources intended for the FDA from the Generic Drug User Fee
11 Act have the potential to expedite application reviews and inspections. FDA also should work
12 to improve communication about existing drug shortages in a transparent fashion in order to
13 promote confidence in their entire process.

14
15 Given the ongoing nature and clinical implications of drug shortages in the U.S., it is
16 important that this issue be closely monitored and that our AMA continues to work to prevent
17 and mitigate drug shortages and educate its members on this issue.

18
19 **RECOMMENDATION**

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21 The Council recommends that the following statement be adopted and the remainder of the
22 report be filed.

23
24 That Policy H-100.956(6,7) be amended by addition and deletion to read as follows:

25
26 6. The Council on Science and Public Health ~~will~~ should continue to evaluate the drug
27 shortage issue and report back on progress made in addressing drug shortages as
28 appropriate. ~~at the 2013 Annual Meeting of the House of Delegates.~~ (Modify Current
29 HOD Policy)

30
31 7. Our AMA urges the development of a comprehensive independent report on the root
32 causes of drug shortages. Such an analysis should consider federal actions, the number of
33 manufacturers, economic factors, including federal reimbursement practices, as well as
34 contracting practices by market participants on competition, access to drugs, and pricing.
35 The Council should monitor and evaluate the forthcoming report on drug shortages from
36 the Government Accountability Office and report back on its findings. (Modify Current
37 HOD Policy)

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39 8. Our AMA advocate for government stockpiling of oral and intravenous parenteral drug
40 shortage products, or for removal of government policy price controls to mitigate against
41 an unfair manufacturing free market place.

Fiscal note: Less than \$500

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