CONSIDERATIONS FOR THE USE OF A DUAL PARENTERAL NUTRITION SYSTEM

Drug supply interruptions and the hospital pharmacy: benefits of a dual or redundant systems approach to parenteral nutrition

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EXECUTIVE SUMMARY

Drug supply interruptions are a common challenge encountered by hospital pharmacies in the US and have shown an increase in frequency in recent years. [1-2] Delivery of adequate parenteral nutrition (PN) is critical in a wide array of patients. Components of parenteral nutrition formulations may be subject to frequent supply interruptions[7], which may present major challenges to healthcare providers.

Drug supply interruptions carry concerns related to patient care, as well as pharmacy operations. [12] Appropriate management of supply interruptions involves significant efforts from hospital pharmacy personnel, and requires processes for procurement, communication, and implementation. [12]

Among the approaches available to the proactive hospital pharmacy to minimize or mitigate the burdens of supply interruptions is the use of dual or redundant products / systems. In the case of PN products, this may include the use of in-house compounding or outsourcing compounding to a specialty pharmacy and standardized PN formulations to help avoid the impacts of supply interruptions.

As indicated by data from the American Hospital Association (AHA) revealing nutrition product supply shortages to have been experienced by 89% of US hospitals.[4]

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DRUG SUPPLY INTERRUPTIONS: AN ONGOING CHALLENGE

Drug supply interruptions represent a key concern to clinicians practicing in the hospital setting. Hospital providers face the ongoing challenge of providing safe, efficacious, and equivalent medications to patients without compromising the quality of care.[1] Data from the US Food and Drug Administration (FDA) indicate increasing numbers of drug product shortages,[2] and recent surveys of key hospital and pharmacy stakeholders indicate that drug supply interruptions are widely experienced in hospitals across the country.[3-6] In addition to occurring with growing frequency, drug supply interruptions can be prolonged and many products are subject to repeated interruptions or shortages,[7-8] presenting additional challenges to the hospital pharmacy.

The causes of drug supply interruptions are well-documented and wide-ranging. Common causes arise all along the product supply chain and include manufacturing delays or recalls related to product quality, shortages in raw material supplies, and product discontinuations.[8-10] Manufacturing issues can be of particular concern when the product in question is a generic product with few manufacturers. In this case, production delays or changes in demand can have an impact on supply. [9, 11] Non-manufacturing-related causes of drug supply interruptions include changes in clinical practice, "just-in-time" inventory practices by distributors, stockpiling by end users, natural disasters, and the presence of secondary "gray market" suppliers, which may manipulate the market.[8-10, 12] On top of the many factors that can affect drug availability, healthcare providers are frequently not provided with sufficient advance warning of impending shortages or supply interruptions.[1, 4,3] As a result, these situations can require rapid resolution in a challenging environment. New legislation has been implemented as a result of supply constraints requiring manufacturers notify the FDA when they experience a supply issue. However, preparation or implementation of processes to mitigate the impacts of drug supply interruptions, particularly for products or product classes that are frequently affected, are a key consideration for healthcare providers.[9]

Supply interruptions affect products across a variety of therapeutic classes, with anesthetic and CNS drugs, anti-infective drugs, nutritive agents, oncology drugs, and cardiovascular drugs being the most commonly affected classes, accounting for over two thirds of recent critical shortages in the US.[7] For the past couple of years, sterile injectables represent the majority of drugs subject to shortages,[2] and many PN products, including electrolytes, amino acids, lipids, trace elements, and vitamins as well as oncology drugs, anesthetics for surgery and drugs needed for emergency medicine, have been in short supply at some point in recent years.[14] Interruptions in the supply of products, including PN products, are also widespread, as indicated by data from the American Hospital Association (AHA) revealing nutrition product supply shortages to have been experienced by 89% of US hospitals.[4]

Product supply interruptions are a challenge encountered by the majority of hospital pharmacies. Importantly, these are associated with serious concerns related to patient care and safety, as well as pharmacy operations. Management of supply interruptions therefore necessitates a proactive approach, both in general and with respect to specific drugs or drug classes that are frequently affected, such as PN components.

Drug shortages are common, and PN components have been subject to frequent and widespread supply interruptions.

CLINICAL CONCERNS ASSOCIATED WITH DRUG SUPPLY INTERRUPTIONS

Among the main concerns for clinicians with respect to drug supply interruptions are potential impacts on patient care. Not surprisingly, concerns exist across a number of therapeutic areas, including anesthesiology, oncology, and clinical nutrition.[3, 8, 14-15] Interruptions in product availability have the potential to impact patient care in two ways. Firstly, providers may need to adjust treatment protocols or implement allocations to specific patients groups. Secondly, pharmacies will frequently face the need to acquire equivalent or alternative products. Sources of alternatives can include off-contract purchasing from an established or alternative vendor, borrowing from other institutions, use of third party services, such as compounding pharmacies for sterile injectables, or acquisition from secondary suppliers.[5, 14] Acquisition of alternatives may be difficult during a period of supply interruption or shortage, however, if the interruption is widespread or if suppliers have implemented limited allocations. In addition, concerns exist around sourcing products from outside of the normal supply chain or when using compounding pharmacy services, due to the potential for uncertainty about product pedigree or quality.[12, 16] When satisfactory alternatives can be obtained, concern is still a factor, particularly when using less familiar products or formulations, as is frequently the case when a drug shortage or supply interruption arises.[8, 14]

PN SUPPLY INTERRUPTIONS AND PATIENT CARE

PN involves the delivery of nutritional support (amino acids, glucose, lipids, vitamins, and dietary minerals) intravenously to patients requiring nutritional supplementation. Timely delivery of adequate PN is key to providing sufficient nutrition in many patients in the hospital setting. Missed or delayed PN, resulting from a supply interruption, for example, therefore has the potential to impact clinical nutrition in a number of patient populations. Deficiencies due to missed or delayed PN can require additional resources such as more frequent monitoring and laboratory evaluations.[14] Because of these concerns, healthcare providers may, in addition to seeking out alternative sources of PN products, adjust treatment protocols or implement allocations in order to meet the needs of patients in whom nutritional deficiencies may pose the highest risk, such as neonatal or pediatric patients, or patients with malabsorption syndromes.[20-21] Given the frequency of PN product supply interruptions, consideration of these potential impacts is key for clinical and production stakeholders.

Interruptions in drug supply, including PN products, may have unwanted impacts on patient care, such as delays or changes in treatment or use of non-optimal therapies. Awareness of these potential risks can be used to guide management strategies.

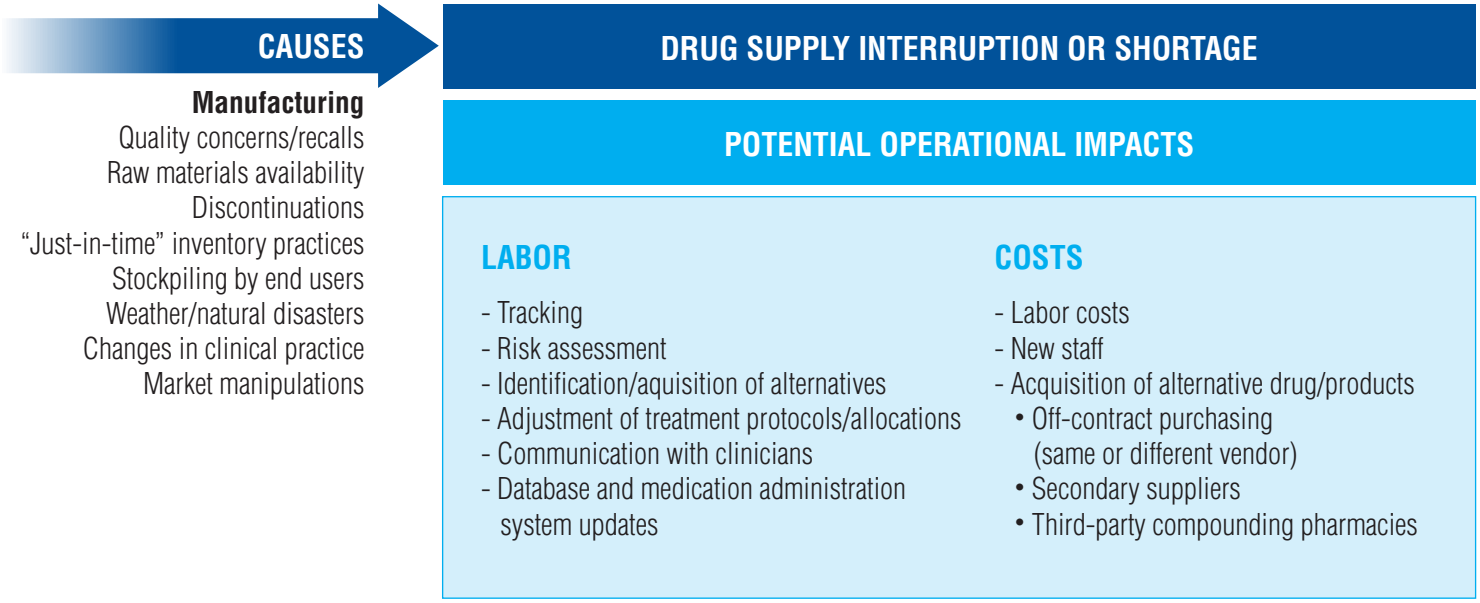
OPERATIONAL CONCERNS ASSOCIATED WITH DRUG SUPPLY INTERRUPTIONS

When a supplier foresees an interruption in the supply of a particular product, it usually communicates this information directly to customers or to agencies providing drug supply updates to customers, such as the FDA and the American Society of Health-System Pharmacists (ASHP).[22] Still, healthcare providers may receive limited advance warning with respect to impending supply interruptions.[1, 4, 13] In addition, product discontinuation plans do not currently need to be reported to the FDA unless the manufacturer is the only supplier of a medication defined as life sustaining or that prevents a debilitating condition.[10] Finally, manufacturers and distributors also implement purchasing allocations based on past usage in order to prevent rapid product

depletion, which can present a significant challenge to pharmacies trying to meet clinical demand within the hospital.[12, 22] As a result of these factors, providers are in many cases required to take a reactive approach to management of product supply interruptions and to seek out alternative product sources, either from other vendors or from non-traditional sources.

While many product supply interruptions or shortages can be effectively managed, this typically involves several critical actions involving a number of stakeholders, including physicians, pharmacists, nurses, dieticians, informatics specialists, and purchasing agents.[5-6, 12] Identification and acquisition of appropriate alternatives involves daily tracking of existing or upcoming interruptions, identification of reliable suppliers, communicating with manufacturers and wholesalers, as well as conducting impact analyses. Once a product has been obtained, effective implementation requires communication with and education of staff and prescribers regarding the product, as well as adjustments to treatment protocols and / or product usage, and updates to electronic databases and medication administration systems.[12, 23] Given the number of critical tasks involved, management of drug supply interruptions can be a significant labor burden on the hospital pharmacy, and may potentially divert pharmacists and other staff from other key activities.[3, 5-6, 13] Data from ASHP indicates that a median of nearly 20 hours per week are dedicated to the management of drug supply interruptions or shortages, with estimated annual labor costs associated with these activities of $25,000 to $48,000, depending on hospital size.[6] Management of drug supply interruptions can also have a financial impact because of higher product acquisition costs, which can arise due to the need to purchase more expensive alternatives, purchase from secondary markets, or use off-site compounding services for sterile injectables.[5, 14] Figure 1 summarizes the potential impacts of drug supply interruptions from both a patient care and an operational perspective.

Figure 1. Causes and potential impacts of drug / product supply interruptions



Though guidelines for the management of drug supply interruptions and shortages have been put forth by the ASHP and ISMP, the successful approach to a given situation typically differs in terms of sourcing, communication needs, and impact on treatment protocols, depending on the product in question, the associated clinical risk, the duration of the interruption, and the cost of alternatives. As a result, not all drug shortages or supply interruptions are successfully managed in the same way. In addition, measures taken to acquire alternatives may not always be successful, depending on the root cause of the shortage. Finally, it is often difficult for the hospital pharmacy to know how much time to dedicate to managing a supply interruption, given that expected duration are frequently not communicated. Avoidance of supply interruptions altogether, when possible, may therefore prevent the best option to providers.

Management of product supply interruptions presents operational and financial challenges to the hospital pharmacy. A proactive approach may help to minimize the effects of supply interruptions.

DRUG SUPPLY INTERRUPTION MANAGEMENT: DUAL OR REDUNDANT SYSTEMS

In light of the frequency and potential severity of interruptions in drug supply, the FDA may take a number of actions to resolve or avoid these situations in a timely way. These include assisting manufacturers in acquiring raw materials, helping to increase production of medications deemed to be medically necessary, and in some cases, importing drugs from outside of the US.[2, 19] The FDA can also streamline approval and provide incentives for manufacturers wanting to produce previously approved or highly utilized drugs.[7] These actions may help to alleviate the number and severity of product supply interruptions, however hospital pharmacies are still faced with frequent supply interruptions, and therefore must have strategies in place to manage or potentially avoid these situations, including planning for alternative or "backup" processes .[9, 12]

From a patient care and operational perspective, a proactive approach to ensuring that the pharmacy is not hampered by drug supply interruptions is recommended. Given that supply interruptions can be unpredictable and that practices such as stockpiling are generally discouraged,[12, 23] an approach including the use of dual or redundant products / systems may help providers avoid complications and costs associated with drug supply interruptions. With respect to PN, there are three approaches / systems used for preparation: in-house compounding, manufacturer-prepared solutions, and outsourcing to a compounding pharmacy. A dual or redundant systems approach to PN can make use of any or all of these systems. The benefits and challenges associated with each approach are summarized in Table 2.
In general, in-house PN compounding offers the ability to tailor PN preparations to individual patient needs in a timely manner.[24] From a logistical point of view, in-house compounding requires that the pharmacy preparing PN adhere to strict sterile preparation standards,[25-26] and therefore have the facilities and staff training in place to do so. Facilitating in-house PN compounding in many institutions is the use automated compounders.[27]

Similarly to in-house compounding, the use of specialty compounding pharmacies for PN preparation gives providers flexibility to prepare PN to meet specific patient needs, and provides an option for pharmacies either lacking the facilities or staff to enable on-site compounding .[28-29] When particular products are in short supply, allocations are typically based on prior use,[23] and hospital pharmacies may rely, in these situations, on large volume buyers such as compounding pharmacies.[30] Operationally, compounding pharmacies are not subject to the same regulations as drug

manufacturers, providing flexibility, but are also limited to filling prescriptions for individual patients and are not permitted to compound commercially available products.[31]

While a large proportion of US hospital pharmacies outsource at least some compounding of sterile injectables,[32] there are serious concerns that exist with compounding pharmacies, most notably with respect to the purity of raw materials used,[12] as well as a number of contamination events that have resulted in compromised patient safety and even fatalities.[33] Of particular concern with the use of compounding pharmacies is that the hospital pharmacy control over the traceability / pedigree of each dose or procedural quality control (e.g. how personnel work practices align with vendor policy and procedure, or how beyond-use dates (BUDs) of compounded sterile products offered to customers are established).[12, 29, 34] Adding to these concerns is the fact that the hospital pharmacy is accountable for quality and safety of the products it dispenses, even when a medication is prepared off-site.[34]

Because of existing concerns, legislation providing tighter oversight of compounding pharmacies,[35] as well as the pharmaceutical supply chain as a whole,[36] has been put forth.

Although it may not be appropriate for all patients in a given facility,[27] the use of standardized PN formulations may offer the benefit of meeting the needs of several patient populations, while helping to simplify the preparation process and potentially reduce preparation errors[37-38] (though the addition of trace elements and vitamins is still required on the part of the dispensing pharmacy[39]). The use of standardized PN formulations, in appropriate patient groups, has the potential to reduce time to administration of the first bag of PN, either initially or following a change to an existing PN order, provided that a standardized PN formulation is appropriate for the patient in question.[38] Using these formulations may also facilitate order preparation in institutions with limited on-site compounding capabilities,38 as well as PN storage.[39] Finally, standardized PN formulations are compliant with US Pharmacopeia Chapter <797> (USP <797>).[39]

Table 2. Features of different PN systems

SYSTEM / APPROACH	BENEFITS	CHALLENGES
On-site compounding	• PN orders tailored to individual patient needs • Flexibility to set up convenient ordering cut-off times • Pedigree & traceability • *Hospital pharmacy control over PN ordering, preparation, dispensing= Quality Assurance*	• Requires adequate infrastructure (trained staff, equipment, space) that may not be available in all facilities • USP Chapter <797>-compliance
Standardized PN formulations	• Available to meet the nutritional needs of many patient populations • Ability to reduce the frequency of compounding errors • Preparation for dispensation can be less time-consuming than on-site compounding • Manufactured in compliance with USP Chapter <797> • Longer shelf life than compounded PN and no need for refrigeration (in overwrap)	• Requires addition of trace elements, vitamins, minerals • Limited formulations, may not be appropriate for all patients

Off-site, third-party compounders	• Flexibility for pharmacies lacking resources for compounding of parenteral nutrition • In times of shortage / supply interruption, may have greater purchasing power than hospital pharmacies or health systems	• Limited oversight by the FDA if not registered as a Voluntary Outsourcing Facility • Hospital pharmacy accountability for compounding pharmacy products • Potential for limited traceability and pedigree in formation for the ingredients used i.e. commercially available injectable products versus bulk, non-sterile products • Uncertainty about how personnel work practices align with vendor policy • Uncertainty regarding procedures for establishing sterility and beyond-use dates (BUDs) of compounded sterile products offered • Uncertainty about calibration of measurement devices used for dose preparation (e.g. by NIST) • Delays in receiving products in hospital pharmacy[28]

With respect to PN, A.S.P.E.N. recommends that healthcare providers assess their patient populations to determine whether standardized PN formulations might be suitable in some of these groups, particularly when faced with a shortage,[20-21] and recommends the use of a standardized PN process, including use of standardized PN formulations and individualized PN solutions, when appropriate.[27] Providers may therefore use a combined approach (e.g. on-site or outsourced compounding plus standardized PN formulations) to deliver PN to all patient populations, while potentially simplifying the preparation process.

On the patient care side, the implementation of a dual or redundant systems approach to PN, including in-house compounding, standardized PN formulations, and / or outsourcing to a compounding pharmacy, may help providers to avoid supply interruptions. As a result, healthcare providers may be able to avoid delayed / missed PN, treatment plans, or use of potentially contaminated products, while still delivering PN to all patients. Further, the use of dual or redundant PN systems has the potential to provide several operational benefits. By implementing this approach, hospital pharmacies may be able to avoid some of the challenges associated with managing supply interruptions (tracking current or impending shortages, identifying, acquiring, and effectively implementing use of alternative products when shortages or supply interruptions arise), as well as mitigate the added incremental costs associated with acquiring products off-contract or from non-traditional vendors. It may also prevent the need for providers to seek out products from secondary "gray market" vendors, which may not be optimal.[17] Because of the potential benefits of a dual or redundant systems approach to PN, healthcare providers should assess their PN options in light of the needs of their patient population, available resources, pharmacy capabilities, and patient care goals.[39]

Implementation of dual / redundant PN systems may help to:

- Meet the PN needs of patients during supply interruptions without the need to find new alternatives
- Avoid the need to seek out products from unfamiliar sources
- Avoid labor burdens and added costs associated with drug supply interruptions

SUMMARY AND CONCLUSIONS

Interruptions in the supply of several drugs / products, including key PN components, are common and present a significant challenge to the hospital pharmacy, which must manage these situations to ensure that quality of patient care is not compromised. While hospital pharmacies have procedures in place to effectively manage most supply interruptions, challenges remain due to the labor and costs associated with procurement of alternatives, as well as limitations in product availability / vendor allocations, and the frequency and relative unpredictability of supply interruptions.

The implementation of dual or redundant systems presents a promising approach to mitigating the impacts these inevitable situations. With respect to PN, the dual systems approach involves the use of on-site compounding, standardized PN formulations, and / or outsourced compounding pharmacy services, all of which come with benefits and disadvantages that must be carefully considered in terms of the hospital pharmacy's capabilities, needs, and the patient populations being served. Provided that the implemented systems can be used to meet patient needs, a dual or redundant systems approach may help healthcare providers reduce the impact of supply interruptions, while continuing to deliver quality patient care.

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USMP/MG1/14-0016(1) 6/14