

ASHP Guidelines on Managing Drug Product Shortages

Purpose

Short-term back orders and long-term unavailability of drug products have been a challenge to pharmacy managers for many years.¹ Nevertheless, these drug product shortages have been increasing in frequency and severity since the late 1990s.^{2–4} The causes are varied and involve all segments of the “supply chain.” Changes in policies and practices among these segments individually and collectively contribute to drug product shortages. The challenge for pharmacy managers is to enable the provision of seamless equivalent drug therapy at comparable costs.

Managing drug product inventories and supply situations is particularly complex for health care organizations because of the large number of monotherapies and mono-products available. Drug product shortages can delay and compromise patient care and increase total costs, including those of alternative therapies, delivery devices, and staff training. The department of pharmacy should take a leadership role in managing shortages by developing appropriate strategies and an awareness campaign.⁵

Strategies for dealing with drug product shortages are similar to disaster planning and risk management contingencies for major snowstorms, mass casualty events, temporary wholesaler shutdowns, and preparations made for the Year 2000.⁶

This guideline describes the factors contributing to drug product shortages and recommends a general process for inventory management in preparing for and working through shortage situations. Included are strategies for identifying alternative therapies, working with suppliers, and collaborating with physicians. Because of the differences and complexities in health care organizational arrangements and practice settings, some aspects of these guidelines may not be applicable. Pharmacy managers should use their professional judgment in assessing and adapting this guideline to meet the needs of their own settings and to comply with the health care organization’s policies and procedures.

Background

Managing drug product shortages has become routine, forcing health care organizations to expend more personnel time and other resources identifying, tracking, and resolving shortage problems. Pharmacy managers, when confronted with the unavailability of a drug product, want information to make decisions about meeting patient needs for the product. They want to know the reason for the product’s unavailability, when supplies of the product will be available, options for obtaining the product from alternative sources, alternative therapies and related information for health services staff, and the cost consequences of alternative sources or therapies. Segments of the supply chain, especially manufacturers, have been inconsistent in providing information and assistance to health care organizations. The difficulty in obtaining information is exacerbated by the many players, complexities, and uncertainties in the supply chain.

Shortages can be the result of one, several, or any combination of factors throughout the supply chain. For the purposes of this guideline, the supply chain includes sources of raw materials, manufacturers, regulators, wholesalers, prime vendors, buying groups, and end-user health care organizations. The “just-in-time” approach to procurement and inventory management among manufacturers, distributors, and end-users has reduced the ability of the supply chain to maintain drug product availability during disruptions. Many end-user health care organizations have reduced on-hand inventories to the extent that they are dependent on daily replenishments from suppliers. Inventories no longer provide an adequate buffer and, under some circumstances, a temporary back order becomes a critical drug product shortage for the end-user. The factors that follow contribute to disruptions in the availability of drug products.

Raw and Bulk Material Unavailability. Disruptions can occur in the availability of raw and bulk materials to manufacturers of finished drug products. This is especially problematic when multiple manufacturers make a drug product with material available from only one source (e.g., the sole source for bulk penicillin G sodium) that discontinues production. Availability problems arise when raw materials come from undeveloped parts of the world or where there are hostilities, animal diseases contaminate tissue used to extract raw material, climatic and other environmental changes depress the growth of plants used to extract raw material, or raw materials are degraded or contaminated during harvesting, storage, or transport.

For example, the dexamethasone shortage was caused by one manufacturer’s change from beef protein to a plant source when the European precautions to prevent bovine spongiform encephalopathy were enacted. Other examples of drugs involved in shortages caused by the unavailability of raw and bulk materials include prochlorperazine, metoclopramide, phenobarbital, isoproterenol, and bretylium.

Manufacturing Difficulties. Shortages can occur when the primary or only manufacturer of a drug product halts production in response to a Food and Drug Administration (FDA) enforcement action concerning noncompliance with Current Good Manufacturing Practices (CGMPs). FDA actions are intended to protect the public from potentially unsafe drug products. These actions are evaluated by the FDA Center for Drug Evaluation and Research (CDER) drug shortage coordinator to determine if the action might cause a medical necessity problem. If necessary, FDA will assist the manufacturer’s return to compliance.

Manufacturing difficulties have been the leading cause of injectable drug product shortages. Immune globulin intravenous pentelate was in short supply for years because numerous manufacturers experienced manufacturing difficulties and related regulatory problems that suspended production. One of several manufacturers of naloxone and tetanus toxoid discontinued production as a result of such difficulties. The remaining manufacturers were unable to meet the demand.

Voluntary Recalls. Voluntary recalls can cause shortages, especially when a sole manufacturer's drug product dominates the market supply. Voluntary recalls usually affect specific lots and are conducted because of a lack of assurance that the recalled product is safe and for nonsafety related reasons, such as technical deficiencies in the drug's labeling. An ethical dilemma could arise when complying with the voluntary recall that may knowingly cause a shortage in a given health care organization.

Manufacturer Production Decisions. Manufacturer production decisions can cause shortages. Occasionally, manufacturers temporarily or permanently reduce production amounts of certain drug products as they shift production or reallocate resources to other products. An apparent practice among some manufacturers has been the halt of production when annual quotas are met.

A manufacturer's reasoned, sound business decision to discontinue production of a drug product because of insufficient financial return can cause a shortage. A shortage of diphtheria and tetanus toxoids and acellular pertussis vaccine absorbed was precipitated when one of the manufacturers, claiming low revenues, discontinued its product. Under this circumstance, FDA might perform a medical necessity evaluation and, if the unavailability of the product puts the public at risk, encourage other manufacturers to produce the product.

Orphan Drug Products. Drug products used to treat rare disorders for a relatively small patient population might be difficult to obtain. The federal Orphan Drugs Program provides incentives for manufacturers who are willing to produce them. In addition, the National Organization for Rare Disorders may become involved through lobbying and other actions.

Restricted Drug Product Distribution. An increase in the number of drug products available only through restricted distribution methods has caused artificial shortages for some health care organizations. As the result of either market approval requirements or postmarketing surveillance, manufacturers limit the availability of specific drug products with known adverse effects, e.g., Propulsid (cisapride) and Tikosyn (dofetilide). Only selected suppliers and end-users that comply with manufacturer agreements are able to obtain the product. A manufacturer can also place restrictions on a drug product that cannot be manufactured in sufficient quantities to meet demand (e.g., Enbrel [etanerept]).

Industry Consolidations. Manufacturer mergers often result in decisions to narrow the focus of product lines, resulting in the discontinuation of drug products. In addition, merged manufacturers of competing products may consolidate production, making product supply more vulnerable should problems arise.

Market Shifts. The addition of a generic product to the market can precipitate a decrease in the production of the innovator product, causing reductions in overall availability. Procurement decisions, such as "closed categories" by large health care organizations, can also shift the market for a given drug product. Military action can also cause an unexpected market shift, as seen during "Desert Storm" when large quantities of albumin were diverted to the conflict.

Unexpected Increases in Demand. Occasionally, an unexpected increase in demand for a drug product exceeds production capacity. This may occur as a result of a product's popularity for new unlabeled uses, a substantial disease outbreak, or unpredictable factors of demand. Shortages could be prolonged when the raw materials are limited or manufacturing processes are complex and are dependent on a long lead time. Succinylcholine was in short supply because of an increase in demand and delays in shipping raw materials. The Enbrel Enrollment program was established to ensure a continued supply for enrolled patients when demand exceeded capacity.

Nontraditional Distributors. The shortage of drug products has attracted several nontraditional distributors who have been able to obtain certain products (e.g., immune globulin, influenza virus vaccine, and dexamethasone injection). When demand exceeded supply through normal channels, these distributors announced the availability of these products at substantially higher prices. How they obtain these products and whether their activities contribute to shortages is unknown.

Compounding pharmacies also have announced the availability of drugs that are in short supply (e.g., dexamethasone injection and hyaluronidase injection). Caution is warranted because preparations from these pharmacies may not have FDA-approved labeling and their sources of raw materials have been questioned.

Natural Disasters. Natural disasters cause drug product shortages when they affect manufacturing facilities, particularly those of manufacturers that are the sole source for a drug product or category of products. For example, hurricane damage to manufacturing facilities in the Caribbean in 1997 caused shortages of several drugs, including gentamicin and the combination of piperacillin and tazobactam.

Process

Health care organizations should develop a contingency planning strategy to prepare for the possibility of a prolonged drug product shortage.⁵ Although it is often not possible to predict when shortages will occur, the process for dealing with them can be defined beforehand. A point person should be identified to implement and monitor this process and establish an organizational approach to decision-making and communication. Committee structures and responsibilities should be determined to assist decision-making during each phase of the process, e.g., pharmacy and therapeutics committee, medical executive committee.

Contingency planning can be divided into three key areas: the assessment phase, the preparation phase, and the contingency phase. Assessment requires a critical evaluation of the current situation and the potential impact of the shortage on the health care organization. An effective evaluation examines the reason for the shortage and the manufacturer's estimated release date and encompasses both internal supply availability and external availability.

The preparation phase focuses on all the activities that can be performed before the actual effects of the shortage are felt. Depending on the health care organization's inventory when a back order or other notice is received, there is often lead time before actual stock depletions. All diseases that are dependent or interdependent on the unavailable drug product and alternative therapies are identified. Since many drug products have limited therapeutic alternatives, outages

can have significant patient care and cost consequences. Preparation should also focus on developing methodologies for implementation and communication.

The contingency phase involves operations and circumstances for which preparation is limited because of incomplete information, financial constraints, or circumstances beyond the health care organization's control. For example, biological products are available only in increments and at a very high cost when no therapeutic alternatives are readily available or when shortages are longer than anticipated. Since direct control over availability is not possible, health care organizations must prepare for the product's unavailability.

Assessment Phase

For each shortage, an assessment is conducted to evaluate its impact. The potential impact is determined by using the shortage's expected duration to conduct a threat analysis and inventory assessment.

Duration of Shortage. Product manufacturers, distributors, FDA, and other sources can be contacted to determine the reason for the shortage and its expected duration. Predictions of when the product will be available help to determine the health care organization's ability to endure and guide short- and long-term strategies.

Although the end result is the same, the time to impact and duration of impact will vary depending on the reason for the shortage and where problems occur along the supply chain, from raw materials to manufacturer, manufacturer to wholesaler, and wholesaler to health care organization. The lack of raw material may affect several manufacturers of the finished drug product. A manufacturer's problems may affect only its product. Effects on distributors are dependent on their inventory levels.

Threat to Patient Care and Costs. A threat analysis evaluates all relevant factors of the shortage, such as duration, current inventory, medical necessity, and alternative sources or therapies, to determine the shortage's potential impact on patient care and costs. Health care organizations will not be equally affected by a given shortage depending on the scope and level of services and service population.

Inventory on Hand. Once a shortage is confirmed, the inventory on hand is counted and the time period it will cover is estimated. Available inventory includes all supplies of the drug product within the health care organization, including the pharmacies, inpatient units and ambulatory care clinics, automated medication storage and distribution devices, floor stock, code carts, and preprepared trays.

Based on available quantities and historical usage, an estimate can be made as to how long the health care organization can endure a shortage. Usage history can be obtained from procurement and issue records held by distributors, the purchasing department, and the pharmacy department. Inventory counts of all alternative drug products should be converted into common measurement units to augment estimates of usage. The assessment of how long the available inventory of the shortage drug product and possible alternative products would last should include both the current usage rates and reduced rates after conservation measures are implemented.

Preparation Phase

Once an imminent shortage has been confirmed, steps should be taken to prepare for known and potential problems in maintaining patient care and controlling costs.

Therapeutic Alternatives. The first step in the preparation phase is to identify therapeutic alternatives to the unavailable drug product. The health care organization should have a formal process for identifying and approving therapeutic alternatives. The point person in the pharmacy who is responsible for managing drug product shortages should initiate this process. Decisions about alternative therapies with other drug products should be made in collaboration with medical, nursing, and pharmacy representatives and approved by the appropriate medical committee(s).

Communication and Patient Safety. Information about the drug product shortage, alternative therapies, temporary therapeutic guidelines, and implementation plans should be communicated to the medical and nursing staffs by the most effective means available within the health care organization. This is essential for patient safety and preventing medication errors caused by confusion over different drug products' dosages, onset, duration, and other factors. Pharmacy department staff responsible for assisting prescribers with medication orders and aiding nursing staff with administration should be thoroughly informed about the alternative therapy decisions and implementation plans. In addition, sustained communication is necessary to reach medical, nursing, and pharmacy staffs working varied shifts or services.

External Relationships with Other Health Care Organizations and Health Systems. The preparation phase includes, where applicable, establishing collaborative arrangements with other health care organizations within a regional network or system. Available supplies of a potentially unavailable product and information about alternative therapies could be shared among the facilities.

Patient Prioritization. In the event of prolonged shortages of drug products, especially when alternative therapies are limited, a patient priority plan may be needed. A multi-disciplinary team should develop criteria for the use of the product. Prescribing could be limited to select patients or services within the health care organization. For drug products with defined durations of therapy, prescribers and pharmacists may have to consult each other to ensure that adequate supplies are available for a patient's entire course of therapy. Carefully written guidelines should be provided to assist frontline pharmacists to appropriately assess and respond to medication orders for drug products under a patient priority limitation.

The health care organization's risk management and ethics staffs or committees should be consulted when developing criteria that would limit a drug product's use and force a prescriber to decide whom should receive a drug product.

Other Supply Sources. Other potential sources of the drug product should be investigated during the preparation phase as early as possible to minimize supply disruptions. Alternative manufacturers and distributors should be contacted to determine availability, contract arrangements, item numbers, and payment terms.

Stockpiling Restraint. Pharmacy managers are cognizant of a drug product shortage's potential impact on patient care and concerns for litigation when optimal care could be compromised without use of the drug product. Nevertheless, they are also challenged by the pressure to control inventory and the pressure to increase inventory in preparation for stock outages.

One of the greatest challenges associated with preparation for shortages concerns inventory management. Despite pressures to do otherwise, good citizenship requires restraint from ordering quantities in excess of normal use that could contribute to the shortage and divert unneeded supplies away from other health care organizations with patients in need.⁷ Health care organizations should refrain from stockpiling (hoarding), which causes two distinct problems:

1. Stockpiling can cause artificial shortages when health care organizations drain the supply chain and exceed manufacturing capacities, and
2. Increased inventory is costly and may not be absorbed by normal usage if shortages do not occur as anticipated.

Speculative purchases in response to a potential shortage also have drawbacks, depending on the likely cause for the shortage and where it might occur in the supply chain. Problems may arise that pose threats to, but do not reach, end-users. This happens when the supply chain, from raw material to finished product, contains several months' supply. With long lead times, many problems are corrected before a shortage actually occurs.

In the event that administration mandates acquisition and maintenance of an emergency supply, quantities should be kept to a minimum and reviewed judiciously, similar to preparations made for a distributor's temporary shutdown. Under real or potential shortage situations, manufacturers and distributors have placed caps on quantities exceeding the health care organization's normal purchasing patterns.

Contingency Phase

The final, or last resort, phase of the process is devising a contingency plan that encompasses those aspects of preparation involving circumstances beyond direct control. When a drug product is only available from a nontraditional, off-contract source, is not available from any source, or does not have acceptable alternative therapies, thought and action are required to minimize the consequences of potential compromises in patient care and budget deficits.

Risk Management and Liability. One potential complication of a shortage is litigation by patients who feel that they have received improper care as a result of delays, prioritization, or alternative therapy. Even though risk management and legal representatives may have participated in earlier phases of the process, they should be notified immediately when all options for obtaining either the drug product or acceptable alternatives have been exhausted.

Budget Considerations. In the event that the drug product is available only from nontraditional distributors, estimates of the costs of using these sources should be prepared. The financial implications are subsequently presented through

budget channels with a request and justification for contingency funds. Additional expenditures caused by drug shortages should be well documented to explain budget variances and to support future budget proposals.

Information Coordination and Communication. The appropriate health care organizational departments and committees should collaborate in preparing a communications strategy to keep staff, patients, and external interests informed of potential drug product shortages. Patients or family members should be counseled when a drug shortage will delay or compromise care, especially when patients have been stabilized on the drug product and alternatives may not be as effective, e.g., antiepileptics or antiarrhythmics.

Communication with the media, national professional or patient organizations, and government agencies may help to raise awareness of the shortage and its potential consequences. Attention may encourage production by other manufacturers, collaborative efforts to develop alternative therapies, and ad hoc training opportunities on the safe and effective use of alternatives.

Government Intervention. FDA is responsible for assisting with drug product shortages to the extent of its authorities. These responsibilities are dispersed among several components of CDER. Limits on FDA's activities are dependent on whether a shortage meets "medical necessity" criteria. FDA will attempt to prevent or alleviate shortages of medically necessary products.

"A product is considered to be medically necessary, or a medical necessity, if it is used to treat or prevent a serious disease or medical condition, and there is no other available source of that product or alternative drug that is judged by medical staff to be an adequate substitute."⁸ Patient inconvenience and cost to the patient, institution, and manufacturer are insufficient bases to classify a product as a medical necessity.

A medical necessity determination involves a risk-benefit evaluation of the compromising issue with the product and the medical need for the product. In drug product shortage situations where FDA has determined that the product is medically necessary, FDA will act within its authorities. Actions may include discussions with pharmaceutical manufacturers to encourage additional sources, technical assistance to manufacturers experiencing CGMP difficulties, or expedited reviews of drug product marketing applications or manufacturer CGMP-related improvements. The FDA may take these actions whether the cause of the shortage involves business decisions to stop manufacturing the product, voluntary recalls, FDA enforcement actions, etc. Information on the availability of medically necessary products is posted on the FDA/CDER Web site (www.fda.gov/cder/drug/shortages).

The FDA encourages consumers and health care professionals and organizations to report drug product shortages. Reports should be made to FDA's CDER Drug Information Branch by calling 1-888-463-6332. Even though a drug product is not medically necessary, the FDA does obtain information about its availability.

CDER is not responsible for biologicals, such as immune globulin and vaccines. These products are the responsibility of the FDA Center for Biological Evaluation and Research, which does not have a comparable shortage program.

Conclusion

Drug product supply issues are becoming more frequent, whether they are the result of manufacturing difficulties or natural disasters that affect production, reductions in the supply of raw materials, voluntary recalls, manufacturer business decisions, FDA enforcement actions to ensure public safety, or artificial shortages due to stockpiling. Although it is impractical to prepare for every potential shortage, proper planning can minimize adverse effects on patient care and health care organization costs and prevent problems from escalating into crises. The key to success will undoubtedly be found in the effectiveness of information gathering, teamwork to assess options, and communication with providers, patients, and administrators.

References

1. Schwartz MA. Prescription drugs in short supply: case histories. New York: Marcel Dekker; 1980.
2. Nordenberg T. When a drug is in short supply. *FDA Consum*. 1997; 31:30–2.
3. Vecchione A. Drug shortages: industry copes as it waits for supplies. *Hosp Pharm Rep*. 1997; 11:1,7.
4. Nelson RE, Biderdorf RI. Nationwide drug shortages: it's time to take the lead. *Nutr Clin Pract*. 1998; 13:295–7.
5. Schrand LM, Troester TS, Ballas ZK, et al. Preparing for drug shortages: one teaching hospital's approach to the IVIG shortage. *Formulary*. 2001; 36:52,56–9.
6. Wechsler J. Pharmacists, health organizations map plans to ensure systems, supplies are ready for Y2K. *Formulary*. 1999; 34:620–1.
7. Myers CE. Artificial shortages of drug supplies. *Am J Health-Syst Pharm*. 1999; 56:727.
8. Food and Drug Administration. CDER Manual of policies and procedures: drug shortage management. www.fda.gov/cder/drug/shortages.

Developed through the ASHP Council on Administrative Affairs and approved by the ASHP Board of Directors on March 28, 2001.

Copyright © 2001, American Society of Health-System Pharmacists. All rights reserved.

The bibliographic citation for this document is as follows: American Society of Health-System Pharmacists. ASHP guidelines on managing drug product shortages. *Am J Health-Syst Pharm*. 2001; 58:1445–50.