Drug Shortages: A Complex Health Care Crisis

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Abstract

National tracking of drug shortages began in 2001. However, a significant increase in the number of shortages began in late 2009, with numbers reaching what many have termed crisis level. The typical drug in short supply is a generic product administered by injection. Common classes of drugs affected by shortages include anesthesia medications, antibiotics, pain medications, nutrition and electrolyte products, and chemotherapy agents. The economic and clinical effects of drug shortages are significant. The financial effect of drug shortages is estimated to be hundreds of millions of dollars annually for health systems across the United States. Clinically, patients have been harmed by the lack of drugs or inferior alternatives, resulting in more than 15 documented deaths. Drug shortages occur for a variety of reasons. Generic injectable drugs are particularly susceptible to drug shortages because there are few manufacturers of these products and all manufacturers are running at full capacity. In addition, some manufacturers have had production problems, resulting in poor quality product. Although many suppliers are working to upgrade facilities and add additional manufacturing lines, these activities take time. A number of stakeholder organizations have been involved in meetings to further determine the causes and effects of drug shortages. A new law was enacted in July 2012 that granted the Food and Drug Administration additional tools to address the drug shortage crisis. The future of drug shortages is unknown, but there are hopeful indications that quality improvements and additional capacity may decrease the number of drug shortages in the years to come.

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Drug shortages pose a significant threat to public health and safety and have affected multiple areas of medicine during the past several years, including oncology, anesthesia, emergency medicine, and nutritional support. These shortages have resulted in delayed treatment for patients, medication rationing, and in some cases treatment being denied because of unavailability of critically important drugs. Addressing shortages remains a top priority for the Food and Drug Administration (FDA); manufacturers and other stakeholders also have important roles to play in ensuring that critical drugs remain available for patient care.

Determining whether a drug shortage exists can be challenging. From a clinician's viewpoint, a shortage exists if a needed medication is not available for a patient. However, this situation is not necessarily always a shortage. The definition of a drug shortage varies, depending on perspective. The FDA defines a shortage as "a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the patient level."[1, p.8] The American Society of Health-System Pharmacists (ASHP) and the University of Utah Drug Information Service (UUDIS) define a drug shortage as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent."[2, p.1400] The slight differences between these definitions results in higher drug shortage totals provided by the ASHP and the UUDIS compared with those provided by the FDA.

Problems with local ordering, local or national distribution, or manufacturing can all result in supply problems that can lead to regional or national shortages. The medication distribution system in the United States is complex and generally operates on a just-in-time inventory system. Just-in-time inventory is a cost-reduction strategy used to avoid costs associated with carrying excess inventory. This means that, in general, there is not an excess of product anywhere in the supply chain.[2] Typically, the medications that manufacturers produce are distributed through wholesalers. The 3 largest wholesalers in the United States are AmerisourceBergen, Cardinal, and McKesson. These wholesalers have distribution centers located throughout the United States. A hospital

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or physician office staff typically orders medications through a wholesaler and receives a delivery from one of the distribution centers. If a problem occurs at any point in the distribution system, it can result in the situation of a clinician or patient not having access to a needed medication. For example, weather can delay shipments anywhere in the supply chain, hospitals or physician office staff can forget to order product, buyers may underestimate how much product is needed, or buyers may order more product than the distributor has on hand. These examples can create regional supply issues that are not problems at the manufacturer level.

If a manufacturer has a supply problem, however, it will often likely result in a national drug shortage, particularly if the manufacturer is the sole source for the medication or has a large share of the market. A given shortage is unlikely to occur at the same time and at the same rate across the country, though, because of varied distribution of product in the United States. The IMS Institute for Healthcare Informatics reviewed the drug shortage problem in 2011 and noted that 13 states (Arizona, Arkansas, Delaware, Florida, Hawaii, Kentucky, Nevada, Maryland, Massachusetts, Nevada, New Jersey, Ohio, and South Carolina) experienced more regional shortages than others; the IMS Institute for Healthcare Informatics could not identify the reason for the regional variation.[3] Whether this trend is consistent for these states is unknown because this analysis has not been repeated.

Once a shortage begins, it is not uncommon for health care systems to order larger quantities than usual because it is virtually impossible in a shortage situation to know when additional supplies may again be available. Survey data from the American Hospital Association in 2011 reveal that 85% of hospitals purchase excess inventory in response to a shortage.[4] This excess ordering can increase the duration of national shortages as manufacturers attempt to clear large backorders for product once their production lines are again operating. Excess ordering also means that some hospitals may have unnecessarily large inventories, whereas others may not have access to product.

Further complicating the issue is the fact that there are few situations when the entire supply of a given drug is completely unavailable. The

typical shortage situation is one where a purchaser can obtain some product but not enough to supply usual use. Health care organizations can choose to manage this type of situation in a variety of ways. One method is to continue using the product until supplies are exhausted. The most common method, however, is to ration or allocate the remaining product for specific clinical situations or defined patient populations where alternatives are not ideal. Rationing decisions, combined with differences in the types of patients treated, can lead to situations of local differences where one hospital is considerably affected by a given shortage but another may be seemingly unaffected. In addition, differences in communication about drug shortages may lead to perceived differences in effect. For example, some facilities may communicate about drug shortages early, whereas other facilities may choose to wait until a shortage worsens and requires immediate action.

DRUG SHORTAGE TRENDS
The UUDIS tracks national drug shortages and provides information on anticipated availability and clinical management strategies designed to minimize the effect of shortages on patients through a publicly available website offered through the ASHP (www.ashp.org/shortage; methods previously published).[2,5] The FDA tracks national drug shortages and the number of shortages prevented each year. The number of new drug shortages identified by the UUDIS that have affected the US health care system in the past decade is shown in Figure 1.[6] These data reveal a decrease in the number of new drug shortages in 2012 and 2013 compared with the number of new drug shortages in 2010 and 2011, a promising figure that is likely due to prevention efforts by the Drug Shortage Program at the FDA. Figure 2 illustrates the increasing number of drug shortages prevented by the FDA each year.[7] Although the decreasing number of new shortages is good news, the number of active and ongoing shortages is at an all-time high: as of the end of the third quarter of 2013, the UUDIS was tracking 294 active drug shortages (Figure 3).[6] For the past 4 quarters, active shortages have exceeded 290. These data, combined, indicate that although new shortages are being prevented by the FDA whenever possible, existing shortages are not resolving, often because many of the

affected manufacturers are continuing to address manufacturing problems that can take years to rectify (depending on the severity of the problem). The net result is essentially a stable number of active drug shortages where the relatively low number of new drug shortages offsets the few drug shortages that are resolving.

The typical drug in short supply is a generic product administered by injection.[1,3] A prevalence study of shortages on June 1, 2011, noted that 11% of all FDA-approved and marketed drugs, vaccines, and biologics were in short supply, with generic injectable agents being the most prevalent (23.1%).[8] Higher numbers were noted later in 2011 in a study by the IMS Institute for Healthcare Informatics when half of the generic injectable market was in short supply.[3] Classes of drugs commonly in short supply include anesthesia medications, antibiotics, pain medications, nutrition and electrolyte products, and chemotherapy agents. It is not uncommon to see shortages of multiple agents within a given drug class. This often occurs when the preferred product (drug A) becomes short, which leads to an increase in demand for an alternative drug (drug B). The manufacturer of drug B may not be able to increase production to meet the national demand, which then results in a shortage of drug B. The net result can be a shortage of all agents within a given class or therapeutic category. For example, in the early 2000s, shortages of steroid injections and diuretics dominated.[5] Anesthesia agents were particularly affected during 2009 and 2010, and chemotherapy drug shortages increased in 2010 and 2011. Most recently, in 2012 and 2013, shortages of electrolyte and nutrition products have been particularly severe. Shortages that affect multiple agents within a class are particularly challenging for health care practitioners.

EFFECT OF SHORTAGES
The effect of drug shortages is widespread, being felt by practitioners, purchasers, administrators, medication safety officers, researchers, and patients. The negative effects can be broadly divided into 2 categories: economic and clinical.

Economic Effects
Drug shortages were noted to have a significant financial effect on health systems in the 2010 survey of health care practitioners conducted
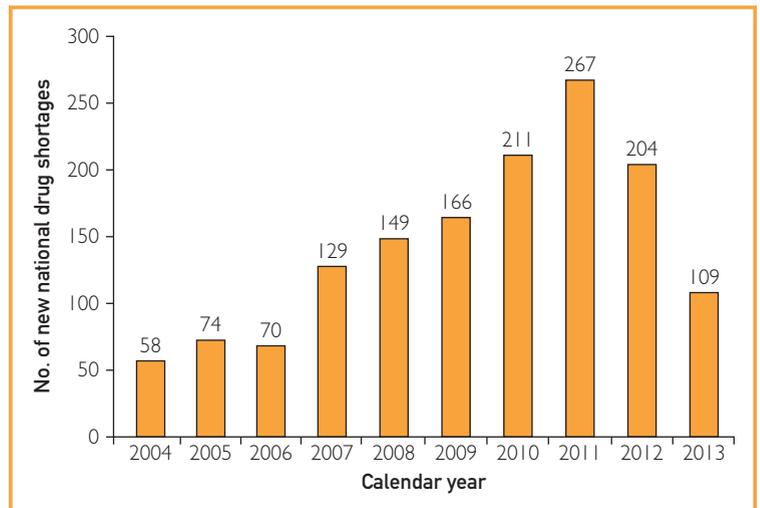

FIGURE 1. Number of new national drug shortages starting in each calendar year, January 2004, to September 30, 2013. Data are from the University of Utah Drug Information Service.[6]

by the Institute for Safe Medication Practices (ISMP).[9] The increased costs stem from both commodity and personnel costs. In an effort to quantify the personnel resources required to manage drug shortages in US health systems, investigators at the University of Michigan, in collaboration with the ASHP, surveyed 1300 directors of pharmacy of health systems across the country.[10] Similar to a study performed by the American Hospital Association,[4] more than
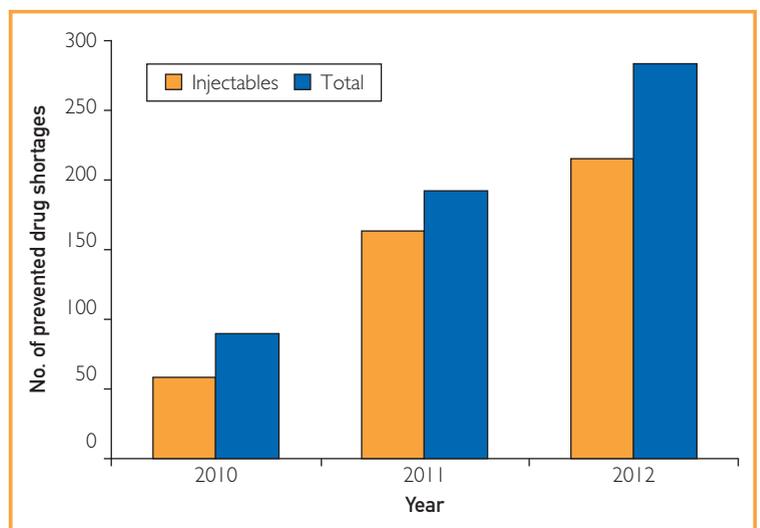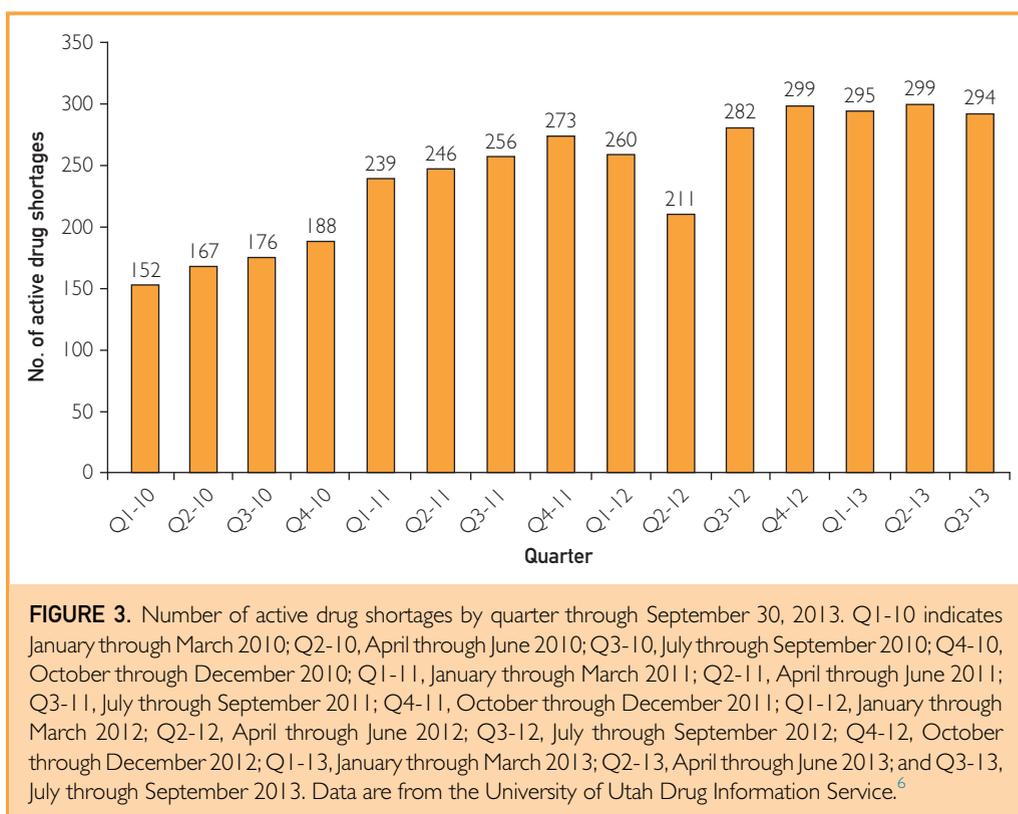

FIGURE 2. Number of drug shortages prevented by the Food and Drug Administration, 2010 to 2012. Data are from Center for Drug Evaluation and Research Drug Shortage Statistics.[11]

FIGURE 3. Number of active drug shortages by quarter through September 30, 2013. Q1-10 indicates January through March 2010; Q2-10, April through June 2010; Q3-10, July through September 2010; Q4-10, October through December 2010; Q1-11, January through March 2011; Q2-11, April through June 2011; Q3-11, July through September 2011; Q4-11, October through December 2011; Q1-12, January through March 2012; Q2-12, April through June 2012; Q3-12, July through September 2012; Q4-12, October through December 2012; Q1-13, January through March 2013; Q2-13, April through June 2013; and Q3-13, July through September 2013. Data are from the University of Utah Drug Information Service.[6]

99% of respondents reported experiencing at least one drug shortage in the previous 6 months; 30% of respondents reported experiencing shortages with more than 30 different drug entities, with larger hospitals being more likely to experience more shortages. Annualized personnel costs associated with managing drug shortages across US hospitals totaled approximately $216 million. These labor resources accounted for time spent by physicians, pharmacists, and nurses on tasks such as investigating alternative agents, developing action plans, managing inventory, adjusting computer systems to use the alterative agents, and educating staff—all actions that pull the clinician away from providing clinical care. Of note, this estimate is now a few years old and was determined on the basis of drug shortage numbers from 2010, when the number of active drug shortages was approximately half of what it is today (Figure 3). In addition, the estimate does not reflect comprehensive personnel costs in the United States because it relates only to costs incurred by hospitals and not all of the other venues affected by drug shortages (eg, ambulatory infusion centers, community pharmacies, and long-term care facilities). In addition, these data do not reflect the cost of drug shortages to patients and society, costs that have yet to be quantified.

Increased commodity costs are another economic concern. Premier Healthcare Alliance, a group purchasing organization (GPO), surveyed 228 of its hospitals and other health care sites (infusion and surgery centers, outpatient pharmacies, and long-term care facilities) in 2010 in an effort to describe and quantify the effect drug shortages were having on commodity costs.[12] Nearly all respondents (98%) experienced a shortage that resulted in an increase in drug costs, paying a mean of 11% more for the drug in short supply often because drugs had to be purchased off contract. In addition, institutions may have implemented other coping strategies, such as adding extra inventory to provide a cushion, purchasing more costly therapeutic alternative agents, and purchasing drugs through the gray market (a quasi-black market for pharmaceuticals as described below), findings that are consistent with those reported by others.[9,12-14] The estimated effect on commodity costs was calculated to be $200 million a year,

costs that are largely absorbed by the health care system.

As mentioned above, some institutions have dealt with shortages by purchasing drugs through the gray market. In the typical product-supply chain, hospitals contract with a GPO, an organization that negotiates product price with the manufacturer on behalf of the customer. Wholesalers then stock product and sell it to hospitals at the GPO price, with a chargeback given to the wholesaler if the purchase price was higher than the GPO-contracted price.[15] In the gray market, product moves through the supply chain outside normal distribution channels, most typically in a manner not intended by the original manufacturer.[14] Drugs may be purchased by secondary wholesalers from end users (eg, hospitals, infusion centers, and home care facilities) and then resold to other end users in small quantities at significantly marked-up prices.[14] Although not technically illegal, the gray market raises not only considerable economic concerns because of price gouging but also concerns about product integrity because of improper storage or handling or potential counterfeit product, a problem that is made worse because of the lack of national pedigree laws.[14,15] Despite these concerns, 52% of respondents in the ISMP survey said they bought product from the gray market, often because of pressure from physicians and patients to get product, findings that have been supported by another recent survey from the Hematology/Oncology Pharmacy Association.[13,14]

The published data attempting to quantify the economic costs associated with drug shortages are now a few years old and were gathered at a time when the volume of drug shortages was approximately half of what they are in 2013. Even with these realities, the combined estimate of labor and commodity costs totals hundreds of millions of dollars for health care systems across the country. The economic effect can also be felt by patients when the formulary-preferred agent on their managed care plan becomes unavailable and a more costly alternative must be prescribed. Some managed care plans have made temporary formulary adjustments, moving brand name products into lower price tiers so there is less out-of-pocket expense to patients.[16] Pharmacy benefit managers, companies that are hired to manage the pharmacy benefit for managed care organizations, government organizations, and private businesses, have also seen the need to take actions to prevent or ameliorate shortages and facilitate access to those in the greatest need. One such action is through additional prior authorization requirements to ensure a patient meets predefined criteria for use of a drug in short supply.[17]

Clinical Effects

Although the economic reality caused by drug shortages is alarming, even more concerning is the clinical effect. The number of patients harmed by drug shortages is difficult to quantify because the United States has no national reporting system to identify or quantify harm caused by shortages. Available data documenting patient harm due to drug shortages are primarily limited to published case reports or survey data and tend to focus on clinically severe events. The best source of aggregate data is the ISMP.[9,18,19]

The risks that medication shortages pose to patient safety can be broadly divided into 2 areas: increased risk of medication errors and adverse patient outcomes. A published failure modes and effects analysis identified areas of high vulnerability in the medication use process. The highest areas of risk exist when a different brand or concentration of medication must be purchased (affecting how the dose is prepared, dispensed, and administered) or when clinicians must order an alternative medication with which they are unfamiliar.[20]

Many drug shortages are invisible to the ordering prescriber because they can be managed by the pharmacy purchasing a different brand or concentration of the same drug entity. Using a different brand of product may not delay delivery of the dose to the patient, but it can increase the risk of medication errors. In a recent survey specific to oncology drug shortages, near-miss errors were reported by 16% of responders, and 6% reported actual medication errors related to shortages.[13] Many organizations purchase specific brands to avoid look-alike or sound-alike errors. If a hospital's preferred brand is unavailable and a different manufacturer's product is purchased in its place, there may be an increased potential for medication errors. For example, in 2008 the ISMP reported a medication error that occurred when 5% sodium bicarbonate solution was used instead of 5% dextrose solution to prepare vancomycin doses for 6 pediatric patients.[21] The error occurred

because the vials looked virtually identical ([Figure 4](#)). Previously, the hospital was purchasing a different brand of 5% sodium bicarbonate solution to prevent this error from occurring. It was not until the preferred product was in short supply that the pharmacy purchased the similar-looking vial.[21]

Sometimes a shortage can be managed when the pharmacy is able to prepare a product that would normally be purchased as a ready-to-use unit. Although seemingly harmless, purchasing different concentrations of products can result in medication errors that cause patient harm. For example, during the shortage of premade heparin bags, many patients received incorrect doses of heparin because of preparation errors.[9] Shortages of sterile products have caused some health systems to rely on product provided by compounding pharmacies, where, in some cases, poor quality compounding resulted in contaminated product and patient deaths.[22] Today's hospitals are highly automated with machinery that may use multiple databases often tied to product name by national drug code. When compounded or imported (eg, propofol) medications are used to manage a shortage, they sometimes do not have bar codes or national drug codes, which creates another area of vulnerability for potential medication errors.

Another area for potential medication errors results when clinicians need to treat patients with an alternative therapy, often one for which they may have limited familiarity. This can result in an increased risk of dosing errors, adverse effects, or drug interactions. Two patients died when hydromorphone was purchased to manage a morphine injection shortage because clinicians were unaware of the differences in potency.[9] Another patient died when methohexital was used as a substitute for propofol during a propofol shortage.[18] The error occurred because of unfamiliarity with diluting and dosing methohexital.[18] Dosing errors occurred with neuromuscular blocking agents when multiple agents were purchased to manage a shortage that affected the entire class.[9] The use of phenytoin injection to manage the fosphenytoin shortage resulted in a patient experiencing arrhythmia and cardiac arrest because the rate of infusion was not adjusted accordingly.[9] The potential harm that can occur from using an alternative agent will depend on the clinical situation. If an alternative agent for treating a given condition must be purchased because the drug of

FIGURE 4. Look-alike vials that contributed to a medication error. Data are from the Institute for Safe Medication Practices.[21]

choice is unavailable, it can cause real patient harm because of higher relapse rates or reduced survival (eg, when a less effective chemotherapy regimen must be used to treat a given tumor).[23]

In some cases, a shortage will result in a delay in therapy rather than use of an alternative agent. Whether a given delay is clinically significant depends on the disease state, product, and the length of time of the delay. For example, a delay of several days or weeks to obtain a vaccine may not be clinically significant, but a delay of even several days can be significant in the case of a shortage of antimicrobials. The clinical effect of other delays, such as delays in clinical trial enrollment for cancer medications caused by a shortage of the study medications (reported to affect 44% of respondents in one recent survey), are more difficult to quantify.[13,24]

Real-World Clinical Implications

Survey data from the ISMP in 2010 outlined high levels of patient harm, including 13 deaths.[9] An additional ISMP survey from March 2011 to March 2012 also revealed patient harm, including 4 additional patient deaths related to medication shortages caused by inadequate alternatives and medication errors related to alternative products.[18] Survey data from the American Society for Parenteral and Enteral Nutrition from May 2012 reported that 70% of responders were rationing multivitamin injection because of shortages.[25] The Hematology/Oncology Pharmacy Association surveyed members regarding oncology shortages during the first half of 2011; 93% of responders reported delays in administration or changes in treatment regimens due to drug shortages.[13] No published data are available outlining the significant emotional and financial effect drug shortages have on patients.

Published reports of patient harm due to shortages are varied in the types of patients affected and in clinical harm incurred. Reports of harm due to shortages of nutrition products include severe dermatitis related to zinc deficiency in premature infants,[26] selenium deficiency in pediatric patients,[27] and anemia and leukopenia in an adult patient due to a shortage of trace elements.[28] Critical nutrients, such as amino acids, vitamins, lipids, and trace elements, are rationed for patients receiving both short- and long-term parenteral nutrition.[29] Shortages of chemotherapy agents delay treatment, result in inferior outcomes, lead to omitted or reduced doses, adversely affect clinical trials, require rationing or substitutions not supported by evidence, and may affect potential cures for patients.[13,18,23,30-35] Shortages of antimicrobial agents seriously affect patient care, leading to poor outcomes, including death and decreased therapeutic efficacy.[9,36-40] Shortages of anesthesia medications increase patient morbidity (eg, hypotension, apnea, aspiration, prolonged mechanical ventilation, nausea, and vomiting), require the use of less effective substitutes, result in longer anesthesia or recovery times, postpone operations, cause medication errors that result in underdosing and overdosing, and, in some cases, have resulted in deaths.[9,18,41-46]

The clinical and economic effects caused by drug shortages are considerable and have resulted in what many are calling a national health care crisis. Managing drug supplies in health care facilities today is not unlike managing a natural disaster or national emergency. However, in the case of drug shortages, there is no single emergency but rather emergencies that occur on a daily basis. Clinicians are regularly focused on minimizing the effect of shortages on patient care. In most cases they are successful, as evidenced by the relatively small numbers of reports of harm compared with the large numbers of ongoing shortages. However, despite these daily successes, health care facilities are routinely operating in crisis mode with respect to the medication supply chain. Patients have been harmed, and rationing of select agents occurs in facilities nationwide. Although rationing decisions can be difficult, guidance is available for clinicians. A transparent and proactive approach should be used, whenever possible.[32,33,47]

CAUSES

Pharmaceuticals are a unique commodity in that demand generally remains constant over time and the consumer is not in control of the choice of product. In addition, the pharmaceutical supply chain is complex and involves many players, including the end user, wholesalers, distributors, GPOs, and the product manufacturer. Delays or errors associated with placing orders or shipping product can

result in short-term supply problems at the local hospital, distributor, or wholesaler level. Although these short-term supply issues are inconvenient for clinicians, they generally do not create long-lasting problems. The reasons behind national drug shortages are varied and complex. There is no single reason for the problem and, therefore, no easy fix. In 2011, the FDA published *A Review of FDA's Approach to Medical Product Shortages*.[1] This review identified the leading causes of drug shortages as manufacturing problems (43%), delays in manufacturing or shipping (15%), and lack of availability of the active pharmaceutical ingredient (10%).[1] Shortages of controlled substances may also be affected by the quota system used by the Drug Enforcement Agency to grant manufacturers supplies of active pharmaceutical ingredient on an annual basis.[48] The extent to which this quota system contributes to shortages is unknown. The Government Accountability Office was asked to review this question in May 2012; their analysis is not yet available.[49]

Generic agents are more susceptible to shortages than brand name medications.[1] Branded products typically have back-up manufacturing lines, thereby providing for redundancy in the production process. In contrast, generic products are typically made on a single manufacturing line, and that line is often used to produce multiple other products.[50] Shortages of generic injectable medications are also more frequent because there are relatively few suppliers that provide these agents; in this highly concentrated market, 3 manufacturers supply 71% of the market volume and more than one-third of products have just 1 or 2 manufacturers.[1,3,15]

Injectable products are at increased risk for quality control concerns because of the complexities associated with manufacturing a sterile product. Manufacturers must adhere to the FDA's Current Good Manufacturing Practices (CGMPs), which are a complex set of standards that provide direction for every aspect of the manufacturing process, including equipment maintenance, raw material handling, data collection, and laboratory results.[51] Although the CGMPs exist to ensure product integrity, quality failures have occurred in factories during the past several years that have put patients at risk of exposure to drugs contaminated with mold, bacteria, and glass, metal, and other materials.

Resolution of these quality issues has caused a significant number of critical long-term shortages at the manufacturer level.

Data summarizing the reasons for sterile injectable drug shortages are given in the Table. Quality problems were the reported cause for 77% of the shortages of sterile injectable products in 2012. However, other causes exist, some of which are compensatory mechanisms in the production system. When a shortage occurs, an alternate manufacturer may be unable to ramp up production to address the product deficit, because their production lines are already at capacity. Manufacturing production schedules are often set months or even years in advance. Deviating from the production schedule may not be possible because it may lead to shortages of other products. Some shortages, such as the recent shortage of propofol, are caused by product discontinuations. When 2 companies discontinued propofol production within months of each other, a single manufacturer was left to supply the market. Occasionally, drug shortages are caused by an increased demand for product, perhaps due to expanded use, resulting in insufficient supplies in the product-supply chain. Shortages of raw materials, although not a common cause of drug shortages, occur. For example, shortages of methylphenidate products may have been, in part, due to a shortage of the raw material and, according to manufacturers, may have been related to quota limits imposed by the Drug Enforcement Agency. Also uncommon is the loss of a manufacturing site, something that can occur due to storms or natural disasters.

TABLE. Reasons for Sterile Injectable Drug Shortages in 2011 and 2012		
	Sterile injectable drug shortages (%)	
Reason	2011	2012
Quality: manufacturing issues	57	35
Quality: delays and capacity	20	42
Discontinuation	9	7
Increased demand	7	7
Raw materials	1	5
Loss of manufacturing site	2	4
Other	4	0

Data are from the Center for Evaluation and Research Drug Shortage Statistics.[11]

An evaluation by the US Department of Health and Human Services' Office of the Assistant Secretary for Planning and Evaluation reported a key source of shortages to be lack of capacity for production.[15] A typical generic injectable manufacturing line produces multiple products.[52] Before the current drug shortage crisis, generic injectable manufacturers were at full production capacity.[15,52] In addition, many manufacturers are operating their production lines nonstop (24 hours daily), often using equipment that is more than 50 years old.[52] The nonstop production schedule allows for only minimum upgrades and little capacity to increase production of a product or add a new product. When manufacturers have an opportunity to produce a new generic product, this situation almost always results in a tradeoff of discontinuation or slowed production of another product. This tight capacity and production schedule allow for little resiliency if a shortage occurs or if additional supplies of a product are needed.

Production problems can also translate into a national shortage. The supply chain is insufficiently resilient to recover when even a single manufacturer has a problem; a national drug shortage is almost a certainty when this occurs. The chemotherapy drug shortages of 2010 and 2011 revealed just how fragile the supply chain can be. In 2009, the UUDIS noted 4 new chemotherapy drug shortages. This number increased to 24 new chemotherapy drug shortages in 2010. The increase was attributed to a single factory closure that occurred in spring 2010.[53] Approximately one-third of the agents manufactured at this factory were chemotherapy agents, and no other company was able to increase production to prevent national shortages. Overall, the severe chemotherapy shortages during 2010 and 2011 were traced to just 3 manufacturers.[50] Another example is the current nutrition product shortage that is related to manufacturing problems at one company involved with 17 of 25 ongoing nutrition product shortages (68%). This company is also the sole source for trace elements injection, a product used almost universally in parenteral nutrition solutions for both adults and pediatric patients.

Although manufacturing problems and capacity issues are noted causes of drug shortages, particularly injectable shortages, the root causes of these problems are still being explored. As the problem with drug shortages continues to weigh heavy on the health care system, many have questioned the role that profit motives play as an underlying cause of drug shortages. The economic and technological drivers of generic sterile injectable drug shortages have also been evaluated.[52] Woodcock and Wosinska[52] hypothesize that the pharmaceutical market does not reward quality because quality is not transparent to those purchasing or administering these products to patients. As a result, there is little incentive for manufacturers to invest in quality. This may, in part, contribute to the types of manufacturing problems currently seen in FDA inspections.[52,54,55] Recently, the International Society for Pharmaceutical Engineering conducted a survey of their members to help identify the underlying causes of drug shortages related to manufacturing and quality issues.[56] Results from this survey indicate sterile products are more likely to have quality problems, findings that are consistent with those identified by the FDA. The International Society for Pharmaceutical Engineering also stated that the problems are multifactorial, with specific quality issues often related to aseptic processing equipment and lyophilization.

Although the causes of drug shortages are complex, the common themes for recent drug shortages are the limited number of manufacturers of a given product and quality control problems. Of the top 7 generic sterile injectable manufacturers in the United States, 3 have had prolonged shutdowns during the past 3 years to address quality problems. Another has reported decreased capacity during the past several years, while working to address quality issues at one of their large facilities. A common misconception is that manufacturing problems are due to outsourcing to overseas facilities. Although there have been recent reports of significant quality problems of overseas firms that supply the US market, the 3 firms noted above are domestic manufacturing facilities.[52] According to the FDA's data, approximately 75% of all shortages of injectable drugs were related to quality or manufacturing issues in 2011 and 2012. In 2011, 20% of the quality-related shortages of injectables were due to remediation efforts, which involved firms shutting down or slowing production to address the quality problems at their facilities. In 2012, remediation efforts

were the cause of half of the quality-related shortages of sterile injectables. The shutdowns and slowdowns that have occurred were voluntary decisions made by the companies to address serious issues, such as mold, particulate problems, and other significant risks to product quality. The CGMP standards that the FDA enforces are the minimum standard that manufacturers must meet. When violations of CGMP occur, the FDA reports the inspection findings on form 483.[57]

ACTIONS TAKEN

Because of the increasing number of shortages in 2010, a Drug Shortage Summit was convened on November 5, 2010, by the ASHP, the American Society of Clinical Oncology, the ISMP, and the American Society of Anesthesiology.[58] In an effort to further determine the causes and effect of drug shortages, the FDA followed with a drug shortage public meeting on September 26, 2011.[53] One of the key recommendations from those meetings was that improved communication was needed among the FDA, manufacturers, and stakeholders. Manufacturers were not routinely sharing shortage notifications or information about shortages with the FDA, and there were no requirements for them to do so, except for sole source drugs that met certain criteria. On July 12, 2012, the FDA Safety and Innovation Act was passed.[59] This legislation requires companies to notify the FDA of any potential supply disruptions 6 months in advance or as soon as practicable. Since the law was enacted, the FDA has seen a consistent 6-fold increase in the number of notifications from manufacturers about potential shortages. These notifications have allowed the FDA to work with manufacturers earlier than before, which has resulted in the prevention of national shortages (Figure 2). Once notified, the FDA is able to use tools, such as expedited reviews and regulatory discretion, to enable drugs to continue to be available while manufacturing issues are addressed. The FDA was able to prevent 195 shortages in 2012 and has prevented 80 shortages in the first half of 2013 due to manufacturers notifying the agency of potential issues.[7]

The FDA considers a shortage to have been prevented if there was an intervention that enabled a drug to stay available. For example, a firm recently lost their raw material manufacturing site and needed to qualify a new supplier quickly to avoid a shortage. Once notified of this situation, the FDA was able to expedite review of the new supplier so that the drug could be made available from the new raw material supply in time to avoid a shortage. Another situation that has commonly occurred in recent years involves manufacturer notification of the FDA regarding a batch of drug that is found to have a specific defect. The defect may be relatively minor, such as a problem with the labeling or packaging, or may involve a more significant risk, such as risk of particulate matter in a sterile injectable. In all cases, when the FDA is notified of a potential problem for a medically necessary drug, the agency works closely with the firm to develop risk mitigation measures. These measures may include a Dear Healthcare Professional letter that is shipped with the drug to notify health care professionals of the potential risk and measures that need to be taken to prevent patient harm (such as use of a filter with a drug that has potential for particulate). Provided there is no undue risk to patients, the FDA works closely with the manufacturers to continue supply and prevent shortages.

Along with improved communications between the FDA and manufacturers, there have been increased communications with other stakeholders. The FDA and ASHP share information for posting on both organizations' websites, allowing for improved transparency and broad communication about shortages. For shortages that affect specific areas of clinical practice, the FDA is continuing with efforts to get more timely information to specialty organizations regarding shortage status and updates. During the recent shortage of nutrition drugs, the American Society for Parenteral and Enteral Nutrition and the ASHP have been in close communication with the FDA so that information could be shared more quickly with health care professionals and patients. The FDA is continuing to explore additional ways that targeted communications with specific stakeholders can be improved. Although these efforts can help minimize the consequences of adverse patient outcomes, they do not address the root of the problem—the lack of available product.

The FDA has seen improvements and progress in the remediation efforts that manufacturers are currently engaged in. Whenever possible,

the FDA is working with firms as they make upgrades, renovate facilities, and add capacity so that critical drugs can continue to be made while the facility improvements are under way. When the primary manufacturer of nutritional products realized it needed to make equipment improvements, the FDA worked with the company to assess whether a staggered shutdown was feasible so that some product could remain. Given the nature of the problem, though, the company believed a complete production shutdown was needed at the end of 2012 to address manufacturing problems. The FDA has worked closely with the company as it prioritizes production and resumes operations. The increased communications that have resulted from the FDA Safety and Innovation Act have resulted in regular discussions with other firms undergoing remediation efforts so that drug supply disruptions are minimized or prevented, whenever possible. The FDA Safety and Innovation Act requires that the FDA submit to the US Congress a strategic plan for preventing and mitigating drug shortages. This plan was released on October 31, 2013, and outlines the FDA's current actions and potential future directions for the FDA and industry.[7] The plan provides 2 clear goals: strengthen FDA's activities around mitigating drug shortages and develop long-term strategies for preventing drug shortages from occurring in the future. Because it is clear that the FDA cannot solve this public health threat alone, as a part of this work, the FDA's Drug Shortages Task Force has sought input from a variety of stakeholders to help find solutions.

It takes time and commitment for firms to address issues that lead to quality breakdowns. In addition, most changes in manufacturing lines must be approved by the FDA before production begins again. If a change is made to address concerns for a product in short supply, the FDA will expedite its review of that change. Although retooling the production lines can be a slow process that results in drug shortages, the long-term result is anticipated to be a more stable supply chain for product that has consistent quality. A potential area for future research is the question of why manufacturers do not add additional production lines and why there are few new manufacturers entering the generic injectables market. Although these additions seem necessary to resolve the drug shortage crisis, the barriers to such additions are unclear. Little is known about whether the barriers are purely economic or whether there are more complex constraints to adding production capacity.

CONCLUSION

The ongoing drug shortage problem in the United States is, in fact, a form of health care rationing that affects clinicians and patients on a daily basis. Stakeholders and the FDA continue to work on identifying potential solutions. Progress has been made because companies are reporting problems earlier to the FDA and many are working to address the underlying issues that are causing shortages. With remediation efforts well under way at many large manufacturing facilities that have experienced quality issues during the past several years, as well as additional capacity being added at many generic firms, it is anticipated that shortages will decrease in the coming years. Further exploration is being performed by the FDA and others to determine whether there are incentives that may be needed for firms to maintain adequate quality and to encourage firms to have backup plans and redundancy built into their operations in case of unforeseen events. The use of quality metrics is another area that will continue to be explored by the FDA and other organizations. Because of the considerable effect drug shortages have had on patients and the US health care system, it is a top priority for all stakeholders, including the FDA, national medical and pharmacy organizations, manufacturers, patients, and others involved with these shortages, to continue to work together on solutions.

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