

2014 Drug Shortages Summit

August 1, 2014



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Table of Contents

- [Background](#)
- [Overview](#)
- [Updates on the State of Drug Shortages—Regulatory, Purchasing, and Manufacturing Perspectives](#)
- [Potential Manufacturing, Production Capacity, and Regulatory Contributors to Drug Shortages](#)
- [Economic Factors in Drug Shortages](#)
- [Contracting and Purchasing Strategies to Address Drug Shortages](#)
- [Increasing Availability of Unit-of-Use Packaging to Address Shortages](#)
- [Conclusion](#)
- [Appendix: Summit Participants](#)

Background

New and ongoing drug shortages are a serious public health crisis. New drug shortages reported per year rose dramatically from 70 in 2006 to a high of 267 in 2011. Although new drug supply interruptions have begun to decline, existing shortages have been slow to resolve and the cumulative number of active shortages increased in the period from 2010 to 2014. According to the Government Accountability Office, the total number of active shortages—new or ongoing—experienced in a given year crossed the 450 mark in 2012.

Legislation enacted in 2012 helped strengthen the Food and Drug Administration's (FDA's) ability to respond to and resolve drug shortages. The FDA Safety and Innovation Act (FDASIA) requires manufacturers to report discontinuation or disruption of supply of certain drugs¹ to the FDA. The legislation

¹Drugs that are life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery. Does not include radiopharmaceuticals.

also allows the FDA to expedite the review of new or abbreviated drug applications to mitigate a shortage, requires the agency to maintain an up-to-date list of drugs in short supply, and mandates an annual report to Congress on drug shortages.

Although the changes enacted by FDASIA enabled the FDA to help reduce the number of new shortages experienced each year, the steadily increasing number of ongoing drug shortages continues to limit patient access to essential medications.

Overview

The 2014 Drug Shortages Summit was held on August 1, 2014, at the Pew Charitable Trusts in Washington, D.C. The purpose of this summit was to examine in depth the manufacturing, economic, and regulatory factors that contribute to drug shortages and consider possible solutions. The summit was organized by the American Hospital Association (AHA), the American Society of Anesthesiologists (ASA), the American Society of Clinical Oncologists (ASCO), the American Society of Health-System Pharmacists (ASHP), the Institute for Safe Medication Practices (ISMP), and the Pew Charitable Trusts. Previous summits were held in 2010 and 2013.

The summit attendees included representatives from additional provider groups (the American Medical Association, the American Society for Parenteral and Enteral Nutrition, and DaVita Healthcare Partners), relevant government entities (the Department of Health and Human Service's Office of the Assistant Secretary for Planning and Evaluation and the FDA's Center for Drug Evaluation and Research), health-system pharmacies (Johns Hopkins, the University of Utah Drug Information Service [UU DIS]), pharmaceutical manufacturing (Actavis, Fresenius Kabi, Mylan, Genentech, and the Generic Pharmaceutical Association), the International Society for Pharmaceutical Engineering, and three group purchasing

organizations (MedAssets, Novation, and Premier Healthcare Alliance). Attendees were selected for their expertise in pharmaceutical manufacturing, key roles in regulating drug manufacturing, roles purchasing drugs that have been in shortage, and experience managing drug shortages in healthcare settings.

Over the course of the day, participants discussed a number of possible contributing—as well as mitigating—factors for drug shortages, focusing on critical topics identified in previous summits. The conference began with a series of presentations providing an update on drug shortages from regulatory, purchasing, and manufacturing perspectives. Following these presentations, discussion was focused on four topic areas: (1) potential manufacturing, production capacity, and regulatory contributors to drug shortages; (2) economic factors in drug shortages; (3) contracting and purchasing strategies to address drug shortages; and (4) increasing availability of unit-of-use packaging to address shortages.

Updates on the State of Drug Shortages—Regulatory, Purchasing, and Manufacturing Perspectives

REGULATORY PERSPECTIVE: CAPTAIN VALERIE JENSEN, U.S. FOOD AND DRUG ADMINISTRATION

Captain Valerie Jensen, Associate Director for the FDA's Center for Drug Evaluation and Research's (CDER's) Drug Shortages Program, presented an overview of the agency's response to drug shortages since the enactment of FDASIA.

Most drug shortage notifications to the FDA in 2014 came from manufacturers and inspectors. Communication between the FDA field officers, who observe issues during inspection, and other agency officials, who coordinate responses to drug short-

ages, has greatly improved and allows for early mitigation through greater collaboration between the manufacturer and the FDA.

According to Jensen, FDASIA has significantly helped increase early information sharing by manufacturers. In addition, the FDA now receives much better information from firms about the root cause of a shortage, what assistance the manufacturer may need to resolve it, and the long-term plans to address the shortage. This more detailed, voluntarily provided information goes beyond mandated notification, and Jensen underscored the usefulness of this context to mitigating or resolving a shortage. Captain Jensen credited this increased transparency to agency efforts to establish good relationships with industry and allay concerns about prematurely posting information on the FDA's public drug shortages list. Jensen also noted that the FDA does not typically receive good information about issues further downstream in the supply chain, such as within the secondary wholesale and repackaging sectors.

Jensen reported that there was a significant decrease in the number of new shortages in 2013, which has continued into 2014. Although new shortages have decreased, the total number has remained relatively high because ongoing shortages, mostly of sterile generic injectables, tend to persist. The main immediate cause of shortages is quality problems, according to Jensen, the most common being sterility issues, presence of particulates, and product formulation problems. She noted particular vulnerabilities associated with sterile drug manufacturing processes and observed that a quality problem with a sterile injectable nearly always results in a shortage. Jensen also cited plant shut downs to address systemic quality issues as a significant contributor to shortages and identified concentration of the market to a few large firms and lack of manufacturing redundancy as additional underlying issues.

Jensen reported that the FDA CDER toolbox for preventing and mitigating shortages had not fundamentally changed and continues to be helpful. These tools include the following:

- Regulatory discretion to allow release of products with quality issues, if not presenting a risk to public health
- Working with other firms to increase production
- Expedited review of production plant changes and upgrades
- Temporary importation, as a last resort

Jensen noted that although trends of decreased new shortages and improvements in early notification are encouraging, not all shortages can be prevented by the FDA because not all causes are within the agency's ability to influence. In particular, the FDA can encourage but cannot require a company to continue to make a drug or increase its production. She noted that low profitability for older products may result in business decisions to discontinue them. Even when firms are actively producing a drug, companies may not have sufficient production capacity to meet a spike in demand. Jensen said that the FDA confronted this issue during the intravenous (IV) sodium chloride shortage this year.

In cases where it is not possible to meet the needs of U.S. patients with drugs approved for the U.S. market, the agency may allow temporary importation of equivalent or similar products from other markets, while continuing to work with regular suppliers on increasing capacity. For persistent shortages, the FDA is actively engaging with firms that either used to make the product, or might have interest in doing so, and exploring expedited review to allow these companies to start production. The agency also uses expedited review for plants currently engaged

in producing shortage drugs to help them get additional sites approved to make these products.

Site approvals depend on inspections, and Jensen reported that these had increased, in part due to additional staff and resources provided through the Generic Drug User Fee Act. Although the FDA's pool of inspectors is the same for all inspection needs, the agency is able to internally prioritize inspections needed to help address a shortage.

More broadly, the FDA is attempting to work with companies to understand how they might increase both capacity and redundancy in general, as well as exploring how to further incentivize quality. The FDA's long-term goals include investigating the underlying causes of shortages, working with outside groups to identify methods to incentivize and prioritize manufacturing quality, and identifying better methods to predict and prevent shortages, such as exploring possible early warning signs.

PURCHASING PERSPECTIVE: ERIN FOX, UNIVERSITY OF UTAH DRUG INFORMATION SERVICE

Erin Fox, Director of the University of Utah Drug Information Service (UU DIS) at the University of Utah Hospitals and Clinics, presented data about recent drug shortages trends and described the impact of shortages in healthcare settings. UU DIS receives voluntarily submitted shortage reports from ASHP and others, confirms them to be a national shortage with the drug firm(s), and then populates ASHP's drug shortages website with up-to-date information on active and resolved shortages. The annual number of new drug shortages posted on the ASHP site has declined since its peak in 2011. However, the number of ongoing shortages has remained consistently high, at approximately 300 for over a year, and many of these shortages continue to be unresolved. Fox also noted a significant number of "fre-

quent flyers"—drugs with a tendency to reappear repeatedly on the shortages list. During discussion, the FDA concurred with this point, noting amino acid, fentanyl, and morphine injections as examples. FDA staff suggested that these recurrences are likely due to capacity limitations, where even a small production interruption can cause a shortage.

Fox reported the top five drug classes for current drug shortages, which together account for over half of all of the active cases:

- Antibiotics
- Chemotherapy
- Cardiovascular drugs
- Central nervous system agents (including pain and anesthesia medications)
- Injectable electrolytes and nutritional products

She stressed that these drug classes make up the basic building blocks of therapy that are crucial for hospitals to use every day. The lack of drugs fundamental to care has had significant implications for patients, clinicians, and hospitals, which include treatment delays, poor patient outcomes, increased costs, and impediments to clinical trials.

Fox used two case studies of facility closures to describe the effects on patient care of serious and long-standing interruptions in the supply of key therapeutics. She noted that a single plant closure can cause 20 to 30 different shortages at one time, some of them sole-source items. One such closure in 2010 involved a number of chemotherapy products (about a third of the company's portfolio). This closure, combined with simultaneous problems at other companies, resulted in an unprecedented number of chemotherapy shortages, some of which continue today. These shortages had the poten-

tial to negatively affect prognosis and outcomes for cancer patients although the extent of harm or potential harm has not been quantified. Fox then described a second closure of a plant that was an important source of trace elements, zinc, selenium, and sodium phosphate. The acute shortage of these commonly used nutrition products—for which there are few, if any, therapeutic equivalents—seriously compromised care in vulnerable populations, including neonates unable to tolerate oral nutrition. Fox noted that although some companies indicate they intend to reopen closed plants, others appear to be permanently closed, and few new suppliers have entered the market to take their place.

According to Fox, lack of timely information significantly hinders effective shortage management. It is very difficult for hospitals to create treatment plans when there is little or no communication about why a product is in shortage, expected shortage duration, and how much product the hospital can expect to receive. Fox stressed that this is essential information for hospitals and clinicians attempting to manage drug shortages, but they often do not receive it, receive too little, or receive it too late to help them plan. As an example, she cited a recent unexpected IV nitroglycerin shortage. Despite this drug's essential role in emergency treatment of heart attack patients, the only notification one hospital received was a message accompanying a partial shipment stating that the organization's allocation had been cut until further notice. Hospital staff had to scramble after the fact to develop protocols for rationing the remaining supplies and substitution of alternative therapies. Despite severely limited inventory, the hospital was able to provide care until imported nitroglycerin was available although close day-to-day management was required.

MANUFACTURING PERSPECTIVE: STEPHEN MAHONEY, INTERNATIONAL SOCIETY FOR PHARMACEUTICAL ENGINEERING

Stephen Mahoney, Senior Director of Global Quality and Compliance at Genentech and member of the Drug Shortage Working Group at the International Society for Pharmaceutical Engineering (ISPE) presented the key findings from the ISPE's 2013 Drug Shortages Survey. The survey sought to investigate the specific quality issues that can lead to supply interruptions. Nearly half of survey respondents identified one or more quality issues to be a major cause of sterile drug shortages. Mahoney reported that problems associated with three of the six systems outlined in the FDA's compliance manual for inspections were identified by the survey as most frequently contributing to shortages, including the following:

- Quality—oversight that ensures compliance with current good manufacturing practice (cGMP) and quality control
- Production—activities and metrics that ensure performance of approved manufacturing procedures
- Facilities and equipment—maintaining appropriate resources and physical environment for drug production

Mahoney expanded on several of these elements. Specific production system problems identified through the survey were nonconformances and issues with production processes; however, it was not clear, based on findings, whether processes were flawed in their design and validation or were improperly executed. It was also not clear whether companies knew about process problems in advance. Problems with equipment systems and facilities centered on aseptic processing equipment. However, in this case underlying reasons were also not clear;

findings did not indicate whether equipment issues arose due to aging, improper use, or insufficient maintenance. Issues with lyophilizers—machines used to freeze-dry materials—were also linked to supply interruptions by survey respondents.

Following completion of the survey, ISPE sought to further explore why companies may not be upgrading older aseptic facilities or equipment. An ISPE task force developed a white paper released in 2014 that examined a number of different contributory factors. Although cost considerations play a role, the ISPE white paper found that the biggest barrier to facility maintenance or modernization is the significant length of time required to implement equipment upgrades. According to ISPE research, regulatory approvals can take up to three years in the United States and the European Union (EU), if no complicating incidents or issues arise, and up to seven years or more for approvals by other regulators internationally. In addition, domestic and international approval activities are conducted sequentially, rather than in parallel. This means companies have to run dual operations—both on older lines awaiting approval and newer lines for the markets where newer lines have been approved until all the required approvals are received. In addition to regulatory approvals, internal company planning and implementation takes time. Transfer of technology to new lines, facilities, or sites is complex and takes about seven months on average. ISPE suggests there may be opportunities for industry to tighten that process by streamlining their timeframes for equipment installation and operational qualifications.

ISPE's survey also identified deficient process governance, lack of clear corporate goals to avoid shortages, and absence of defined metrics for shortages as significant factors. The ISPE task force was charged with the development of a drug shortages prevention plan, and Mahoney summarized the

group's recommended key components for preventing supply disruptions. These interrelated components include the following:

- Corporate culture that supports and advances quality
- Robust quality systems
- Metrics to assess production quality and anticipate problems
- Business continuity planning, including production redundancy
- Communication with authorities
- Building organizational capability to achieve the above

These elements are mainly focused on steps that a company can take to make systems more resilient to supply interruptions. Mahoney also particularly emphasized the need for close technical collaboration and clear communication between drug manufacturers and global health authorities to best address the complex and multifaceted problem of drug shortages. In October 2014, ISPE released a Drug Shortage Prevention Plan, which describes the elements listed above in greater depth.

Potential Manufacturing, Production Capacity, and Regulatory Contributors to Drug Shortages

MANUFACTURING CONSIDERATIONS

Participants discussed the various quality issues that underlie the production interruptions, which can lead to drug shortages. Although there was general agreement that manufacturing complications are multifactorial, a few problems were cited as salient,

including issues with production equipment and discovery of particulate matter in drugs.

Problems with aseptic production equipment were one of the signals identified by the ISPE survey. Participants commented that aging equipment may be a problem, although it is not the exclusive problem, because older equipment can function well if properly maintained. However, if companies are running at very high capacity there may be a reduced frequency of preventive maintenance, which could result in equipment wearing out more rapidly.

Particulate matter in drugs was seen by participants as a troublesome and ongoing problem, but its origin in each case is not always known: complex manufacturing processes contain many potential sources of particulates. For example, particulates may be introduced into sterile injectables by equipment failures, packaging materials, or glass vials. One participant noted that there are only three commonly used manufacturers of glass vials for sterile drugs worldwide, suggesting that a problem with vials from one such company would have broad effects if not detected and resolved by the drug firm. Another participant noted that as technologies for detecting particulates improve, the tolerance for levels of particulate matter in drugs may decrease and cause a previously acceptable product to fall outside quality specifications

A number of other concerns were mentioned. One participant raised the issue of the quality of water used during production. Manufacturers make significant investments in water quality systems because of their importance to aseptic production, yet there has been at least one recent example of microorganisms discovered in the water used at a manufacturing plant. Another participant noted that when working with contract manufacturers, insufficient communication can also present challenges: contract manufacturers may not share information

about potential supply interruptions with the companies selling the product, hindering anticipation of manufacturing problems that will cause shortages.

Participants discussed the need for better, standardized measures of quality to help signal early issues to companies and regulators. Although many companies currently use quality metrics internally, these may differ among organizations. The FDA is in the early stages of developing a set of standardized quality metrics that the industry might at some future date regularly report to the FDA. Some metrics under consideration include out-of-specification rates, manufacturing times, deviations, complaint rates, laboratory issues, and the number of “right first-time” processes. Although not new, reporting these data to the FDA would be new practice. Regulators could potentially use this information to engage with companies earlier and address potential problems before they necessitate more disruptive remediation. Reporting to the FDA also has the potential to change the amount of attention these metrics receive within companies.

CAPACITY CONSIDERATIONS

In addition to manufacturing quality, group discussion covered shifts and constraints in manufacturing capacity that may affect shortages with a focus on producers of generic sterile injectable products.

Over the past several years, manufacturing problems have resulted in a number of plant or line shut-downs. At the 2013 Shortages Summit, one manufacturing representative estimated that 25 to 30 percent of capacity in the sector was off-line. Participants noted that the industry is currently in a cycle of capacity upgrades, but, as noted previously, these initiatives take time. Upgrading equipment and increasing capacity, including building facilities and adding or updating production lines, can take several years to complete, and participants

were not optimistic about any immediate alleviation of ongoing drug shortages. In addition, in light of shut downs of some major manufacturing plants in recent years, participants expressed uncertainty about when, if ever, some plants will come back to full production.

The group also discussed differences in capacity between brand and generic drug producers, noting particular challenges that increase risk for multiple shortages in the generic sector. For generic sterile drugs, a small group of manufacturers produce the majority of product volume, and these companies might be making up to 60 different products on a single production line. If problems occur, a plant may not have the overall capacity to shift multiple products to different production lines or facilities. In addition, moving products to another line can take place only after the firm obtains regulatory approval of the new line for making those products. Brand drug manufacturers usually produce just one product on a given line, which lowers the risk that a manufacturing interruption will impact multiple products. The decision to build new capacity as a shortage prevention strategy is also not a simple one—it is difficult for a generic company to predict the market they will be serving several years in the future, complicating the business case for investments

Capacity concerns within the generic sector also vary by product. Participants from industry expressed hope that capacity problems for producers of sterile injectables are being addressed; however, they said that new capacity issues for producers of large volume infusion solutions, such as 0.9% sodium chloride injection, may require different solutions because these drugs are produced under a business model with a margin that, according to participants, is quite narrow compared to other generic injectables. One participant noted that companies making these IV solutions may

need to run the lines at extremely high capacities to offset the low prices these products command in the current competitive market.

REGULATORY CONSIDERATIONS

Finally, the group discussed relevant regulatory issues, such as approval processes that impact a drug manufacturer's ability to respond quickly to supply interruptions by changing production lines. Moving a drug to a new production line requires a Prior Approval Supplement (PAS), which can take 12 to 18 months for FDA approval even with an expedited review, although it was noted that there have been cases where this has moved as quickly as four months.

Participants affirmed the finding from ISPE's white paper, discussed above, that it can take several years to upgrade a facility and secure multiple approvals from global regulators. Although the United States and the EU may approve new facilities fairly efficiently, other regulators can take much longer. As previously noted, companies that sell products globally may then have to run dual operations while they wait for additional approvals, which can have broad effects on operations, impacting even U.S. market activities.

Participants made a few suggestions for ways to improve efficiency during approvals. One suggestion was to have manufacturers work with regulators to move internal implementation steps and approval steps in parallel, rather than consecutively. Another suggestion was to allow companies to sell batches of drugs produced for validation testing if regulatory requirements are met, although validation testing sometimes takes so long that the drugs may expire before use.

One industry representative proposed a closer working relationship between the FDA and firms when remediation is required. For example, more detailed

feedback from the FDA about corrective action plans submitted in response to FDA Warning Letters could affirm for firms that they are on the right track before they initiate remediation or allow them to correct course if necessary. This information could also help manufacturers save time, improve production quality and help avert future shortages. FDA attendees responded that the agency does not have sufficient staff to give detailed feedback on every Warning Letter response, but historically the agency has done so in critical shortage situations and will continue to do so. Lastly, manufacturers called for coordination and harmonization of FDA standards with those in other countries.

Economic Factors in Drug Shortages

Meeting participants examined economic factors that might affect drug shortages, discussing both the health of the generic injectable market and whether external incentives to stimulate the market were worth consideration.

Joseph Hill, Director of Federal Legislative Affairs at ASHP opened the discussion by posing two questions to the group:

- Are economic incentives needed in the marketplace to stimulate capacity, encourage redundancy, or promote competition?
- What specific economic incentives would most likely encourage manufacturers to bring new technologies online to increase capacity and redundancy?

HEALTH OF THE MARKETPLACE

The group began by discussing the health of the market. Participants explored the tensions between significant price competition, inconsistent market predictability, and challenges in justifying capacity investments.

The generic injectable market was described as strongly influenced by pricing. Existing low prices are a significant barrier to market entry because it is difficult for new companies to compete. Profit margins, especially for older products, can be very slim, and manufacturers generally perceived that purchasers look for the lowest-priced products. One participant from the provider side stated that hospitals are reimbursed a fixed amount for services associated with a particular diagnosis, including drugs, so they may not be able to recoup higher drug costs if prices were to increase. Manufacturers also reported a hesitancy to change price for fear of alienating customers and further that it may be difficult to alter prices because they are often stipulated by contract.

Attendees also characterized the sterile generic injectable market as tight and fragile, with a limited pool of suppliers for a given product. Certain events, such as a firm departing the market or experiencing manufacturing problems, can quickly disrupt the equilibrium. When that happens, market shares can dramatically shift, and suppliers often cannot increase production to meet spikes in demand. Although the overall demand for many commonly used products is predictable, manufacturers do not always know the percentage of the market they will need to supply, especially when products are in shortage and normal production elsewhere in the sector is in flux. One manufacturer described responding to swings in demand ranging between 10 and 100 percent of the market for a product three times within the past two years. Several participants acknowledged that inability to predict market shares may discourage companies from committing to the production of certain drugs.

Manufacturers emphasized the importance of accurate demand forecasting, both to optimize production operations, and to support the business case

for capacity investments. According to one participant, guaranteed demand allows them to plan production and to justify the infrastructure investments necessary to sustain production capacity. When the business case is clear, manufacturers can more easily pursue capacity investments. Otherwise such investments may not be forthcoming.

Because of the competitive market, manufacturers of generic injectables or other low-margin sterile products like large-volume infusion solutions make full use of their available capacity. For this reason, *flex capacity*—the ability to move product manufacturing among different lines—may be the most important tool for manufacturers responding to shifts in production needs. One manufacturer described continually assessing which products to make on which line and in what quantities. These decisions are not only based on medical necessity, but also on competition and price margins for batches of the product, suggesting that more profitable products could be prioritized for production in certain cases.

Having flexible production capacity to accommodate movement of products between lines is not without cost. A manufacturer has to stop operations and clean the line every time a changeover occurs, which can take 8 to 12 hours. As noted above, it is not clear whether manufacturers are easily able to adjust prices to defray those costs. One manufacturer participant noted that his firm is less competitive on the pricing of certain products but that he could not lower his prices any further and maintain the ability to flex his capacity.

ASSESSING THE NEED FOR INCENTIVES

Participants had mixed views on the role of externally applied market incentives to increase capacity and redundancy and reduce drug shortages, but most agreed that there is no one “magic bullet” incentive. There was agreement on the importance of

ensuring sufficient supply of needed medicines but uncertainty about the ability of incentives to successfully and appropriately influence the market. It was also unclear whether it would be more important to spur increases in production capacity or increase the ability to move products around more flexibly—goals that may have different drivers. Another concern raised was the risk of creating a perverse incentive to perpetuate shortages if an external incentive yields financial or market advantages.

Despite concerns, participants were open to a discussion of incentives, recognizing that drug production is unlike other markets—the products are necessary, not optional. The consequences of shortages can be patient harm or even death. One participant asked whether some drug suppliers should be seen as too big to fail.

TAX INCENTIVES

Tax incentives were the first specific option considered by the group. Although there was some interest in tax breaks to defray the cost of entry to the market, there was general agreement that these are not likely to stimulate capacity expansion or modification to address shortages. The long period of time it takes to move from a decision to increase production to the actual increase itself, which could be three to five years, may render a discrete financial benefit on the front end less useful for a longer term effect. In addition, over this time period, specific drug shortages might be resolved, making it challenging to focus such incentives on drugs currently in short supply.

GOVERNMENT SUPPORT OF THE MARKET

Participants next considered whether the government could support the market by promoting investments in production of specific products and/or providing some degree of guaranteed demand. Existing

examples of such programs are Project BioShield, established in 2004, and the Biomedical Advanced Research and Development Authority (BARDA), established in 2006. Project BioShield funding is used to procure medical countermeasures for which there is no commercial market, such as chemical or radiological antidotes. Under BARDA, the government provides funding for the development and purchase of vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies.

The group was unconvinced that government funding to build additional capacity would be successful in this market. Even if companies were incentivized to build new lines and plants, it would not make financial sense to leave them idle as backup capacity in the case of shortages. Rather, one industry representative said that companies will maximize all of the capacity they have to produce products in their portfolio and flex as necessary, meaning it could still be challenging to increase production of a specific product when a shortage occurs.

Participants were more interested in the potential for the government to provide some guarantee of demand for certain products. One participant noted the government would need to guarantee to a company that it would purchase a specific volume of products at a specific price in order for such a program to work. Otherwise, the potential for competitors to offer a lower price and take away market share would continue to make investing in additional production risky. At the same time, participants cautioned that such a program would need to involve all market participants to provide a better safety net given the strained capacity in the sector. Involving all market participants also removes concerns about interference with trade. Finally, participants warned against putting the government in the role of medicine allocation. A government program should incentivize manufacturers to do their best to sell a product, but it would also provide a guarantee

that the government would help buy a product that was unsold.

If a program to support continuing availability of certain products in the marketplace is contemplated, participants recommended a carefully considered process to identify which drugs are most critical to receive this support. Participants were interested in looking at drugs frequently in shortage, as well as those considered most important to patient care. One participant had experience creating a list of critical oncology drugs—there have been concentrations of shortages in oncology products in recent years. Electrolytes, amino acids, and local anesthetics were also offered as products frequently in shortage, where the utility of targeted market support could be explored.

EXCLUSIVITY

The third incentive considered was offering limited market exclusivity to make producing older, lower profit margin products more attractive to manufacturers. Exclusivity for a single company was not seen as appropriate to drive equipment or capacity investments in circumstances where there are already multiple market participants as competitor companies would have little incentive to remain in an already concentrated market. But participants felt that in cases where older products are simply unattractive to produce, limited exclusivity could potentially make market entry more financially viable and appealing.

An exclusivity incentive, if considered, would be most appropriate to encourage market entry in cases where there is no one reliably producing a needed drug, according to participants. One industry representative suggested that firms might see an opportunity to “reset the market” (i.e., make it more profitable to produce older molecules that have persisted on the shortage list).

The cost of market entry can be an impediment to companies. As summarized by one participant, the ability to set a higher price point would be helpful in making business case to reintroduce a product. A time-limited incentive for the first to come to market might help encourage production of older or unattractive molecules. Exclusivity periods suggested ranged from 250 days to 3 years.

Participants also explored the tensions between using exclusivity to incentivize market entry and the countervailing effect of reduced competition. Attendees from the healthcare sector expressed several concerns about the risk of reduced competition, particularly in a market where increasing the mix of manufacturers is desired. Creating a situation where there is just one producer of a product for a prolonged period of time means there will be no backup options if that producer breaks down. One idea to address this was a shared exclusivity program, where a short-term market guarantees would be given to more than one player at a time.

REIMBURSEMENT-RELATED INCENTIVES

The group briefly discussed incentives linked to reimbursement, but there was general agreement that increases in reimbursement rates to healthcare providers would not be likely to benefit manufacturers. There is no incentive or requirement for purchasers to pass increased revenue from higher reimbursement rates back to their suppliers by paying more for drugs over time. For example, increasing Medicare's reimbursement rates for Part B drugs, which currently provide a six percent margin to hospitals over the average sales price for a given drug (known as *ASP plus 6*), would not likely result in additional funds paid to manufacturers.

Contracting and Purchasing Strategies to Address Drug Shortages

The group explored how contracting and purchasing could incentivize higher quality and more resilient product supply, the need for more transparent market differentiation, and the dominant factor of price competition.

RECENT CHANGES TO CONTRACTS TO ADDRESS SUPPLY INTERRUPTIONS

Manufacturers generally supply drugs to hospitals under a contract established between the manufacturer and a group purchasing organization (GPO) that negotiates pricing on behalf of multiple providers, facilities, and/or settings of care. These contracts also include negotiated administrative fees that manufacturers pay to GPOs when a provider purchases the contracted product. Participants described changes that have occurred in GPO contracts over the past several years to help better ensure consistent supplies of drugs.

First, failure-to-supply (FTS) clauses in contracts have been strengthened. These clauses require manufacturers to compensate purchasers if they need to buy more expensive products when the manufacturer has a supply interruption. FTS clauses have been an unreliable safeguard when a shortage affects the entire market because penalties do not apply when there is no alternative source of supply. GPOs have sought to strengthen these clauses in contracts, and although specific contractual details were not disclosed, one participant commented that he had issued a new request for proposal (RFP) and negotiated a new contract when a supplier was not willing to honor FTS obligations.

At the beginning of the discussion, Dr. Marta Wosinka, Director of Economics Staff at CDER, FDA, presented a recent study on FTS clauses. The study supported a carrot and stick approach to reducing shortages: increased penalties in FTS clauses combined with increases in the drug's price to incentivize investments to prevent supply interruptions. This finding underscores the recommendation in the 2011 Issue Brief for the HHS Assistant Secretary for Planning and Evaluation that “[purchasers] can help to alleviate future shortages by strengthening the FTS requirements in their contracts in exchange for increases in price.” The authors suggested that this approach would lead manufacturers to invest in shortage prevention.² Although participants showed interest in this approach, questions remain about the enforceability of such contracts as well as whether healthcare organizations could absorb increased costs when there are reimbursement-side limitations. Conversely, participants did acknowledge that health systems currently devote significant financial resources and staff to addressing shortages.

GPOs also described efforts to provide manufacturers with greater market predictability through contracts. Some have pursued a private-label program that allows GPOs to provide more predictable purchasing quantities for participating manufacturers. Some GPOs also have contracting strategies for certain suppliers that guarantee a purchase for a specific volume. If the GPO members do not buy the guaranteed amount, the GPO will reimburse the manufacturer for the difference. This strategy was called *failure to buy*—the counterbalance to *failure to supply*.

Additional strategies to provide greater market predictability include longer-term contracts and sole-

source awards. GPO participants had mixed views on sole-source awards. They may provide greater certainty for a manufacturer, but they may also reduce competition.

ABILITY OF CONTRACTS TO INCENTIVIZE OR REWARD CAPACITY AND QUALITY

Participants at the summit differed on whether the contracting process incentivized or rewarded capacity and quality. GPO participants noted that price is not the only factor, or even the top factor, they consider when awarding contracts. One participant described conducting extensive assessments of manufacturer quality and reliability, such as looking at FDA findings and keeping track of unsuccessful hospital ordering attempts. GPOs maintain detailed scorecards about suppliers and may also conduct site visits.

However, most manufacturers felt that although price is not the only factor, it is the dominant one. A company must be price competitive to secure business regardless of its ability to show greater reliability. This dominance may act as a disincentive: manufacturers who invest in capacity may not see a market advantage if they cannot also compete on price. One industry representative suggested that GPOs should weigh supplier reliability more heavily before switching to another manufacturer with lower prices.

In addition, manufacturers noted that although they worked well in partnerships with GPOs, contracts did not always provide the level of market certainty that they might want. Manufacturers under contract can still lose market share to other suppliers that offer a lower price. Even a sole-source contract does not guarantee a manufacturer a certain market and price; it only secures the right of first refusal when a cheaper competitor approaches a purchaser.

Manufacturers also shared the concerns expressed by other participants that sole-source awards,

²Kevin Haninger, Amber Jessup, and Kathleen Koehler, Economic Analysis of the Causes of Drug Shortages (Washington, DC: ASPE Issue Brief, October 2011).

although they help with predictability, can leave the market short if the sole-source producer encounters a production problem. One participant suggested a bifurcated award, wherein one supplier serves 80 percent of the market, and another supplier serves the remaining 20 percent but is permitted a price premium so as to stockpile active ingredients and step in when needed to help address shortages.

Rewarding capacity and quality also depends on the ability of manufacturers to demonstrate higher quality and reliability. Many purchasers at the Summit felt they did not have as much information as they would like to make this assessment. Some information is hard to get, such as details about a company's ingredient suppliers. The group discussed efforts by the FDA, ISPE, and others to develop common quality metrics that could provide better indications of quality. GPO participants expressed hope for transparency around these metrics to help raise the bar for quality and allow good performers to be appropriately rewarded.

Increasing Availability of Unit-of-Use Packaging to Address Shortages

The conference concluded with a discussion of the role of unit-of-use packaging as a possible mitigation strategy for shortages. The discussion was led by Lisa Pearlstein, Senior Pain Medicine and Federal Affairs Manager at the American Society of Anesthesiologists.

Pearlstein provided several examples of drugs used by anesthesiologists that are not available in doses that are most commonly used. These included labetalol, dosed in 1-mL increments but available only as a 20-mL size; neostigmine, dose in 2- to 5-mL increments, available in a 10-mL size; and certain contrast media, used in 3- to 5-mL increments but packaged in 30- to 50-mL sizes. In some cases, manufacturers

make smaller packaged sizes, but they are not as readily available or are much more expensive.

If drugs are packaged in single-dose containers, any remaining medication must be discarded after a practitioner removes the needed dose because the sterility of the remaining product may be compromised. When drugs are packaged in volumes larger than a usual single dose, waste of drugs can be significant and is especially concerning for drugs in shortage.

Although there was general agreement that unit-of-use packaging can help alleviate a shortage by reducing waste and avoiding contamination, there were also business concerns raised by manufacturers about its feasibility. One manufacturer said they believe there is market demand for unit-of-use containers, the challenge is assessing which products, and in what volumes, to make the business case. Other challenges are the different dose preferences of healthcare providers and the complex regulatory requirements to bring products to market that may offer little revenue. Regulatory approvals are particularly complex for combination products that include both drug and device elements.

Despite the noted challenges, manufacturers expressed interest in communicating with providers about their drug packaging needs and suggested that agreement on a standardized list of drugs and commonly used doses would facilitate interest in new product presentations.

Conclusion

The 2014 drug shortages summit validated a number of existing efforts to address the quality, regulatory, and economic issues that may underlie drug shortages and also identified new potential solutions that merit further consideration.

Although no single over-arching solution was identified, it is clearly important to understand and address both the immediate manufacturing problems linked with drug shortages as well as the business and market factors that may underlie them. Building or upgrading plants is complex and expensive, and regulatory approvals take time. Uncertainty in a manufacturer's expected market, which is compounded when there are drug shortages, can make it additionally challenging to justify these investments.

Potential measures to address shortages for further consideration and discussion:

1. Improved quality systems to better prevent production problems that can lead to shortages, with a focus on well-functioning aseptic processing equipment and facilities
 - The International Society for Pharmaceutical Engineering has made relevant recommendations in their 2014 Drug Shortage Prevention Plan, which include fostering a corporate quality culture, robust quality systems that are integrated with the supply chain to help companies better detect the need for maintenance and upgrades, and business continuity planning to ensure continuity of supply.
 - The FDA is currently working to identify a standard set of quality metrics that manufacturers could report to the FDA to support early collaborations on quality issues. If these metrics, once established, were also reported to purchasers, it could better differentiate manufacturers that invest in quality and reliability.
2. Identification of efficiencies in the regulatory review of plant upgrades and fixes to address production issues that can cause shortages
 - Greater harmonization and perhaps synchronization of regulatory reviews by different global agencies to shorten overall time to full approvals and minimize the need for dual operations by drug firms seeking to expand capacity
 - Allowing commercialization of trial batches of drugs that meet quality specifications to help mitigate losses during plant or line upgrade approvals
 - Closer collaboration between the FDA and industry on developing and implementing effective corrective actions when remediation is required to ensure approaches are in line with FDA expectations
3. Exploration of measures to drive greater investment in production capacity for products that experience shortages
 - Exploring in greater depth whether there are barriers in the generic injectable and IV drug markets that impair market health
 - Incentivizing capacity and reliability through contracts, such as through increased penalties in FTS clauses combined with increases in the drug's price to incentivize investments to prevent supply interruptions
 - Supporting the market through better guarantees of demand by committing to the purchase of a specified volume of certain products from a manufacturer, whether by a GPO or through a government program

- Granting limited exclusivity to incentivize market entry for needed products where there are no active producers
- Standardizing commonly used doses and concentrations to facilitate and incentivize industry commercialization by concentrating demand

Some of these measures, such as improved quality systems to better prevent production problems, are actionable now. Work to develop harmonized quality metrics is already underway and should continue. Other measures, such as identifying efficiencies in regulatory review processes, will require greater collaboration and discussion between manufacturers and regulators. Finally, external economic incentives should be studied further to understand what, if any, programs, could help prevent drug shortages by stabilizing the market.

Appendix: Summit Participants

Actavis

Brent Fisk, Manager, Government Affairs

American Hospital Association

Roslyne Schulman, Director, Policy

American Medical Association

Barry Dickinson, Director, Science and Biotechnology

American Society for Parenteral and Enteral Nutrition

Beverly Holcombe, Clinical Practice Specialist

American Society of Anesthesiologists

Nora Matus, Director of Congressional and Political Affairs

Lisa Pearlstein, Senior Pain Medicine and Federal Affairs Manager

American Society of Clinical Oncology

David Bernstein, Assistant Director of Research Policy

American Society of Health-System Pharmacists

Bona Benjamin, Director, Medication Use Quality Improvement

Joe Hill, Director, Federal Legislative Affairs

Chris Topoleski, Director, Federal Regulatory Affairs

Amber Wilcox, Contractor

DaVita Healthcare Partners

David Sanders, Director, Federal Affairs

Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation

Amber Jessup, Senior Economist

Food and Drug Administration, Center for Drug Evaluation and Research

Captain Valerie Jensen, Associate Director, CDER Drug Shortage Staff

Jouhayna Saliba, Drug Shortages

Marta Wosinska, Director, Economics Staff

Catherine Gould, Team Leader, Recalls and Shortages Branch, Office of Compliance

Grail Sipes, Senior Regulatory Counsel, Office of Regulatory Policy

Fresenius Kabi

Brent Eck, Executive Vice President

Genentech

Karen Hirshfield, Senior Compliance Specialist, Compliance Policy and External Collaborations

Generic Pharmaceutical Association

David Gaugh, Senior Vice President for Sciences and Regulatory Affairs

Institute for Safe Medication Practices

Allen J. Vaida, Executive Vice President

International Society for Pharmaceutical Engineering

Stephen Mahoney, Senior Director, Global Quality and Compliance, Genentech

Johns Hopkins

Melissa Lindamood, Director, Federal Affairs
Brian Pinto, Assistant Director, Medication Use Policy and Clinical Informatics

MedAssets

Ron Hartmann, Senior Vice President, Pharmacy

Mylan

Joseph Hendrickson, Vice President Product Strategy

Novation, LLC

Lee Ross Day, Director, Pharmacy

Premier Healthcare Alliance

Margaret Reagan, Government Affairs
Wayne Russell, Senior Director

The Pew Charitable Trusts

Gabrielle Cosel, Manager, Drug Safety Project
Elizabeth Jungman, Director, Drug Safety and Innovation

University of Utah Drug Information Service

Erin Fox, Director, Drug Information Service





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