

Provisional observations on drug product shortages: Effects, causes, and potential solutions

Summary of a stakeholders' meeting on drug shortages convened by the American Medical Association and the American Society of Health-System Pharmacists

Washington, D.C.
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Even though most drug products on the U.S. market are adequately available, shortages of some routinely used products are causing inordinate difficulties for providers and their patients. Physicians and health-system pharmacists are challenged every day to find an adequate supply of a growing list of drug products—for the most part, sterile injectable products—and to implement other therapies in place of products that are difficult or impossible to obtain. Health care facilities are devoting considerable resources to (1) identifying available supplies, (2) purchasing products outside their usual supply channels, and (3) purchasing products to use in place of those that are not available. The use of products that may not be familiar to a facility's health care personnel or the lack of a product can put patients at risk.

The American Medical Association (AMA) and the American Society of Health-System Pharmacists (ASHP) invited representatives of various stakeholders, including the American Society of Anesthesiologists, the Food and Drug Administration (FDA), pharmaceutical manufactur-

ers, the trade associations for research-based and generic pharmaceutical manufacturers and for distributors, group purchasing organizations (GPOs), the American Hospital Association (AHA), the Institute of Medicine (IOM), and the Department of Veterans Affairs pharmacy benefit management group to a one-day meeting to share their perspectives and ideas on the drug shortage problem. The objectives of the meeting, held July 12, 2002, in Washington, D.C., were (1) to identify and categorize potential causes of and solutions to the problem of drug shortages and (2) to create an imperative for resolving the problem. Vaccine shortages were not considered at this meeting, because they are being addressed in other forums. (IOM has identified many factors contributing to shortages of vaccines and antimicrobials.)

This document summarizes the provisional observations of key stakeholders on (1) the effects that drug product shortages are having on patient care, costs, providers, and health care organizations, (2) the major factors contributing to shortages, and (3) potential solutions for preventing or more effectively resolving

shortages. The potential solutions are presented in a table format with scores for feasibility and relative impact representing the collective opinions of the meeting's participants (Tables 1 and 2). No attempt was made to reach a consensus on the merits of the potential solutions or their relative importance. Nevertheless, these may provide guideposts for next steps. The problem of drug product shortages requires deliberate study; it cannot be resolved quickly and without a great deal of thought and detailed analysis. Studying the problem and coming up with the right solutions could take at least one year. IOM is interested in doing this and is looking for a sponsor or sponsors.

The experience and consequences of drug shortages

AMA members have been contacting the association with increasing frequency since early 2001 to complain about drug product shortages. A substantial number of physicians suspect there may be market manipulation behind at least some of the shortages.

A report to the AMA House of Delegates at the December 2001 in-

Table 1. Provisional Assessment of Potential Solutions to Drug Shortages^a

	Feasibility		Impact	
	Mean ± S.D. Score	n	Mean ± S.D. Score	n
	Category and Solution			
<i>Communication</i>				
FDA, manufacturers, group purchasing organizations (GPOs), distributors, hospitals, physicians, pharmacists, and other stakeholders should establish better communications regarding drug product shortages, including notifications about imminent shortages and future availability.	4.3 ± 0.8	10	3.8 ± 0.9	10
FDA and manufacturers, in collaboration with hospitals, other health care organizations, and professional organizations (e.g., medical specialty societies, pharmacy associations) should educate practitioners, and sometimes patients, on issues related to drug product shortages.	3.7 ± 1.0	10	3.4 ± 1.1	10
Pharmaceutical manufacturers should enhance internal communications, providing more timely information about a drug product shortage, including whether it is due to a time-limited back order or a true shortage, to all employees who have contact with providers and purchasers, such as field or sales representatives, medical information representatives, and customer service representatives.	3.6 ± 1.1	10	3.9 ± 0.7	10
Manufacturers should clearly communicate and justify to purchasers when price increases are necessary to stabilize the manufacturer's cost position on a drug product and, therefore, enable the manufacturer to continue supplying the product.	3.0 ± 1.3	10	3.0 ± 1.3	10
There should be a centralized source of information on alternative therapies for specific drug products that are experiencing shortages so that physicians, pharmacists, and other providers have ready access to reliable information.	3.5 ± 1.3	10	3.8 ± 1.0	10
FDA, in collaboration with professional associations, should encourage physicians, pharmacists, and other providers to report drug product shortages to FDA and should educate them on how to do this.	4.1 ± 1.2	10	3.3 ± 0.8	10
<i>Manufacturing</i>				
Manufacturers should apply the necessary resources to manufacturing, upgrading equipment, and retaining experienced personnel and should rely less on subcontractors to reduce the number of problems related to good manufacturing practices (GMPs) problems.	2.3 ± 0.5	10	3.9 ± 1.1	10
Manufacturers should consider strategic stockpiling of raw materials for certain drug products in order to have a reserve supply if a shortage occurs; any stockpiling of raw materials should be coordinated so that short-term, artificial "shortages" of raw materials are not created.	2.6 ± 0.8	10	3.9 ± 0.9	10
Manufacturers, especially generic manufacturers, should limit production of finished drug products (in short supply) to the dosage forms and package sizes that practitioners demand so that bulk drug is used optimally.	3.2 ± 1.4	10	3.3 ± 1.2	10
Manufacturers should reassess inventory trigger points for initiating production cycles to prevent disruptions in supply.	3.6 ± 0.8	10	3.5 ± 0.9	10
<i>Distribution and inventory management</i>				
Manufacturers and FDA should conduct proactive analyses of foreign markets for certain drug products (e.g., what/how much of a drug product is being produced, what the availability of raw materials, etc.) in anticipation of product availability from foreign sources if shortages of United States-manufactured products occur.	2.7 ± 1.2	10	3.7 ± 1.1	10
Manufacturers should deter self-created (artificial) drug product shortages caused by extremely large orders; manufacturers should question the motives of purchasers of unanticipated large orders and, as necessary, place limits on such orders.	3.0 ± 1.3	9	3.0 ± 1.0	9
Distributors, group purchasers, hospitals, and providers (e.g., pharmacies) should reestablish inventory replenishment trigger points to gain flexibility in the event of disruptions in supply.	3.3 ± 1.0	9	3.3 ± 0.7	9
Manufacturers should develop standards for triggering the allocation of reserve inventory based on the anticipated length of a back order or the severity of a drug product shortage. Manufacturers allocation programs should be user-friendly, fair, and adequately communicated to all stakeholders.	3.8 ± 1.1	9	3.9 ± 0.6	9
Manufacturers and distributors should develop mechanisms to improve their forecasting of provider demand for drug products.	3.1 ± 0.9	10	3.1 ± 0.9	10
Manufacturers should develop mechanisms for providers, group purchasers, and distributors to have a better awareness of the industry's capacity to produce adequate supplies of a drug product.	3.0 ± 1.2	9	2.3 ± 0.7	9
All stakeholders should increase inventory levels throughout the supply chain of medically necessary products.	2.8 ± 1.0	9	3.4 ± 1.0	9
Manufacturers should develop a more transparent system of inventory, margins, and payment to discourage inventory manipulations when quarterly and annual sales quotas are reached.	2.6 ± 0.9	8	3.3 ± 0.9	8

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Table 1. (Continued)

	Feasibility		Impact	
	n	Mean ± S.D. Score	n	Mean ± S.D. Score
Regulation and enforcement				
Federal law should require manufacturers to provide prior notification to FDA when any drug product is to be discontinued. (Broader than the current law, which only requires reporting the discontinuance of a sole-source product that is lifesaving, re: Section 506C of the Food, Drug, and Cosmetic Act.)	10	3.1 ± 1.4	10	4.0 ± 0.8
FDA should receive additional resources to address drug product shortages, including (but not limited to) increasing the frequency of inspections of manufacturing facilities, employing greater flexibility what is a "medically necessary" product, and enhancing collaborative efforts with manufacturers to resolve shortages.	10	3.0 ± 1.1	10	4.4 ± 1.0
FDA/Drug Enforcement Administration (DEA) should enhance cooperation on determining quotas for Schedule II drug products to more effectively avoid shortages of Schedule II products (e.g., if one manufacturer cannot supply a product, the DEA must facilitate the capability of another manufacturer to fill the void.)	10	3.5 ± 1.1	10	3.4 ± 0.8
The FDA should more aggressively pursue foreign manufacturers as a means to identify alternative sources of (high-quality) drug products to fill the void when United States-made products are in short supply.	9	2.8 ± 0.8	9	3.4 ± 1.3
FDA should facilitate review of important new drug products, or of drug products that would help to alleviate an ongoing shortage.	9	3.6 ± 0.9	9	3.4 ± 0.9
The federal government should require manufacturers to notify the FDA of potential drug product shortages (not just "sole-source" products and not to be confused with notification requirements for product discontinuance) and to provide an estimate of the duration of the shortage (e.g., weeks, months, or years). FDA should use this information to initiate necessary and appropriate actions to ensure public safety.	9	3.2 ± 1.5	10	4.2 ± 1.0
Economic incentives				
The federal government should provide incentives to manufacturers (e.g., tax credits, government bids, fast-track marketing approval, exclusivity) to increase their capacity to make certain drug products (industrial expansion), including older, routinely used, but less profitable products, or to encourage other manufacturers to produce them.	10	2.8 ± 1.1	10	4.2 ± 0.8
Research and study				
Investigate the impact of alternative/secondary, "gray-market" distributors during drug product shortages (e.g., who are these entities, what is the verifiable integrity of the products they are selling, are the inflated prices a form of "price-gouging" and is it legal, could enforcement of the Prescription Drug Marketing Act [to prevent drug diversion] limit their activity?).	10	2.7 ± 0.9	9	2.7 ± 0.9
Analyze whether the model for disaster preparedness (National Pharmaceutical Stockpile) would be applicable to prevention/resolution of drug product shortages.	10	3.0 ± 1.2	10	2.5 ± 1.0
Commission a study by a body of experts (e.g., Institute of Medicine, RAND Institute, etc.) to describe and analyze the complex factors that result in drug product shortages and to propose solutions.	10	3.4 ± 1.6	9	2.9 ± 1.4
Examine the concept of multiple sourcing of certain drug products, i.e., several manufacturers making the same drug product, to reduce vulnerability to shortages. (If one manufacturer cannot supply the product, other manufacturers will fill be able to the void.)	9	2.0 ± 0.5	9	3.2 ± 0.8
Assess whether broadening FDA's current definition of "medically necessary" for drugs subject to sustained shortages would result in more effective agency responses to drug product shortages, or would it just be an added drain on valuable resources?	10	3.6 ± 1.2	10	3.2 ± 1.0
Examine the procurement practices of large purchasers (e.g., GPOs, Department of Veterans Affairs, Department of Defense) to determine if these purchasers are contributing to drug product shortages.	10	3.3 ± 0.9	10	3.0 ± 0.7
Examine the relationship/interactions between regulation (enforcement) and manufacturing to determine if improvements can be made to prevent or more effectively resolve drug product shortages (e.g., resolve GMP problems more efficiently.)	10	3.8 ± 1.0	10	4.2 ± 0.8
Reassess the "just-in-time" inventory model, especially for medically necessary products, to determine if greater flexibility would effectively prevent or mitigate the effects of drug product shortages.	9	3.0 ± 1.0	9	3.2 ± 0.4

^aMeeting participants were asked to assess each solution for its feasibility and impact on a scale from 1 to 5; the higher the number, the greater the feasibility or impact. Ten participants submitted assessments. Participants sometimes chose not to score a potential solution, so scores for some solutions are based on less than 10 responses. Participants from the Food and Drug Administration (FDA) submitted a single assessment representing their collective views. No attempt was made to reach a consensus on the potential solutions.

Table 2.
Rank Order of Potential Solutions to Drug Shortages

Solution	Mean Score		Total
	Feasibility	Impact	
1. Food and Drug Administration (FDA), manufacturers, group purchasing organizations (GPOs), distributors, hospitals, physicians, pharmacists, and other stakeholders should establish better communications regarding drug product shortages, including notifications about imminent shortages and future availability.	4.3	3.8	8.1
2. Examine the relationship/interactions between regulation (enforcement) and manufacturing to determine if improvements can be made to prevent or more effectively resolve drug product shortages (e.g., resolve good manufacturing [GMP] problems more efficiently).	3.8	4.2	8.0
3. Manufacturers should develop standards for triggering the allocation of reserve inventory based on the anticipated length of a back order or the severity of a drug product shortage. Manufacturer allocation programs should be user-friendly, fair, and adequately communicated to all stakeholders.	3.8	3.9	7.7
4. Pharmaceutical manufacturers should enhance internal communications providing more timely information about a drug product shortage, including whether it is a time-limited back order or a true shortage, to all employees who have contact with providers and purchasers, such as field or sales representatives, medical information representatives, and customer service representatives.	3.6	3.9	7.5
5. FDA should receive additional resources to address drug product shortages, including (but not limited to) increasing the frequency of inspections of manufacturing facilities, employing greater flexibility in deciding what is a "medically necessary" product, and enhancing collaborative efforts with manufacturers to resolve shortages.	3.0	4.4	7.4
6. The federal government should require manufacturers to notify FDA of potential drug product shortages (not just "sole-source" products; also, this requirement is not to be confused with notification requirements for product discontinuance) and to provide an estimate of the duration of the shortage (weeks, months, or years). FDA should use this information to initiate necessary and appropriate actions to ensure public safety.	3.2	4.2	7.4
7. FDA, in collaboration with professional associations, should encourage physicians, pharmacists, and other providers to report drug product shortages to FDA and should educate them on how to do this.	4.1	3.3	7.4
8. There should be a centralized resource of information on alternative therapies for specific drug products that are experiencing shortages so physicians, pharmacists, and other providers have ready access to reliable information.	3.5	3.8	7.3
9. Federal law should require manufacturers to provide prior notification to the FDA when any drug product is to be discontinued. (Broader than the current law, which requires reporting only the discontinuance of a sole-source product that is lifesaving, re: section 506C of the Food, Drug, and Cosmetic Act.)	3.1	4.0	7.1
10. Manufacturers should reassess inventory trigger points for initiating production cycles to prevent disruptions in supply.	3.6	3.5	7.1
11. FDA and manufacturers, in collaboration with hospitals and other health care organizations, and professional organizations (e.g., medical specialty societies, pharmacy associations) should educate practitioners, and sometimes patients, on issues related to drug product shortages.	3.7	3.4	7.1
12. The federal government should provide incentives to manufacturers (e.g., tax credits; government bid, fast-track marketing approval, exclusivity) to increase capacity to make certain drug products (industrial expansion), including older, routinely used, but less profitable products, or to encourage other manufacturers to produce them.	2.8	4.2	7.0
13. FDA should facilitate review of important new drug products, or of drug products that would help to alleviate an ongoing shortage.	3.6	3.4	7.0
14. FDA/Drug Enforcement Administration (DEA) should enhance cooperation on determining quotas for Schedule II drug products to more effectively avoid shortages of Schedule II products (e.g., if one manufacturer cannot supply product, the DEA must facilitate the capability of another manufacturer to fill the void).	3.5	3.4	6.9
15. Assess whether broadening FDA's current definition of "medically necessary" for drugs subject to sustained shortages would result in more effective agency responses to drug product shortages, or would it just be added drain on valuable resources?	3.6	3.2	6.8
16. Distributors, group purchasers, hospitals, and providers (e.g., pharmacies) should reestablish inventory replenishment trigger points to gain flexibility in the event of disruptions in supply.	3.3	3.3	6.6
17. Manufacturers should consider strategic stockpiling of raw materials for certain drug products in order to have a reserve supply if a shortage occurs; any stockpiling of raw materials should be coordinated so that short-term, artificial "shortages" of raw materials are not created.	2.6	3.9	6.5

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Table 2. (Continued)

	Solution		
	Feasibility	Impact	Total
18. Manufacturers, especially generic manufacturers, should limit production of finished drug products (in short supply) to the dosage forms and package sizes that practitioners demand, so that bulk drug is used optimally.	3.2	3.3	6.5
19. Manufacturers and FDA should conduct proactive analyses of foreign markets for certain drug products (e.g., what/how much of a drug product is being produced, what the availability of raw materials, etc.) in anticipation of product availability from foreign sources if shortages of United States-manufactured products occur?	2.7	3.7	6.4
20. Examine the procurement practices of large purchasers (e.g., GPOs; Department of Veterans Affairs; Department of Defense) to determine if these purchasers are contributing to drug product shortages.	3.3	3.0	6.3
21. Commission a study by a body of experts (e.g., Institute of Medicine, RAND Institute, etc.) to describe and analyze the complex factors that result in drug product shortages and to propose solutions.	3.4	2.9	6.3
22. Manufacturers should apply the necessary resources to manufacturing, upgrading equipment, and retaining experienced personnel, and they should rely less on subcontractors in order to reduce the number of GMP problems.	2.3	3.9	6.2
23. All stakeholders should increase inventory levels throughout the supply chain of medically necessary products.	2.8	3.4	6.2
24. FDA should more aggressively pursue foreign manufacturers as a means of identifying alternative sources of (high-quality) drug products to fill the void when United States-made products are in short supply.	2.8	3.4	6.2
25. Reassess the "just-in-time" inventory model, especially for medically necessary products, to determine if greater flexibility would effectively prevent or mitigate the effects of drug product shortages.	3.0	3.2	6.2
26. Manufacturers and distributors should develop mechanisms to improve their forecasting of provider demand for drug products.	3.1	3.1	6.2
27. Manufacturers should clearly communicate and justify to purchasers when price increases are necessary to stabilize the manufacturer's cost position on a drug product and, therefore, enable the manufacturer to continue supplying the product.	3.0	3.0	6.0
28. Manufacturers should deter self-created (artificial) drug product shortages caused by extremely large orders; manufacturers should question the motives of purchasers of unanticipated large orders and, as necessary, place limits on such orders.	3.0	3.0	6.0
29. Manufacturers should develop a more transparent system of inventory/margins/payment to discourage inventory manipulations when quarterly and annual sales quotas are reached.	2.6	3.3	5.9
30. Analyze whether the model for disaster preparedness (National Pharmaceutical Stockpile) would be applicable to prevention/resolution of drug product shortages.	3.0	2.5	5.5
31. Investigate the impact of alternative/secondary "gray-market" distributors during drug product shortages (e.g., who are these entities, what is the verifiable integrity of the products they are selling, are the inflated prices a form of "price-gouging" and is it legal, could enforcement of the Prescription Drug Marketing Act [to prevent drug diversion] limit their activity?).	2.7	2.7	5.4
32. Manufacturers should develop mechanisms for providers, group purchasers, and distributors to have a better awareness of the industry's capacity to produce adequate supplies of a drug product.	3.0	2.3	5.3
33. Examine the concept of multiple sourcing of certain drug products, i.e., several manufacturers making the same drug product, to reduce vulnerability to shortages. (If one manufacturer cannot supply the product, other manufacturers will be able to fill the void.)	2.0	3.2	5.2

terim meeting identified many reasons for drug shortages. In preparing that report, AMA held discussions with FDA, the Pharmaceutical Research and Manufacturers of America, and ASHP. Among the report's recommendations was to ask the secretary of the Department of Health and Human Services to establish a task force to explore the causes of drug and vaccine shortages and identify appropriate solutions based on the input of stakeholders. As part of this initiative, the Secretary would commission research by experts to identify solutions to the underlying problems.

AHA receives many communications from state hospital associations and hospitals about drug shortages. Economic pressure on hospitals has resulted in reduced inventories of drugs and less flexibility to respond to shortages. Hospitals are more sensitive to shortages and to the cost of alternatives and are reluctant to buy "off contract." Hospitals are frustrated by the limited ability of the federal government to address some of these issues. They are concerned about how medically necessary drugs are defined and frustrated that regional shortages are not addressed in the same way as national ones.

ASHP saw a dramatic increase in communications from members about shortages in 1999. Some pharmacy directors had difficulty believing that routinely used products were unavailable nationally. Substantial amounts of staff time were being devoted to tracking back orders and seeking alternative sources. As the number of back orders increased and inventories diminished, members complained about the lack of information available from manufacturers, wholesalers, and FDA. They needed to know if the shortage of a given product was real, why there was a shortage, how long it might last, if there were alternative sources, and if there were any acceptable alternative therapies.

ASHP met with FDA representatives in December 1999 to express members' concerns about drug product shortages. Subsequently, FDA staff participated in a presentation at the ASHP Annual Meeting in June 2000, where many pharmacy practitioners learned about the far-reaching effects that shortages were having on patients, physicians, pharmacists, nurses, and hospital administrators. Pharmacists, in collaboration with physicians, were making choices about conserving and rationing remaining inventories. Some patients were receiving suboptimal care. Medical procedures were being delayed or canceled, and patients' hospital stays were being prolonged. Medication errors and adverse drug reactions were occurring when other therapies had to be used in place of an unavailable drug. The risk of errors is increased, because providers might be unaware that alternative drug products, even within the same therapeutic category, have differences in strength, dosage, time to onset of action, and duration of action, among other variables. An example of this problem was the use of sufentanil when fentanyl was unavailable. Many other opiate agonists could have been used, but some practitioners used sufentanil, which is more potent than fentanyl. Some practitioners assumed that they should give the same number of micrograms of sufentanil as of fentanyl; as a result, some patients received an overdose.

Other anecdotes were described that illustrate the serious consequences of shortages of lifesaving drugs used in emergencies. These included

- The difficulty of a level 1 trauma center in obtaining succinylcholine, a rapid-acting neuromuscular blocking agent used in positioning endotracheal tubes for emergency airway management,
- Patients' suffering when methylprednisolone was not available for treating acute back pain from slipped disks, and

- Unavailability of ephedrine to treat hypotension during surgery. Phenylephrine had to be used but was a poor substitute because it is less selective.

Pharmacists are spending increasing time communicating with pharmaceutical manufacturers and suppliers about drug product shortages. Within their institutions, pharmacists are having to take time to provide inservice education about alternative therapies and proper dosage and administration in order to minimize the potential for errors in patient care.

In 2001, ASHP entered into an agreement with the University of Utah Drug Information Service (UUDIS) to use bulletins developed by UUDIS to address pharmacists' questions about shortages. Also in 2001, ASHP published guidelines on managing drug product shortages and launched a Drug Product Shortages Management Resource Center on its Web site (www.ashp.org/shortage/). The resource center includes: (1) drug product shortage bulletins that provide, for specific drug products in short supply, information about availability, alternative agents, and management; (2) availability of drug products experiencing some supply disruptions; and (3) an e-mail link for reporting drug product shortages to ASHP. Since its launch, the resource center has received about 60 reports of shortages each month. More than 50 products are currently represented in shortage bulletins on the site, and information about availability is provided for another 20 products.

UUDIS had reports of shortages of 80 products in 2001, compared with 20 or fewer in preceding years. Nationwide, shortages of 120 products were reported in 2001. A nationwide shortage may not affect every facility, depending on the facility's patient population and what drugs the institution has under its contracts.

In 2002, data available through

June seem to indicate fewer shortages than in 2001. Shortages of fewer than 25 products were reported to UUDIS, and fewer than 40 nationwide. However, many of the shortages reported in 2001 and 2002 have been of long duration. In July 2002, 57% of the 2001 shortages and 70% of the 2002 shortages were ongoing.

Usually there is no advance warning of a widespread shortage. The first indication of a shortage to a health-system pharmacy may be a fax from a company stating, "We have drug X available"—usually at a cost far higher than that charged by the pharmacy's usual source. This suggests to pharmacy directors that a product may be in short supply and that they may need to order an additional supply. It is difficult to obtain information on how long a shortage will last and on good sources of other products that might be used in place of a product that is unavailable. Using alternative sources is often time-consuming and costly to the health system.

For pharmacies and health care organizations as a whole, drug shortages increase purchase costs. At one 800-bed hospital, purchases of alternative products and purchases off contract caused a \$25,000 per month increase.

Increased staff time to deal with shortages is also costly. Health care professionals' time is being reallocated; some institutions have one half to one full-time-equivalent position devoted to monitoring and addressing shortages. Pharmacists are spending additional time educating physicians and other providers about alternative drug products and proper dosing and administration.

There may be no available alternative for a drug in short supply. When there is an alternative, the quality of a product is usually acceptable; however, the quality of a product purchased from a distributor of unknown reputation may be in question. Compounding a product or purchasing a compounded product that cannot be

obtained commercially also requires extra safety precautions.

Possible factors contributing to shortages

The complexity of the pharmaceutical supply chain makes it difficult to identify the reasons for drug product shortages. UUDIS has been unable to identify a reason for one fourth of the shortages it tracks. Drug manufacturers cannot always share information affecting their products, and companies may have no central source of information about shortages and how long they will last. When the primary use of a product is an unlabeled use—an indication not listed in the FDA-approved labeling—it can be especially difficult to get information about a shortage.

Manufacturing. Manufacturing factors may include raw-material shortages, problems with manufacturing processes, FDA regulatory issues, business decisions, and natural disasters affecting manufacturing facilities. Producing pharmaceuticals involves complex manufacturing processes, and problems can occur at many stages. There can be regulatory problems, recalls of defective products, or problems with sources of raw materials, such as finding a new source of active pharmaceutical ingredients and obtaining FDA approval of new suppliers. More than 80% of the raw materials used in pharmaceuticals come from outside the United States.

Manufacturers must make a variety of critical decisions about entering the market and whether to stay in the market with a product. Manufacturers must look at potential return on investment when considering making a product. Generic manufacturers particularly look at market size, patents that are expiring, and whether other manufacturers are leaving the market. A manufacturer that has both proprietary and generic products might question the eco-

nomics of continuing to make a generic product when the margin on the generic falls below a certain threshold. Also, the pharmaceutical industry has a finite capacity for certain processes, such as lyophilization, and that finite capacity may be applied to selective products.

After deciding to make a generic product, the manufacturer identifies a source of raw materials, and FDA has to approve the facility supplying the raw materials. In the case of a foreign source, FDA inspects all sites to ensure that the imported product meets U.S. requirements. Then the company develops a formulation, selects a container and closure system, formulates the product, and verifies its stability.

The generic manufacturer files an abbreviated new drug application with FDA for a product that has to be quantitatively and qualitatively the same as the reference brand-name product to be eligible for a waiver of in vivo studies. A factor in some of the shortages today is difficulty obtaining the reference product with which to compare the generic one. Some injectable reference products, for example, have been off the market for a long time. Parenteral products are required to list all their ingredients in the labeling. Manufacturers can request guidance from FDA's Office of Generic Drugs on a case-by-case basis for products that are unavailable in the marketplace. The latest approved labeling can be obtained through the Freedom of Information Act. If a drug product is listed as discontinued in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"), the manufacturer will also need to ask FDA if the drug product was withdrawn for safety or efficacy reasons.

A manufacturer is vulnerable when raw-material suppliers leave the market. In some cases, manufacturers know in advance about problems with raw-material supply. How-

ever, even a year's notice may not be enough for a drug manufacturer to establish a new source of supply.

Communication. When one manufacturer of a product exits the market and competitors do not have advance notice of this, the remaining manufacturers may have to respond quickly to try to fill the void. When FDA knows of specific manufacturer problems, it tries to give other manufacturers of the product as much lead time as possible to increase capacity. However, when a manufacturer tries to respond to a shortage by increasing production of a certain product, the supply of another product that is run on the same line can be affected.

If a manufacturer decides to leave the market, it cannot (for antitrust reasons) call a competitor to say that it is leaving the market and give the competitor a signal to increase production. Some voluntary efforts at partnership between industry and government regulatory divisions have been successful in this regard, however.

A manufacturer may know it is going to have a manufacturing problem or a short supply of a product, but that information may be proprietary. Contracts with purchasers may contain specific requirements for notice, and advance notice to customers could allow them to switch to another supplier, if one is available. However, a manufacturer could be less than forthcoming with shortage information out of fear of a competitor's gaining market share.

When the FDA drug shortage program receives notification from a manufacturer of plans to discontinue a product, the discontinuation notice may be posted on the FDA drug shortage Web site (www.fda.gov/cder/drug/shortages). But manufacturers are not required to notify FDA of a discontinuance, except in the case of a sole manufacturer discontinuing a lifesaving product. FDA has no authority to compel a manufacturer to continue to make a product.

Economics. Multiple manufacturers of specific drug products provide a measure of safety with respect to preventing drug product shortages. For some drug products, though, there are no second suppliers. Incentives, such as tax credits, might enable manufacturers to resume producing some of the drug products that do not have large-volume use or reasonable profit margins. The Orphan Drug Act could be a potential model for this. An additional incentive might be a bidding process set up in a way that helps manufacturers gain regulatory approval for these products. One additional barrier for manufacturers is the difficulty in getting information on the quantity of a drug product that is actually needed by providers.

Generic drug products may have a low profit margin because such products are subject to the commodity business model. Pricing depends on how many manufacturers there are, and competition may reduce prices. Some manufacturers eventually drop out, but prices tend not to go up.

Distribution and use. Most hospitals and health systems obtain their drug products through wholesalers. Once the product gets into the wholesale distribution channel, the manufacturer loses the ability to allocate the available supply. Manufacturers can hold back some product so that it can be ordered directly, but hospitals may resist doing this because it deviates from their normal supply chain. Nevertheless, manufacturers could arrange payment methods that might make it easier for hospitals to buy directly from them.

Some observers believe that manufacturers may ration the amount of product they release into the supply chain. When a manufacturer meets its sales quota for a product, it may hold back supplies and not ship them. Some purchasers believe that this has long occurred during the last quarter of the year and that it is now happening quarterly.

Overuse of a product and poor ordering practices are other causes of shortages. In addition, when a large government entity, perhaps in reaction to needs that were not foreseeable (e.g., Operation Desert Storm, the September 11 attacks, epidemics), orders a large volume of drug products, the manufacturer may have no choice but to ship what was ordered. However, the product may go unused because it is not needed or deteriorates from improper storage. Purchasers may also unnecessarily stockpile products, which causes demand to exceed supply.

Drug-use factors that contribute to shortages include changes in clinical practice, allocation of the inventory of a product to certain populations or conditions, a manufacturer's discontinuation of a product that is used infrequently, and a war or other crisis that changes the need for certain products.

Regulation and enforcement. Manufacturing problems or a lack of adherence to good manufacturing practice (GMP) regulations are a major cause of drug recalls, and recalls can lead to shortages. FDA's Office of Compliance has recently seen an increasing number of GMP-related problems at certain large pharmaceutical production facilities. The Office of Compliance theorizes that these increases may be due to

- Use of antiquated manufacturing equipment,
- A shift of resources from maintenance of equipment and facilities to research and development,
- Loss of manufacturer personnel experienced in production and compliance issues as a result of company mergers or retirements,
- GMP-related problems with subcontractors who supply products to multiple pharmaceutical manufacturers and manufacturers' increased use of such subcontractors, and
- Limited FDA resources for manufacturing site inspections; in some in-

stances, when the amount of time between inspections at a manufacturing site increases, the GMP-associated problems identified by FDA inspectors are more numerous and more serious than if inspections occurred more frequently.

When FDA finds GMP-related problems during an inspection of a manufacturing facility, it provides a written list of the deficiencies to the manufacturer for review, response, and correction. The written list is provided on an FDA form, which is available on the FDA Web site or through a Freedom of Information Act request. Typically, the manufacturer provides a written response to the deficiency list describing corrective actions it plans to take to address them. FDA may then follow up with another inspection to ensure that the deficiencies previously noted have been corrected. If a manufacturer does not fix its problems satisfactorily, FDA can take enforcement action, such as issuing an injunction against the manufacturer or seizing its products. Such actions are taken when FDA has lost confidence in a manufacturer's ability to correct its GMP problems on its own.

If FDA is contemplating an enforcement action that involves a medically necessary product, the agency considers the effects of each action on the availability and future supply of the product. FDA currently defines a product as medically necessary if it is used to treat or prevent a serious disease or medical condition and there is no other available source of that product or an alternative drug that is judged by FDA's medical staff (with occasional consultation with outside experts) to be an adequate substitute. To ensure continued availability of a medically necessary product, FDA may request additional in-process or end-product testing, work with the manufacturer to correct its manufacturing problems, or qualify additional manufacturing sites.

Although it is usually desirable to keep the product available, in some cases this is not possible because of the seriousness of the product defect. Such defects may include a product containing no active ingredient, injectable products containing rubber gasket material or metal shavings, and products for intravenous injection containing particulate matter, bacteria, or mold.

If a medically necessary product cannot be manufactured domestically in sufficient quantity or quality to avoid a shortage, FDA may have to exercise enforcement discretion to permit importation of the product from a foreign manufacturing source. This is done only when FDA is able to collect specific and sufficient information from the foreign product manufacturer and when there is a U.S. distributor for the product. The product's ingredients, labeling, and manufacturing conditions are reviewed by FDA, and strict controls over distribution, process changes, and adverse-event tracking are established prior to U.S. distribution. For example, FDA permitted a Canadian company to supply the opiate antagonist naloxone hydrochloride when it was likely that U.S. supplies of this lifesaving drug would run out. Such decisions consider the public health benefit versus the risk. Information on such products will always be less complete than that on an FDA-approved product.

When FDA receives information about a possible drug shortage, that information is verified and evaluated by the FDA drug shortage program. FDA posts this information on medically necessary products on its drug shortage Web site, noting that a product will be in short supply or that there is an allocation program and giving a telephone number for the company. The agency is limited in what it can say; the term "manufacturer difficulty" may be used. FDA also communicates with practition-

ers through its MedWatch program; information is sent to health care organizations that can, in turn, transmit it to their members. The FDA drug shortage program can be contacted for shortage questions via an e-mail account (drugshortages@cder.fda.gov).

Potential solutions

The primary objectives of this stakeholders' meeting were to (1) identify and categorize potential solutions to the problem of drug shortages and (2) create an imperative for resolving the problem. During the meeting, participants suggested potential solutions. These were sorted into six categories (Table 1). The participants scored the categorized proposed solutions for their potential feasibility and impact. Table 2 presents the potential solutions in rank order by the total of the average scores for feasibility and impact.

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■ **SPECIAL FEATURE Drug product shortages**

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