

ASHP Guidelines on Managing Drug Product Shortages

Purpose

Drug product shortages can adversely affect drug therapy, compromise or delay medical procedures, result in medication errors, and cause patient harm.¹⁻³⁸ In addition to these potential problems, healthcare professionals are also increasingly concerned about the tremendous resources required to address shortages, estimated at \$209 million in 2013 for the purchase of more-expensive substitutes alone, which excludes other significant costs (e.g., drugs purchased “off contract,” therapeutic alternatives, added labor).^{39,40} Drug product shortages adversely affect healthcare organization finances by increasing the cost of delivering patient care, largely through the personnel costs required to manage the multiple pharmacy automation systems and electronic medical record changes that must be adjusted in the face of a drug shortage.⁴⁰ In addition, shortages create high levels of frustration and stress for everyone involved, including purchasing agents, pharmacists, pharmacy technicians, nurses, physicians, and patients.^{15,41,42} Pharmacy leaders need to educate all members of the healthcare team as well as organizational leadership about the complex and challenging nature of the drug shortage problem as well as what is being done to manage shortages.

Managing drug product shortages is particularly complex for practitioners in hospitals and other acute care settings because these facilities routinely treat patients with acute or emergent conditions, use a significant number of medically necessary or single-source products, and use high-cost new drugs and technologies. These healthcare providers are challenged during drug product shortages to ensure the provision of seamless, safe, and therapeutically equivalent drug therapy, preferably at comparable costs. The pharmacy department must take a leadership role in efforts to develop and implement appropriate strategies and processes for informing practitioners of shortages and ensuring the safe and effective use of therapeutic alternatives. Strategic planning is required for managing drug product shortages, just as it is for disasters such as major weather events or mass casualty incidents.⁴³ The purpose of these guidelines is to provide a framework for healthcare teams in patient care settings that can be used to develop policies and procedures that minimize the effects of drug shortages on quality of care. These guidelines are focused on minimizing the impact on patient care because it is impossible for healthcare organizations to prevent drug shortages from happening. Although drug shortages are a symptom of broader problems in the U.S. drug product marketplace, these issues are beyond the scope of this document.⁴⁴⁻⁴⁷

Patient Safety

Drug shortages are a cause of significant patient safety concerns. Medication errors are more likely to occur (1) when a pharmacy alters how a product is ordered, prepared, or dispensed or (2) when prescribing practices change to less-familiar alternative agents, especially agents that are less

efficacious, have a worse adverse-effect profile, or require an unusual or difficult dosing regimen. Best practices for managing drug shortages must first consider the potential impact on patient safety. Data documenting patient harm due to drug shortages are limited to case reports and survey data. The Institute for Safe Medication Practices (ISMP) is the leading source of aggregate data.^{13,15,16} A medication-error reporting and review system is an essential component of a medication safety system. Errors and near misses should be reported internally and externally, and analyzed.^{48,49}

Factors That Contribute to Drug Product Shortages

For the purpose of these guidelines, a drug product shortage is defined 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. Shortages can be the result of 1 or a combination of factors throughout the supply chain. The supply chain includes producers of raw materials, manufacturers, regulators, wholesalers/distributors, prime vendors, group purchasing organizations, healthcare organizations, and the patient. Factors that contribute to drug product shortages include the unique market for drug products, manufacturing and quality problems, production delays and lack of manufacturing capacity, manufacturer business decisions, shortages of active pharmaceutical ingredients (APIs) or raw materials, restricted distribution and allocation of drug products, and inventory practices.

Unique Market for Drug Products. Drug products are a unique commodity because they do not follow the fundamental economic laws of supply and demand. A first-line agent remains a first-line agent, regardless of price. Unlike other markets, consumers (i.e., patients) have little or no control over prescription product selection in healthcare organizations. In addition, because there is no required disclosure of information regarding manufacturers or manufacturing sites, purchasers of drug products are unable to make educated purchasing decisions based on the quality of a supplier. Purchasers of drug products are unable to make selections based on the quality of a supplier because there is no required transparency regarding the manufacturer or manufacturing site of a drug product.⁵⁰

Manufacturing and Quality Problems. The majority of drug shortages are caused by a production delay due to a failure of quality management at the final product’s manufacturing site.⁵¹ For example, the most recent data available show that 46.6–55.1% of sterile injectable anti-infective and cardiovascular drug shortages from 2012 through 2014 were from manufacturing plants that received a warning letter from the Food and Drug Administration (FDA) for failure to comply with manufacturing standards.⁴⁴ Quality is not rewarded in the drug product marketplace, because manufacturing is not transparent. The current pass-fail system of FDA approval provides no opportunity for purchasers to favor companies

with higher manufacturing standards over companies with lower standards.⁵¹ Although FDA has plans to require manufacturers to provide quality metrics, such as batch failure rates or the number of complaints, neither FDA nor purchasers of drug products have any method to review even these simple metrics.⁵² FDA has focused its responsibility for quality on the Office of Pharmaceutical Quality, whose mission is to ensure that quality medications are available for the American public.⁵³

Production Delays and Lack of Capacity. Manufacturing capacity issues or delays were the cause of 30% of drug product shortages from 2011 through 2013.⁵⁴ Many production delays actually stem from quality problems that delay production for a single manufacturer, and other manufacturers do not have the capacity to make up for the difference. Generic drug products are particularly susceptible to shortages because, unlike branded products, redundancy is typically not built into the production process. Generic products are typically manufactured on lines that prepare multiple products. An additional manufacturing line is generally not available as a contingency for generic products.⁵⁵ These types of shortages frequently occur with generic injectable agents, as tight profit margins and the complexities of production limit the number of manufacturers and lead to high market shares; in many cases, a single manufacturer may have over 50% of the market share for specific therapeutic categories.⁵¹ A small number of manufacturers (fewer than 7) comprise the vast majority of all injectable drug products,⁵¹ and more than one third of injectable drug products are produced by just 1 or 2 manufacturers.^{51,55}

Manufacturer Business Decisions. Manufacturers' business decisions are based on a variety of factors, including availability of generic products, market size, patent expiration, drug approval status, regulatory compliance requirements, and anticipated clinical demand. Frequently, the decision to manufacture a new product forces production tradeoffs because many generic manufacturers function at full capacity.^{51,56}

Shortages of APIs or Raw Materials. Shortages of APIs or raw materials are rare but can result in drug product shortages.^{51,55} An API shortage can be particularly disruptive if there is only 1 supplier; however, manufacturers' sources of API are considered proprietary and are rarely publicly disclosed.

Restricted Distribution and Allocation of Drug Products. Most healthcare organizations obtain the majority of their drug products through wholesale distributors. Restricted distribution methods that bypass the normal supply chain can also contribute to shortages. Manufacturers may limit the availability of and access to specific drug products to selected pharmacies, clinicians, and patients complying with manufacturer agreements based on market approval requirements and/or postmarketing surveillance. A manufacturer can also place restrictions on the availability of product by requiring healthcare organizations to order directly from the manufacturer or through a specialty distributor to receive an allocation.

Inventory Practices. Inventory reductions permitted by advanced communication and transportation efficiencies

within the supply chain may amplify the effects of a shortage on healthcare organizations. Most manufacturers, distribution centers, and healthcare organizations use just-in-time inventory management to reduce the cost of inventory on hand, increase inventory turns, minimize expenses, and optimize cash flow. This strategy is recognized as sound business management but allows unexpected shortages at any stage in the supply chain to significantly impact purchasers and patients. Some manufacturers and distributors use inventory management strategies that minimize end-of-quarter or end-of-year product inventories or limit shipment based on yearly quotas.⁵⁷ Poor ordering practices, stockpiling before announced price increases, hoarding caused by rumors of an impending shortage, and unexpected delivery delays may also affect inventory levels in individual healthcare organizations. Hospitals in rural areas face additional inventory challenges caused by distant distribution centers and the inability to easily borrow an item from a nearby hospital. Drug product shortages may also occur when hospitals in an area disproportionately use the same wholesaler. Some shortages are wholesaler dependent, as shortages of drugs can occur when contracts with suppliers are delayed.

Planning for Drug Product Shortages

The pharmacy department can lead effective drug shortage management by ensuring that its organization has the necessary infrastructure and a well-defined management strategy in place before a shortage occurs. To effectively respond to drug product shortages, several essential elements of infrastructure must be in place before a shortage occurs: a drug shortage team, a resource allocation committee, and established processes for approving alternative therapies and addressing ethical considerations.

Drug Product Shortage Team. The first step is to identify an interdisciplinary team of key staff who can make decisions and access information. The drug product shortage team needs to understand the organization's processes for change and how to expedite results. At a minimum, the drug product shortage team should be able to identify persons responsible for the following activities: data gathering and monitoring; purchasing alternatives; changing storage, preparation, and dispensing procedures; deciding to conserve or ration; implementing technology changes; and communications. The drug shortage team should develop a list of ad hoc stakeholders to consult for specific shortages. A specific point person should be designated to lead drug shortage efforts, but no single person can manage all drug shortage planning and response activities alone.

Resource Allocation Committee. Although consideration of the ethical implications of drug shortages may be discussed within the organization's existing committee structure (e.g., the ethics committee), a resource allocation committee should be formed to directly oversee the allocation of scarce resources such as drug products. The resource allocation committee should include, at a minimum, representatives from the departments of pharmacy, nursing, social work, and medicine; a patient representative; and a representative from the organization's ethics committee.⁵⁸ When a drug shortage affects a specific therapeutic area, other departments or disciplines may need to be represented, and a clinician with

expertise in that area should provide representation on the committee. Committee members should be identified in advance and be available to assume membership on the committee when the need arises.^{58,59} All members of the committee should disclose any bias or potential conflicts of interest in advance if possible.⁶⁰

The committee should carefully determine appropriate patient characteristics and clinical evidence for prioritization and rationing of medications.^{58,59,61,62} Because drug shortages will evolve, ethics protocols should allow for feedback and amendment.⁶² Standardizing the ethics framework in advance avoids the need for bedside decisions and allows clinicians to contemplate complexities and appropriate rationales before difficult choices need to be made.^{60,62,63} Protocols should also address how to manage the distress clinicians can experience when making such difficult decisions.⁶⁰

Interruption of clinical trials is another potential consequence of drug shortages that has potential ethical implications. Organizations must ensure that study sponsors and principal investigators are aware of drug shortages that may affect clinical trials. Healthcare organizations should appropriately allocate remaining medications, halt trial enrollment, or continue patients on the standard-of-care treatment only as necessary until the drug shortage has resolved.⁵⁸

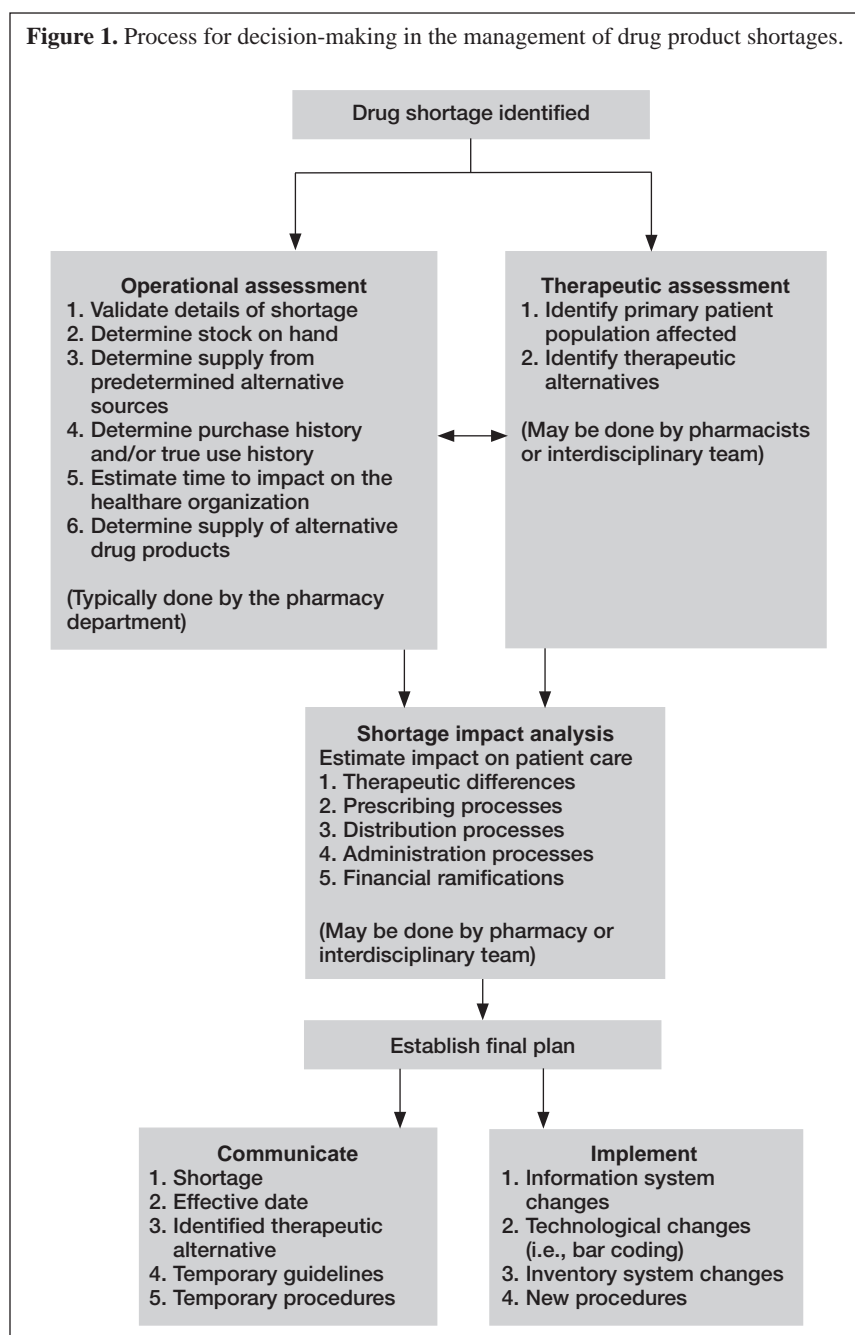
Process for Approving Alternative Therapies. A formal process for identifying and approving therapeutic alternatives for the healthcare organization should be established. The healthcare organization's decision-making process about alternative agents should involve timely collaboration among representatives of medicine, nursing, pharmacy, and other affected disciplines, and those decisions should be approved by the appropriate medical committees as promptly as possible. Organizations should follow the same steps and processes used in changing any drug product in their system to ensure that key steps in managing automation and technology are not missed.

Process for Addressing Ethical Considerations. As drug shortages have become more common, healthcare organizations and providers have become more adept at identifying and utilizing therapeutic alternatives. Nevertheless, situations arise in which it is difficult to simply substitute an alternative agent, if available at all.⁵⁸ Drug shortages have become a barrier to clinicians providing the most appropriate and evidence-based care to patients and may create mis-

trust between patients and providers.^{64,65} The appropriate management of drug shortages requires carefully balancing what is good for an individual and what is good for a group of individuals or society.^{60,61}

As the number of drug shortages has grown, several ethical frameworks for appropriately rationing these resources have been proposed.^{58,60,66} One method that reflects the fundamental healthcare principles of justice, beneficence, and nonmaleficence is an adaptation of Daniels and Sabin's⁶⁷ "accountability for reasonableness," amended by several authors to address drug shortages.^{58,60,61} Because there isn't 1 ethical framework to provide complete guidance for all drug shortage dilemmas, the framework should be adapted by organizations to address their particular circumstances.⁶³ The main principles of this method are as follows:

Figure 1. Process for decision-making in the management of drug product shortages.



- *Transparency:* details of the process are made public and available for scrutiny.
- *Relevance:* a neutral observer would be able to apply the process to a broad range of differing situations.
- *Appeals and revision:* those who feel wronged by the process have a way to appeal and have the original decision reversed if appropriate.
- *Enforcement:* the process is mandatory, and its results are required to be applied.
- *Fairness:* the process is to be applied to all, regardless of the type of patient or prominence of clinician treating that particular patient.^{58,60,66}

Just as the therapeutic management of drug shortages requires healthcare organizations to prospectively institute guidelines or restrictions, ethical procedures and protocols should be developed and put into place before the need for them arises.⁶⁵ Variations in these protocols may be necessary for different classes and uses of drugs; the rationing of anti-infectives and oncological agents, for example, is quite different.^{59-61,66}

Responding to Drug Product Shortages

The identification of a shortage initiates a cascade of events surrounding drug procurement and therapeutic decision-making (Figure 1). When a shortage is identified, the drug product shortage team should conduct an operational and therapeutic assessment to evaluate its potential impact. A shortage impact analysis based on the 2 assessments and an evaluation of procedural and financial implications should be used to assess the potential impact on patient care. The drug shortages team should use that impact analysis to develop a final action plan for approval and implementation. An institution's success in responding to shortages is typically dependent on how well the system can change drug products in their system under nonshortage conditions.

Operational Assessment

The operational assessment should be performed by the point person or that person's designee, working with others as necessary. The assessment validates the details of the shortage, estimates the supply of the drug product in shortage available on hand and from alternative sources, evaluates past usage, and estimates the supply of alternative therapies.

Details and Duration of Shortage. The pharmacy team can contact product manufacturers, distributors, FDA, the Centers for Disease Control and Prevention (CDC), and other sources to determine the cause of the shortage and its expected timing and duration. This information may already be available on the ASHP Drug Shortage Resource Center website (www.ashp.org/Drug-Shortages) or the FDA Drug Shortages website (www.fda.gov/Drugs/DrugSafety/DrugShortages). If it is not, visitors to the sites should report the shortage online. Predictions of when the product will be available help the healthcare organization develop its short- and long-term strategies. Because the status of a shortage can change quickly, follow-up communications with manufacturers may be required to obtain updates on previous estimates of product availability.

Inventory on Hand. Once a shortage is identified, pharmacy staff should assess the inventory on hand and estimate the time period it will cover. Available inventory includes all supplies of the drug product within the healthcare organization, including the pharmacies, inpatient units, ambulatory care clinics, automated medication storage and distribution devices, floor stock, code carts, and prepared trays. The pharmacy should estimate how long the healthcare organization can endure a shortage based on available quantities and historical usage, converting inventory counts of alternative drug products into common measurement units (e.g., common dose, days of therapy) to augment estimates of use.

Therapeutic Assessment

The therapeutic assessment can be performed by the point person, that person's designee, or other members of the drug shortage team as necessary. The assessment identifies the primary patient populations affected and identifies therapeutic alternatives.

Patient Prioritization. When a limited supply of a drug remains available and alternatives for specific patient groups are undesirable, a healthcare organization may prioritize use of the drug for specific patient groups. National organizations (e.g., CDC or an organization of healthcare specialists) may provide guidance on patient prioritization. Medication-use evaluation data on prescribing and utilization trends, if available for the drug in question, may be useful in developing prioritization criteria to guide appropriate drug use. Additional criteria, such as therapeutic use (curative versus palliative), may also be helpful in guiding appropriate use of the drug. Such criteria are particularly helpful in dealing with long-term shortages. To restrict product use for select patients or services in the healthcare organization, criteria should be developed by an interprofessional team. An ethical framework for allocating particularly scarce or lifesaving products is essential as is evidence-based decision making with regard to alternatives.^{58,63}

Therapeutic Alternatives. Therapeutic alternatives should be inventoried and availability assessed to ensure adequate supplies to meet new demand. In many cases, supplies of the best alternative agent may be affected by the response to the shortage. If therapeutic alternatives are not on the formulary or not currently stocked in the system, there should be a process to expedite adding the new product to all systems (e.g., the electronic health record [EHR], smart pump libraries, automated dispensing cabinets [ADCs]). If a compounded medication is an appropriate alternative, organizations must decide whether resources are available to compound inhouse or if the best solution is to purchase the compounded medication from an FDA-registered outsourcing facility.

Shortage Impact Analysis

A shortage impact analysis evaluates all factors relevant to the shortage (e.g., duration, current and available inventory, medical necessity, affected patient populations, alternative therapies) to determine the shortage's potential impact on patient care and costs. Such analyses should include a threat analysis for severe shortages to determine whether surgeries or other treatments must be canceled. Healthcare orga-

nizations should develop a mitigation strategy for patients whose treatments are no longer available. This strategy may include sending patients to another facility that has the drug in stock or developing a process to postpone elective surgeries. Shortages affect safe medication practices throughout the medication distribution and administration process within a healthcare organization. When considering alternative dosage forms or therapies, pharmacists must consider changes in look-alike/sound-alike procedures, barcoding, distribution paths, and the impact on automation, contract compliance, and final product preparation.⁶⁸ Healthcare organizations should evaluate the time required to implement any changes into electronic systems. The extent to which a healthcare organization will be affected by a given shortage depends on the severity of the shortage's impacts; the organization's scope, level of services, and service population; and the organization's agility in switching drug products given the constraints of information system changes (e.g., EHR, smart pump libraries, ADCs).

Financial Ramifications. Drug shortages result in increased costs due to a variety of causes: the higher cost of off-contract purchases of drug products or more-expensive alternative agents and the increased personnel costs to develop plans, relocate or compound drug products, and make changes to the EHR and other information systems. Healthcare organizations should make every effort to track all drug and personnel costs related to shortages as well as lost revenue from canceled treatments or surgeries. An accounting of these costs is helpful when explaining budget variance or proposing plans for additional staff or funds.

Final Action Plan

The healthcare organization should develop a final action plan prior to sending a comprehensive communication about the shortage. The final action plan can be used to double-check all elements of the management plan. The plan should state whether a conservation approach will be used to conserve remaining supplies or smaller future allocations or if the shortage will require use of an alternative agent. Examples of management and conservation strategies include par adjustments, centralization of inventory (e.g., removing from ADCs and floor stock), repackaging into smaller dosage units, extending beyond-use dating (when approved by FDA and manufacturer or verified through *United States Pharmacopeia* chapter 797-compliant process), i.v.-to-p.o. conversion, discontinuing nonessential therapy, limiting use of product to uses supported by evidence, and using a different strength or size of product. In some cases, a combination of these actions will be necessary for optimal clinical efficacy. For shortages that require canceled surgeries or treatments, the rationing plan for remaining supplies should be included. The organization should coordinate a specific time for making changes in information systems (e.g., EHR, smart pump libraries, ADCs, and other databases) and ensure that sufficient staff are available to re-enter orders, move stock between ADCs, or take other follow-up actions. Finally, it is essential that everyone understand their roles and the timing required for effective implementation as well as the dynamic nature of drug shortages that may require revisions to the plan.

Communication

Clear communication with all affected clinicians about the status of a shortage is vital. Administrators should also be included in communications, particularly if the shortage may result in canceled surgeries or treatments or significantly increase costs. Multiple communication methods are better than a single strategy. The EHR can also play a communication role to provide prescribers information at the time of medication order. The shortage management team should understand each member's role and share information quickly, efficiently, and in a timely manner. Information should be shared prospectively about both anticipated and confirmed shortages to allow appropriate preparation. Communication within the pharmacy department should include all staff members, including pharmacy technicians. Pharmacists who specialize in a specific clinical area (e.g., intensive care, transplantation) can be especially helpful in relaying information about shortages to their healthcare colleagues during rounds. All pharmacy shifts should receive the same message, and the communication methods should be adapted to the organization's culture, using multiple methods whenever possible (standing meetings, texts, emails, intranet, blogs). Communications to affected prescribers and other healthcare providers should include those in training (e.g., students and residents). Some healthcare organizations may designate a specific department to manage communications; others may find that a collaborative strategy involving various organizational departments and committees works best.

Disclosure to Patients. Healthcare organizations should establish policies and protocols regarding the disclosure of drug shortage information to patients and the extent of such disclosures.^{59,65} Patients or family members should be counseled when a drug product shortage will delay or compromise care, especially when patients have been stabilized on the drug product and alternatives may be less effective.^{58,63,69,70} Disclosure may vary depending on the type of clinical situation. In an emergent situation, decisions about disclosure need to balance transparency and other critical factors involved in providing care. In the case of an elective procedure, it must be decided how patients will be provided an understanding of the potential risks from less efficacious drugs or those with more adverse effects.⁶⁵ When the patient's need for a drug will recur, communications should address, before drug initiation, the possibility that the full course of treatment may not be available. Concerns that the full course of the regimen may not be available may warrant consideration of alternatives.

Communication with Media. Media outlets may be interested in reporting on severe shortages; working with the media can highlight the impact that drug shortages have on patient care. Organizations and individuals should work with their public affairs officers before speaking to the media and should keep in mind that updates may be necessary, especially when a shortage resolves. For all communications, it is important to balance timeliness and completeness and to be transparent about how decisions to ration are made and whether there is a method for appeals or exceptions.

Inventory System Changes

Stockpiling Restraint. Inventory management is a challenge in the face of a shortage. Stockpiling (hoarding) and speculative purchasing in advance of an anticipated shortage can exacerbate the shortage, disrupt efficient distribution, and divert supplies away from healthcare organizations with patients in need.⁷¹ Healthcare organizations should refrain from stockpiling drugs anticipated to go into shortage as well as alternatives. Stockpiling causes 2 distinct problems: (1) stockpiling can cause artificial shortages when healthcare organizations drain the supply chain and demand exceeds manufacturing capacity, and (2) stockpiled inventory is costly and may not be absorbed by normal usage if shortages do not occur as anticipated.

Speculative purchasing in response to a potential shortage has drawbacks as well, depending on the likely cause of the shortage and where it might occur in the supply chain. Problems may arise that appear to pose a shortage threat but never reach end users, because the supply chain, from raw material to finished product, may contain several months' supply; that long lead time allows corrections that avert the shortage. Finally, during shortages, manufacturers and distributors often allocate product on the basis of past usage, so an initial stockpile order generally has no impact on increasing an allocation.

Purchasing from Outside Pharmacies And Inhouse Compounding. Healthcare organizations must establish clear guidelines for dealing with situations in which a product is available only from a compounding source or non-traditional source or when a critical drug is not available at all. Each healthcare organization must determine its philosophies on purchasing drugs from the gray market or compounding pharmacies and on inhouse compounding. These decisions should be made before the pressure and emotion of a specific shortage occur. Each option and its potential effect on patient risk should be evaluated. Nontraditional drug product sources (e.g., secondary wholesalers) have extremely limited supplies, and the quality of these products may be questionable, as the provenance of the medication may be unknown. Pedigree requirements of the Drug Supply Chain Security Act may alleviate these concerns as they are implemented.⁷² Products from compounding pharmacies may also present risks to patients (e.g., inefficacy, adulteration, lack of sterility); tragically, several deaths have been associated with improperly sterilized compounded products. Healthcare organizations may choose to compound products if they can meet the necessary guidelines; however, obtaining raw materials may be difficult in some cases.

Conclusion

Drug product supply issues are a frequent problem affecting healthcare organizations. Organizations can mitigate the effects of shortages by establishing an infrastructure for dealing with shortages before they occur. Although it is impractical to prepare for every potential shortage, proper planning can reduce adverse effects on patient care and healthcare organization costs and prevent problems from escalating into crises. The keys to success will undoubtedly be found in the effectiveness of information gathering; teamwork to assess options; ability to rapidly make changes in information

systems; and communication with providers, patients, and administrators.

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