

2013 Drug Shortages Summit: *Evaluating Long-Term Solutions*

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American Society of
Anesthesiologists 

ASCO[®]
American Society of Clinical Oncology


American Society of
Health-System Pharmacists[®]


INSTITUTE FOR SAFE MEDICATION PRACTICES

2013 Drug Shortages Summit: Evaluating Long-Term Solutions

Background

Between 2006 and 2010, the number of new drug shortages reported each year to the American Society of Health-System Pharmacists increased from 70 to 211 and unavailability of critically needed drugs became a public health crisis. In November 2010, a group of stakeholders held the Drug Shortages Summit to discuss the scope and impact of drug shortages and propose actions to better manage or prevent them.

Volunteers from the Summit subsequently formed workgroups that continued exploring causes for, and possible solutions to, drug shortages for a two-year period following the meeting, during which time drug shortages escalated to a record high of 267 by the end of 2012. The workgroups studied the complex regulatory, economic, business, and supply chain factors that influence drug shortages.

While concluding that no one solution would fix the problem, the group agreed that an essential first step should be two legislative changes. The first should require drug manufacturers to notify

the Food and Drug Administration (FDA) of actual or anticipated disruptions in supply and the second should require the FDA and the Attorney General to collaborate on shortages of controlled substances. Both these recommendations were included in drug shortage legislation enacted in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). In addition, and as recommended by the workgroup, the FDA increased the number of Drug Shortage Program staff to manage their growing workload.

Summit Overview

On April 18, 2013, many of the stakeholders involved in the original Summit reconvened with the goal of identifying long-term solutions to drug shortages. The meeting was coordinated by the American Hospital Association (AHA), American Society of Clinical Oncology (ASCO), American Society of Health-System Pharmacists (ASHP), Institute for Safe Medication Practices (ISMP), and American Society of Anesthesiologists (ASA), who hosted the meeting at its headquarters in Washington, D.C.

Summit participants included representatives from the FDA, American Medical Association, American Society for Parenteral and Enteral Nutrition, Centers for Disease Control and Prevention, Children's Hospital Association, Generic Pharmaceutical Association, Healthcare Distribution Management Association, Healthcare Supply Chain Association, Hospira, Inc., two group purchasing organizations (Premier and MedAssets), and West-Ward Pharmaceuticals. A list of attendees is attached (Appendix 1.)

The meeting opened with brief remarks by Mr. Joseph M. Hill, ASHP's Director of Federal Legislative Affairs and facilitator of the meeting. After review of applicable antitrust constraints, Mr. Hill requested that participants speak candidly about their concerns during the meeting and focus on long-term solutions. Speakers at the meeting included Captain Valerie Jensen, from the FDA Drug Shortage Program, and Dr. Enrique Seoane-Vazquez, Ph.D., Director of the International Center for Pharmaceutical Economics and Policy, Massachusetts College of Pharmacy and Health Sciences.

Mr. David R. Gaugh, Senior Vice President for Sciences and Regulatory Affairs at the Generic Pharmaceutical Association (GPhA) and Ms. Julianna Reed, Vice-President of Government Affairs at Hospira, Inc., provided the industry perspective on the causes of drug shortages and recommended solutions. Mr. Gaugh provided an update on GPhA's Accelerated Recovery Initiative (ARI), a voluntary industry program that allows participants to report detailed drug shortage information to an impartial third party, which in turn evaluates supply gaps and gauges the amount of production capacity available to respond.

The majority of the meeting was dedicated to discussion among stakeholders of the current trends and challenges of drug shortages, the effect of recent drug shortage legislation, and potential long-term solutions.

Presentations and Briefings

FDA spokesperson, Captain Valerie Jensen presented an overview of progress on the Agency's strategic plan for drug shortages and its Drug Shortage Program. She also reviewed current drug shortage statistics and offered FDA's perspective on the causes of drug shortages, which were as follows:

- Industry concentration to seven major manufacturers of generic injectables, many of which are sole-source manufacturers
- Lack of manufacturing redundancy and flexibility. Production lines run at full capacity around the clock, seven days a week and multiple products may be scheduled for production on the same line
- Complex manufacturing processes that are problem-prone and not simple to fix
- Low cost of generic products, which requires higher volume of sales for profitability

FDA staff in attendance noted that even before the early notification requirement in FDASIA became law, the Agency began receiving numerous supply disruption reports from manufacturers. The FDA has been able to use this information to prevent new drug shortages and better manage existing ones. FDA also receives reports from the health professions and wholesalers.

Captain Jensen described specific tactics the agency uses to prevent and mitigate shortages, such as:

- Using its regulatory discretion to allow a manufacturer with low-risk quality issues to continue production of medically necessary drugs,
- Requesting other firms to ramp up production,

- Expediting regulatory paperwork, and
- Facilitating temporary importation in rare cases.

Captain Jensen also noted that while FDA can expedite regulatory procedures and work with firms to get them back into production, these actions can only go so far. At a certain point firms must take steps to remediate problems so their products don't pose a threat to public health. Captain Jensen also stated that not all drug shortages can be predicted or prevented, but that FDA takes the problem of drug shortages very seriously and has dedicated significant resources to resolving it.

The Agency is now maintaining a database of drug firms currently marketing products in other countries that have expressed interest in assisting with shortages should they occur. Some of these firms have begun to seek approval for their products so they can market them in the U.S., which may create additional sources for drugs in short supply.

FDA has also requested that manufacturers with unreleased shortage products that are nearing expiry or that have already expired submit any data that the Agency can use to support extending expiration dates. In response to an attendee question, Captain Jensen stated that the Agency will consider doing the same for products already in the field. However, she noted that while some firms have submitted data in the former situation, none have done so for the latter.

Attendees offered anecdotal reports of end users submitting their expired or near-expired products to commercial laboratories for testing to extend product expiry.

Captain Jensen concluded by re-emphasizing FDA's commitment to preventing and resolving drug shortages and urging the industry to adopt a new culture

of quality. The Agency's strategic plan for addressing drug shortages, which was required by FDASIA, was expected to be made public in July 2013, but has yet to be released as of the date of this report.

In the question and answer period, an attendee asked whether FDA has considered waiving abbreviated new drug application (ANDA) fees for generics as a financial incentive. FDA staff responded that the fee for an ANDA is low, less than \$100,000, compared to \$1,900,000 for a new drug application, and would not be a meaningful incentive.

The next speaker, Dr. Enrique Seoane-Vazquez discussed key findings from his research on the economic causes of drug shortages and market failures that prevent resolution. He also suggested a number of strategies to address these factors.

Pharmaceutical manufacturers must weigh the cost of production and drug shortage risk-reduction programs against the likelihood that profit margins will recover these costs. Market competition and payer policies keep profits from generic drug products low and may not completely cover expensive risk reduction programs, such as manufacturing redundancies.

When this happens, firms may choose to either continue production with higher tolerance for the risk of a drug shortage or reduce or discontinue production, which usually precipitates a shortage. When the shortage occurs, other manufacturers of the shortage product are unable to respond quickly due to the difficulties of switching production lines, just-in-time production practices, and obligations to contracted customers. In contrast, tolerance for risk is much lower with patented products, due to potentially high financial losses. Unlike generics, manufacturers can set the price of patented drugs high enough to cover the cost of programs to avoid shortages.

Dr. Seoane-Vazquez stated that manufacturers, insurers, healthcare providers, group purchasing and managed care organizations do not experience the full negative consequences of drug shortages; therefore, these stakeholders are not willing to bear the cost of preventing them. As healthcare providers are unable to ascertain a particular drug company's exposure to the risk of shortage, they are not able to use this information when making buying decisions. Contrary to a normal competitive market, where production and price would increase to take advantage of market needs, the pricing and reimbursement of a product in shortage are likely to remain fixed, reducing the ability of the market to resolve the shortage. Stakeholders may actually worsen drug shortages by reacting to incomplete or ambiguous shortage information with hoarding or stockpiling.

Dr. Seoane-Vazquez suggested three strategies that might be effective in preventing shortages:

- Policies requiring robust risk-reduction programs that include improved quality systems, manufacturing redundancies, and maintenance of extra inventory,
- Drug pricing that reflects the cost of risk reduction programs, thereby addressing market failures, and
- Systematic risk monitoring throughout industry and disclosure of risk to stakeholders.

He also suggested that the Centers for Medicare and Medicaid Services (CMS) might play an influential policy role by (1) requiring that health care providers contract only with those manufacturers and distributors that can ensure uninterrupted supplies, (2) requiring reimbursed organizations to ensure availability of formulary medications, (3) unbundling drugs from reimbursement for inpatient services to

increase price flexibility, and (4) using shortages as a performance measure.

Dr. Seoane-Vazquez noted a number of significant barriers to implementing effective policies that address economic factors, such as FDA's limited scope of authority, potential impact on the competitive market, potential antitrust issues, coordination of industry-wide risk monitoring, and the cost of risk-reduction programs.

In light of these barriers, he also recommended that these policies be implemented in a progressive manner to allow capacity building and to manage any unintended consequences. He also acknowledged that the cost of low-volume generic drugs will likely increase. Attendees did not openly disagree with Dr. Seoane-Vazquez's concepts, but appeared doubtful that tactics proposed for CMS that could potentially penalize healthcare providers would be effective, stating that many factors influencing drug shortages are not within the end user's control or ability to change.

Juliana Reed, representing Hospira, reported on the company's recommendations submitted in response to FDA's call for comment on implementing drug shortage requirements in FDASIA. She placed emphasis on the importance of FDA and industry collaboration to find a "workable pathway," i.e., one that allows firms to upgrade and remediate without shutting down or closing numerous production lines. While these two types of activities are challenging to balance, firms that are successful may prevent a drug shortage or avoid worsening an existing shortage. The "workable pathway" approach is particularly relevant for sole-source manufacturers. Hospira committed to simultaneous remediation and production early on, as the company is a major supplier of U.S. generics and the sole source manufacturer of many of these products.

Noting that manufacturers do not receive a share of provider reimbursement, Ms. Reed discounted the theory that low reimbursement rates imposed by the Medicare Modernization Act are a significant economic cause of shortages. Nor did she fully concur that low pricing of quality injectables affects maintenance of quality conditions in manufacturing facilities. Stating that current Good Manufacturing Practices (cGMP),¹ are the minimum standard for quality and that hospitals are under pressure to reduce costs, Ms. Reed appeared unconvinced that further evidence differentiating degrees of quality among pharmaceuticals would persuade buyers to pay higher prices for drugs.

Ms. Reed described Hospira's close working relationship with FDA's Drug Shortage Program staff and the company's support of mandatory notification of pending shortages to the Agency by manufacturers. Specific suggestions she provided to the FDA Task Force to help resolve shortages are summarized below.

- Clearly defined FDA standards that are developed and updated every two years through a public process, that includes input from stakeholders, and is applied consistently across the industry
- Adequate time for notification and implementation of new requirements or improvements
- Incentives, such as tax credits, grants, offset of filing fees, or expedited review vouchers, for firms that invest in production of drugs that cost less to buy than produce or that build in redundancy or other contingencies.

¹Food and Drug Administration: Facts About Current Good Manufacturing Practices (cGMPs). <http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm> (accessed 2013 Aug 7)

- Extension of the Biomedical Advanced Research and Development Authority (BARDA)² model to include unplanned drug shortages
- Allow commercial production with active pharmaceutical ingredient batches from new suppliers that are used during the research and development period for exhibit and validation after the supplier is approved by FDA

Mr. David Gaugh, speaking on behalf of GPhA, described the Accelerated Recovery Initiative (ARI) as a supplement to FDA's drug shortage prevention toolbox. The proposed plan calls for manufacturers, who voluntarily participate in the program, to provide their current and projected production and supply schedules to IMS, an independent third party. IMS would then use this information and its own market data on specific products to project total demand, assess total current supply, and gauge industry-wide production capacity for a specified period. IMS would then forward its conclusions about the likelihood of a drug shortage and its potential scope to FDA staff for action by the Agency, if warranted.

Mr. Gaugh advised the group that ARI, like other proposed drug shortage solutions, would not eliminate drug shortages, but would address urgently needed drugs in short supply. The ARI, which was tentatively projected to launch in July 2013, had not been implemented as of the date of this report.

Stakeholder Discussion of Quality Issues

Mr. Gaugh of GPhA opened the discussion period with an overview of his organization's perspective

²Office of the Assistant Secretary of Preparedness and Response: Biomedical Advanced Research and Development Authority (Accessed 2013 November 7)

on drug shortages. Roughly 30% of total industry production capacity is currently inactive for various reasons, Mr. Gaugh said, a situation he estimates may take 5-10 years to fully resolve. He cited a number of factors that may positively influence this timeline:

- The FDA Drug Shortage Program staff's unprecedented collaboration with industry on alleviating shortages
- A number of new companies that are preparing to enter the generic market for the first time
- The recent passage of legislation enacting generic drug user fees (after a 2-year industry ramp-up period.)

However, Mr. Gaugh also stated that a large backlog of abbreviated new drug applications are awaiting review and approval by FDA while companies with fixed production capacity continue to add drugs going off patent to their portfolio, which may prevent an early resolution to drug shortages.

Hospira stated that their product shortages will likely be resolved much sooner than the GPhA estimates—a view that was echoed by the FDA. The generic drug industry is investing in facility upgrades and other remediation activities that will significantly expand production capacity and overcome many of the quality issues that contribute to current drug shortages. Hospira and GPhA both acknowledged that remediation is industry-wide, and recommended staggering the timing of future remediation efforts so that the maximum number of plants can remain in operation. Hospira added that remediation would be facilitated if FDA afforded firms more lead time to implement the Agency's expectations for new procedures or new technology.

The group then discussed surge capacity, which is the flexibility to switch production capacity quickly in order to manufacture critically needed products. Hospira and others discussed the recommendation that the Biological Advanced Research and Development Authority (BARDA) model might be a useful source of ideas for developing surge capacity. Attendees recommended that an emergency response to drug shortages should be limited to a short essential drug list, and one suggested that the World Health Organization essential drug list³ might be a starting point. Dr. Michael Cohen of the Institute for Safe Medication Practices volunteered to compile a potential list, with input from other stakeholders.

The BARDA program, administered by the Office of the Assistant Secretary for Preparedness and Response, maintains national emergency preparedness for chemical, biological, radiological, and nuclear accidents, incidents and attacks, pandemic influenza, and emerging infectious diseases. BARDA funds the development and procurement of medical countermeasures, such as antidotes and vaccines. It also supports manufacturing surge capacity for influenza vaccine and special training to maintain a capable bio-manufacturing workforce.

One attendee questioned whether the BARDA program could at least be extended to include emergency supplies of the suggested essential list of drugs, in order to allow the FDA more time to implement other strategies, such as importation or to expedite regulatory issues, such as plant inspections. An FDA stakeholder commented that the government funds financial incentives for participating in the BARDA program, but did not expect that the program could be sufficiently funded to manage the capacity and stockpile replacement activity required for the scope and scale of current drug shortages. Nevertheless,

³World Health Organization Model Lists of Essential Medicines. Accessed 2013 November 5)

FDA agreed the idea was worth exploring. The group determined that it needed more information about BARDA before making specific recommendations.

Stakeholder Discussion of Economic Issues

In addition to Dr. Seoane-Vazquez's presentation on economic causes of drug shortages, attendees were given an article entitled "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages"⁴ by Dr. Janet Woodcock, Director, and Dr. Marta Wosinska, Director for Economics Staff, Office of Program and Strategic Analysis at FDA's Center for Drug Evaluation and Research (CDER) in background materials for the summit.

While noting that many factors, economic and otherwise, may precipitate or contribute to drug shortages, the authors suggest that the fundamental cause of generic injectable shortages is the lack of financial incentives for the industry to invest in quality systems. Buyers consider generic versions of a product equivalent because they cannot discern differences in production quality. Further, buyers do not appear take note of quality-related supply disruptions, perhaps considering them to be temporary failures in an otherwise reliable U.S. drug market. Therefore, generic manufacturers must compete on price, rather than quality and reliability of supply. This inverse relationship between product profitability and risk tolerance is similar to conclusions presented by Dr. Seoane-Vazquez, who also suggested that manufacturers are willing to tolerate higher risk of shortages in production of low-profit drugs.

Two attendees representing group purchasing organizations (GPOs) disagreed, responding that they do not always award a contract to the lowest bidder; reliability of supply is an important consideration as well. In the current acute drug shortage environment, pharmacy decision-makers are willing to pay more for a guarantee of availability.

Premier, the Children's Hospital Association, and MedAssets, the three GPOs present, all stated that awarding two contracts is a common strategy to assure availability of supply. A discussion of the non-transparent nature of price determination followed. Practitioners continued to reiterate that paying more for drugs in the face of intense pressure to control or cut costs would be a challenge to justify if differences in quality are minor or imperceptible.

Hospira added that GPOs, while formed to negotiate volume discounts on medications, may not know that some pharmaceuticals cost as much to produce as they do to buy. Firms must price their patented products accordingly to find the right balance. Some participants suggested that generic companies should set hard minimums on their prices, however others commented that this would not stop competitors from stepping in and offering lower prices, only to raise them after cornering all the business. Similarly, if a GPO decided to award a contract that paid higher prices in exchange for an ironclad guarantee of supply, said one industry representative, the contract would likely not prevent them from buying the same products at a lower price, if available.

Another participant commented that some of drug cost is determined by manufacturers of active pharmaceutical ingredients (API). A Premier representative noted the risks of using single-source API manufacturers (i.e., power to both set higher prices and single-handedly cause a shortage if supply fails). As firms do not disclose the name or the number of API man-

⁴Woodcock, J, Wosinska, M. Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages. *Clinical Pharmacology and Therapeutics*. 93-2: 170-176 <http://www.nature.com/clpt/journal/v93/n2/pdf/clpt2012220a.pdf> (Accessed 2013 Aug 7)

ufacturers they use, this information cannot be used for buying decisions.

The discussion concluded with a consensus among attendees that it is in the best interest of buyers for multiple manufacturers to remain in the market so that prices are controlled by competition and multiple sources of product are available.

Other Discussion

Attendees briefly discussed supply chain factors that may influence shortages, specifically how availability varies among regions of the country or sometimes among hospitals in the same city.

The Healthcare Distribution Management Association cited manufacturer allocation practices as one cause of variable availability. They also stated that distributors typically base their allocation on customer purchase history. Stakeholders did not have sufficient information to determine whether distribution practices are equitable or whether and to what extent stockpiling of scarce medications takes place. With regard to the latter, one attendee noted that systems to trace medications throughout the supply chain stop at the door of the hospital or other care setting. Without information about the final disposition of products (i.e., whether or not products are administered to patients), the extent of stockpiling cannot be assessed.

Citing ongoing problematic shortages of analgesics, anesthetics, and stimulants, several attendees inquired whether the FDA had taken further actions to facilitate approvals of controlled substance quotas. The current time frame to authorize new quotas is 6 weeks. FDA responded that FDASIA requires the FDA Drug Shortage Program staff to notify the Drug Enforcement Administration (DEA) when the additional quota is needed by a firm to resolve a drug shortage. However, that is the extent of their author-

ity. FDA cannot compel DEA to authorize additional quota and authorization is subject to DEA determination of necessity.

Attendees briefly discussed whether there are incentives for manufacturers to make alternative vial sizes and concentrations of drugs. The CDC explained the importance of reserving “single dose” or “single use” medications for use in a single patient for a single case/procedure/injection. CDC acknowledged that repackaging (e.g. splitting doses) of unopened SDVs by the pharmacy may need to occur in times of critical need, such as during drug shortages, but that it is imperative that this be performed by qualified personnel in accordance with United States Pharmacopeia (USP) Chapter 797 standards. The CDC and USP are working together to better clarify existing standards for safely handling sterile medications. GPhA explained that manufacturers need data for a business case to show the viability of alternative vial sizes on the market. Manufacturers must develop and present to the FDA a “suitability” petition and meet certain requirements to make a new vial size. There is no fee for a suitability petition.

Conclusion: Recommended Areas for Further Exploration

The list below summarizes potential long-term solutions that participants recommended as areas for further exploration. In general, the group agreed that most of the recommendations had merit, although those intended to address economic factors require more study. The meeting concluded with co-conveners offering to share recommendations from the meeting with other stakeholders in order to develop potential next steps.

- Accelerate and streamline Drug Enforcement Agency controlled substance quota approval procedures

- Consider corporate tax credits and other incentives for manufacturers who maintain robust quality and facility maintenance programs
- Consider multiple contract awards by group purchasing organizations to ensure alternate suppliers during shortages
- Encourage collaboration between industry and healthcare stakeholders to develop better methods for demand forecasting
- Encourage manufacturers to provide single-dose medications in smaller volumes to reduce waste
- Engage payers, including the Centers for Medicare and Medicaid Services, to develop solutions for drug shortages
- Enhance FDA communication to providers on its mitigation plans and actions, and include more reliable information on when availability will be restored
- Establish a process for FDA to obtain data that allows the Agency to extend expiry during critical shortages
- Establish a list of critical drugs similar to the World Health Organization's Model List of Essential Medicines for prioritizing drug shortage resolution efforts
- Establish traceability of medications to determine patterns of distribution
- Evaluate the existing Biomedical Advanced Research and Development Authority (BARDA) model for applicability to managing drug shortages
- Provide FDA with sufficient resources to conduct inspections, process paperwork, and resolve other regulatory issues that contribute to drug shortages

- Use FDA metrics for manufacturers' quality and reliability to drive purchasing and reimbursement decisions

Appendix 1. Drug Shortage Summit 2013 Attendees

American Hospital Association

Roslyne D.W. Schulman, Director, Policy Development

American Medical Association

Barry Dickinson, Director, Division of Science and Biotechnology

American Society of Anesthesiologists

Lisa Pearlstein, Pain Medicine and Regulatory Lobbyist

Eli Loch, Resident Scholar

American Society of Clinical Oncology

Karen Hagerty, Director of Reimbursement Policy

American Society of Health-System Pharmacists

Bona E. Benjamin, Director of Medication-Use Quality Improvement

Joseph M. Hill, Director, Federal Legislative Affairs

Christopher J. Topoleski, Director, Federal Regulatory Affairs

Centers for Disease Control and Prevention

Michael Craig, Public Health Analyst

Michael Bell, Acting Director, Division of Healthcare Quality Promotion

Children's Hospital Association

John VanEeckout, Vice-President for Clinical Services

Food and Drug Administration,**Center for Drug Evaluation and Research**

Kalah Auchincloss, Office of Regulatory Policy

Catherine Gould, Office of Compliance

Capt. Valerie Jensen, Drug Shortages

Jouhayna Saliba, Drug Shortages

Emily Thakur, Drug Shortages

Douglas C. Throckmorton, Regulatory Programs

Russell Wesdyk, Office of Pharmaceutical Sciences

Marta Wosinska, Office of Program and Strategic Analysis

Generic Pharmaceutical Association

David R. Gaugh, Senior Vice-President for Sciences and Regulatory Affairs

Healthcare Distribution Management Association

Kristen L. Frietas, Director, Federal Government Affairs

HealthCare Supply Chain Association

Curtis Rooney, President

Hospira

Juliana M. Reed, Vice-President of Government Affairs

Jill Dowell, Director of Federal Government Affairs

Institute for Safe Medication Practices

Michael R. Cohen, President

Allen J. Vaida, Executive Vice-President

Massachusetts College of Pharmacy and Health Sciences

Enrique Seoane-Vazquez, Director, International Center for Pharmaceutical Economics and Policy

Associate Professor, Division of Pharmaceutical Sciences

MedAssets

Ron Hartmann, Senior Vice-President, Pharmacy

Pew Charitable Trusts

Alan Coukell, Senior Director of Drugs and Medical Devices

Premier Healthcare Alliance

Wayne L. Russell, Senior Director, Pharmacy Purchasing

West-Ward Pharmaceuticals

Michael Raya, Chief Executive Officer

Stephen M. Kaplan, Vice-President, Human Resources



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