

Integrity of the pharmaceutical supply chain: Product sourcing for patient safety

HEALTH INDUSTRY GROUP PURCHASING ASSOCIATION

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Executive summary

Pharmacists face the daily dilemma of delivering safe and effective medication therapy to patients. The Health Industry Group Purchasing Association's (HIGPA's) group purchasing organization (GPO) pharmacy leaders are sensitive to the potential impact on patient care and increased costs caused by the difficulty and inability to source products when needed.

Drug shortages, product integrity, and primary and secondary distribution channels all present unique challenges in ensuring the safety of products for patient care. Shortages of critical medications, which require finding alternative products, often cause providers to expend more resources and increase the complexity of providing patient care.

The intent of this document is to address the impact of the secondary distribution channel on the supply chain, as well as provide some suggestions that health care providers

should consider as they contemplate accessing this distribution channel. Additionally, this paper discusses the recently enacted Medicare bill, including the provisions relating to the importation and reimportation of pharmaceutical products and its significance to patient safety. The suggestions in this document should assist the purchaser in taking the steps necessary to improve the integrity and safety of pharmaceutical products.

The decision to obtain product outside of the routine distribution channel is a complex one and often is made in response to a critical and immediate need to treat a patient. Due to the urgency that often occurs, the HIGPA Pharmacy Working Group suggests that the following process be followed whenever possible prior to the urgent need to obtain product from alternative sources:

- Establish the integrity of the source prior to the need.

- Require that the alternative source provide the following as a minimum:
 - Provide a pedigree back to the previous source.
 - Certify that it is not a diverted product.
 - Certify that actions by the alternative source will not alter any original manufacturer warranties or guarantees.
 - Certify that the product has been stored and handled consistent with product labeling requirements.
- Consider development of a list of key pharmaceutical products that will not be purchased from sources other than the manufacturer or authorized distribution channel.

Pharmacy leaders will continue to advocate for systems that increase the security and reliability of the pharmaceutical supply chain.

Introduction

HIGPA participated in the Drug

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Availability Task Force coordinated by the Healthcare Distribution Management Association (HDMA), as well as a similar initiative by the American Society of Health-System Pharmacists. One result of the cooperation with HDMA was the creation of a white paper entitled "Ensuring Product Availability" (September 2003). That document addressed many issues involved with the causes and mitigation of product shortages. Areas not addressed by that white paper include the role of the secondary distribution channel^a and the alternative distribution channel.^b Both are potential solutions, as well as potential contributors, to the problem of shortages. The primary focus of this document is those segments of the distribution channel.

Pharmacists face the daily dilemma of delivering safe and effective medication therapy to patients while, at the same time, minimizing drug expenses to meet the fiscal demands of their health care organizations. GPO pharmacy leaders are sensitive to the potential impact on patient care and increased costs caused by the difficulty and inability to source products when needed. Therefore, the objectives of this document are to

- Address the impact of the secondary distribution channel on the supply chain,
- Provide assistance to the purchaser in deciding whether to access the secondary distribution market for a product, and
- Provide background information to assist pharmacy practitioners in educating physicians and hospital executives regarding product shortages, potential impact of those shortages, and the secondary distribution market. A companion presentation will be available to facilitate this education process for health care executives and providers to use when these issues are addressed locally.

Products sourced through the secondary distribution market may be

perfectly acceptable and fill an important patient care role. The intent of this document is to further define the role of this alternative source, as well as provide some suggestions that health care providers should consider as they contemplate accessing the secondary distribution channel. Potential issues involved in outsourced compounding services will not be specifically addressed in this document, but many of the concepts outlined below may also apply to this alternative source of products. The responsibility to validate the quality of pharmaceuticals purchased from any distribution channel participant, including secondary distributors, rests with each purchaser. The difficulty for the purchaser today to effectively do that is limited by the current inability to provide a product pedigree from "cradle to grave." This technology is under development, but it may be several years before it is widely available for all pharmaceutical products.

Provider and patient care perspectives

Drug shortages, product integrity, and primary^c and secondary distribution channels all present unique challenges in ensuring the safety of products for patient care. The following provides information on each.

Impact of drug shortages. The issue of drug shortages has been a continuing challenge and source of frustration for all practitioners. Shortages of critical medications, which require finding alternative products, often cause providers to expend more resources and increase the complexity of providing patient care. Valuable pharmacy resources are consumed to

- Find alternative product sources, placing multiple small orders to obtain sufficient quantity to meet the organization's need when allocation programs are in place or if one source does not have a sufficient supply.

- Evaluate the quality and legitimacy of the product source (i.e., secondary distributor or outsourced compounding pharmacy).
- Assess the duration of the shortage, collaborate with the medical staff to identify acceptable therapeutic alternatives, and in some cases make formulary changes.
- Establish patient qualification criteria for selecting patients who will be eligible to receive products in limited supply, which then results in the identification of patients who will not receive the medication.
- Modify internal distribution systems to control and conserve products in short supply.
- Reschedule procedures based on critical product supply.
- Determine whether the acquisition cost of products purchased through the secondary market is acceptable compared to the need for the product.
- Educate nurses and physicians on new drugs, doses, or delivery systems associated with alternative products.
- Manage the potential increase for medication errors if alternative products must be utilized.

The last two points, in particular, can be even more problematic when treating pediatric and neonatal patients.

Product integrity. In addition to the increased chance for medication errors introduced by unfamiliar products and treatment delays, another safety issue to consider is product integrity. When products are obtained from outside the primary distribution channel (as defined earlier), the risk of the entry of adulterated or counterfeit products may be increased. Uncertainty about the storage conditions or the distribution path to which the product has been subjected may also raise concerns about the product's integrity and the potential impact on patient care.

Some pharmacists and pharmacy buyers may choose not to purchase

drugs through the secondary market for economic reasons or because they question the product integrity. However, others may choose to participate in the secondary market regardless of cost, either because they find it convenient or they incur pressure to obtain products that are in short supply.

The Joint Commission on Accreditation of Healthcare Organizations's standards require establishing procedures to manage drug shortages. If an organization's process includes using products obtained from secondary wholesalers, the purchaser must identify the details of how and when to use secondary wholesalers to acquire needed medications.

Primary and secondary distribution channels. Health-system pharmacists purchase the vast majority of their pharmaceuticals through pharmacy wholesalers and most of their remaining needs directly from the manufacturer. Pharmacy wholesalers obtain the overwhelming majority of their medications directly from pharmaceutical manufacturers, but many obtain some medications from secondary wholesalers or distributors who participate in the alternative distribution channel.

In general, wholesalers are currently evaluating their processes and decision criteria with respect to this activity and appear to be making significant progress in establishing better control of these alternative procurement practices. Manufacturers, GPOs, state boards of pharmacy, and other supply chain participants are also making decisions or recommendations that wholesalers purchase products directly from the manufacturer.

The secondary distribution channel may be one avenue for the entry of adulterated or counterfeit medications into the distribution channel. The recent announcements by manufacturers outlining their efforts to increase the integrity of the supply chain are aimed at specifically addressing this issue. Major U.S.-based

pharmaceutical manufacturers recently announced they would no longer sell their drugs and devices to U.S. wholesalers who also obtain the manufacturers' products from sources other than the drug makers. The companies took the action to thwart counterfeiters of their products. Other U.S. manufacturers have announced specific initiatives as well. Some pharmaceutical companies may unilaterally take similar steps as they formulate their individual strategies to address this issue. However, smaller pharmaceutical companies may confront resistance from the distribution sector because the smaller companies may lack the clout to require distributors to purchase their products directly from them. Such resistance could take several forms, such as refusal to stock the product or requests for increased fees.

An industry report to the Food and Drug Administration (FDA) in 2001 noted that more than 6500 licensed wholesalers operate in the United States. When discounted goods are offered by manufacturers to meet sales targets or reduce inventory, these secondary distributors are willing to risk substantial capital to acquire them. These purchasers then turn the product over quickly by selling it to their network of customers, which might include other distributors, including those in the primary distribution channel, as well as drug dispensing organizations.

Some small wholesalers may build inventory by stocking medications nearing their expiration dates or by taking advantage of regional variations in supply. Secondary distributors usually focus on providing a small target list of medications to a relatively small number of customers, often contacting customers by fax on a frequent basis. These companies do little advertising or sales promotion.

Within the secondary distribution channel, products may change hands

many times before reaching the provider. It is also important to understand that the frequency of these transactions is not a true measure of the availability of the problem product. It is very inexpensive for the secondary market players to send out a multitude of faxes, even though they may have just a few packages of the problem product in stock. This perceived abundance of supply, when measured by the multitude of communications, then fosters credibility concerns by the provider with respect to whether manufacturers and primary wholesalers and distributors have a legitimate reason for not being able to supply the product at the usual selling price. This credibility concern is then directed at the hospital's pharmacy department and is exacerbated when a physician receives an unsolicited offer from a secondary supplier for a product that appears to be of limited availability in the hospital. The physician may have the impression that there is an abundant supply without realizing that these unsolicited offers generally are for very limited quantities of product.

The presence of the secondary distribution channel may serve a need by providing options for obtaining necessary medications. However, in light of the reality of prolonged drug shortages, the secondary supply channel often serves to contribute to greater frustration on the part of patient care providers. This alternative distribution channel also creates a situation where critical products are stockpiled for economic reasons. Small amounts of product are divided among many distribution outlets rather than being more centrally available in the primary distribution channel.

During times of limited availability, these organizations often offer limited supplies of critical medications at increased prices. Purchasers may have to call the secondary distributor for the current price, which sometimes can be as much as 5 to 10

times the normal price. For example, at the height of the methylprednisolone injection shortage in 2003, one secondary distributor offered a 500-mg vial of this product for \$40, which was more than 500% above the normal price. An example documented in a story in the *Washington Post* (October 19, 2003) revealed that a vaccine purchased by one wholesaler for \$23.65 per vial during the flu vaccine shortage of 2000 eventually was sold to an end user for \$147.00 per vial. The cost of small quantities of medications from these distributors may not necessarily be prohibitive, but when substantial quantities are required during a product shortage, significant excessive costs can be incurred by the provider.

Product shortage frequency. As of the end of the third quarter of 2003, the drug information center of the University of Utah Health System reported 39 new drug shortages during the year. While that figure has decreased from a total number of shortages of 119 in 2001 and 87 in 2002, the absence of critical medications remains a prominent patient care issue. In addition, of the 119 shortages identified in 2001, 35 were still present in 2003. As a result, pharmacists and providers will continue to face the pressure of whether to access medications that are in short supply through secondary or alternative distribution channels.

Legal and regulatory considerations

It is important to understand that the U.S. marketplace is a free market system and, as such, entrepreneurs are free to engage in business activities, provided that they are legal and meet licensing or regulatory requirements. Some practitioners have suggested that some of the smaller secondary distributors who elect to charge prices for selected products, often in short supply, several times above the customary price should be prohibited from such practices. How-

ever, there appears to be no price control, law, or regulation in the U.S. system that prevents such activities, and the authors are unaware of any specific violations of other related regulatory requirements.

The origin of the product, as well as how it made its way through the supply chain, are questions to be asked when the purchaser is considering whether to obtain products from a secondary source. This is especially important when the purchaser has not previously validated the integrity of the seller. Three examples are outlined below.

- *Diverted product.* One example of diversion is when a product is purchased at a discounted price under a GPO contract and then resold in breach of the GPO contract to an entity that is not eligible for that price. The appropriate action to be taken by anyone with knowledge of such activity would be to report it to the GPO and manufacturer.
- *Counterfeit or adulterated product.* This is definitely a patient care issue due to the questionable safety and efficacy of the product. Another related concern is the redistribution of expired stock. Selling counterfeit or adulterated products is a clear violation of FDA laws and regulations. However, the product integrity issue might not be known prior to patient administration and may first be discovered when a patient experiences an untoward effect. Concerns regarding safety and product integrity should be reported to the state board of pharmacy and FDA. Other agencies, such as the Drug Enforcement Administration (DEA), may need to be involved depending on the situation.
- *Stockpiling and market timing.* A savvy purchaser with good market connections could possibly hoard unadulterated product until such time that the market price increased significantly due to the short supply. This would not be a violation unless the product

was obtained through diversion. It is unlikely that any regulatory or legal action could be taken with respect to this type of profiteering, unless it was determined that the product was obtained illegally.

An article titled "Florida Medicaid Fraud Costs Millions, Report Says" in the December 19, 2003, issue of the *Washington Post* references a report by a statewide grand jury that identified instances where medications were diverted by Medicaid patients in exchange for cash. The report also describes one situation where a temperature-sensitive product was purchased on the street and stored in a hot van before being sold back into the distribution channel. These instances raise both legal and patient safety issues.

Several state and federal agencies are concerned with health care product supply issues; however, their authority is limited. The following are some examples of how various agencies might get involved in the different aspects related to these issues:

- The authority of the Center for Medicare and Medicaid Services (CMS) may be limited to factors affecting cost or quality for the patients enrolled in CMS programs.
- FDA is primarily responsible for the safety, security, and protection of public health.
- The Federal Trade Commission investigates potential collusion or restraint of trade issues.
- The U.S. Justice Department is involved in the investigation and prosecution of violations of antitrust, FDA, and health care fraud and abuse claims laws.
- State boards of pharmacy regulate the practice of pharmacy within each state and will become involved in investigations and proceedings where pharmacy rules and regulations may have been violated. Wholesalers and distributors are regulated by states and are therefore subject to state laws

and regulations. Controlled drugs are regulated by DEA.

Some of the areas identified for improving the security of the supply include

- Significant enhancement of penalties for tampering, counterfeiting, and diverting.
- Revision of the pedigree aspects of the Prescription Drug Marketing Act to require establishment of a product pedigree.
- Implementation of technology, such as electronic product codes via radio frequency identification (RFID) to create an electronic pedigree, which will provide information about the route of a specific product package from “cradle to grave.” Such an initiative can also secure the supply channel to identify inappropriate importation of products.
- Creation of a centralized and secure database of pedigree information for access by authorized parties to validate the integrity of a product.
- Coordination of regulatory initiatives at the federal level to avoid conflicting language and requirements between states.
- Improved oversight by state boards of pharmacies of wholesalers and distributors, including onsite inspection at reasonable intervals.
- Development and implementation of appropriate controls on returned goods to increase integrity in the system while still allowing returns and redistribution, where appropriate, of pharmaceutical products.

Considerations for evaluating product sourcing options

The decision to obtain product outside of the routine distribution channel is a complex one and often is made in response to a critical and immediate need to treat a patient. Due to the urgency that often occurs, the HIGPA Pharmacy Working Group suggests that the following process be followed whenever possi-

ble prior to the urgent need to obtain product from alternative sources:

- Establish the integrity of the source prior to the need. Where possible, establish a list of approved secondary suppliers. The evaluation of secondary suppliers, in advance, may be difficult due to the sporadic nature of availability. The secondary supplier who fulfilled the last need may not have the current product available, which then necessitates the consideration of another alternative supplier in the secondary channel.
- Require that the alternative source provide the following as a minimum:
 - Provide a pedigree back to the previous source. Unwillingness to do this should be a cause for caution. Recent legislation in Florida requires pedigrees for a specific list of products that either have been targets for counterfeiters or are likely candidates. FDA has convened a task force and conducted a public hearing in an effort to evaluate this issue. Technology currently under development may facilitate the capture and maintenance of product pedigree information. RFID is one technology that has this potential. Ideally, there should be a “cradle to grave” pedigree available and certified by all parties in the supply chain that handled a specific product. Today, however, the technology and systems available do not support this, even in the primary distribution channel. New technologies, such as RFID, should provide this capability over the next several years.
 - Certify that it is not a diverted product.
 - Certify that actions by the alternative source will not alter any original manufacturer warranties or guarantees.
 - Certify that the product has been stored and handled consistent with product labeling requirements. The purchaser should make every effort possible to vali-

date that the product was stored properly throughout the distribution process for any product that requires special handling and storage, such as a narrow temperature range.

- Consider development of a list of key pharmaceutical products that will not be purchased from sources other than the manufacturer or authorized distribution channel. This list should be based on patient care needs, the likelihood of tampering or counterfeiting, and the potential risk to the patient. The list in the Florida law referenced above may be a useful reference for creating this list.

Importation and reimportation

Although the recently enacted Medicare Prescription Drug Improvement and Modernization Act of 2003 directs the U.S. Department of Health and Human Services (HHS) to issue regulations permitting the importation^d (or reimportation^e) of prescription drugs from Canada, such action is not allowed unless HHS certifies that importation will not create any additional risk to public health and safety and will lead to significant cost savings for U.S. consumers. In that regard, the new law is not very different from the old and should not be expected to lead to the lifting of restrictions on imports in the near-term. Even so, the new law’s importation provision is limited to Canada.

More generally, the HIGPA Pharmacy Working Group reviewed the issues surrounding drug importation (and reimportation) by health care providers and patients. Based on this review, the following issues have been identified:

- The integrity of an imported product may be questionable, and there is no current pedigree^f process available to validate the integrity of the product.
- Due to the lack of currently available systems and technology that facilitate the assignment and tracking of

serial numbers for individual packages, there is no secure method to separate imported stock from stock obtained through primary distribution channels.

- There currently is no available technology in use to validate that an imported or reimported product was stored according to *U.S. Pharmacopeia (USP)* standards. Storage outside of the standards may adversely affect the activity and safety of a pharmaceutical product.

The following list outlines the minimum safeguards that HIGPA's Pharmacy Working Group believes to be critical to have in place prior to importation or reimportation of any pharmaceutical product:

- Electronic pedigree that can provide secure tracking of product at the individual package level throughout the supply chain, regardless of its source.
- Development by FDA of acceptable and efficient regulations on reimportation and importation to ensure product integrity of the imported product.
- Development of technology that tracks storage conditions and validates conformance to *USP* standards for products that require storage within a narrow temperature range throughout the supply chain.
- Assurance that entities in other countries that export products to the U.S. market are regulated appropriately, using the same standards used by U.S. supply chain participants.

These are in addition to the recommendations on general product sourcing outlined in other sections of this document.

Pursuing importation as a cost savings strategy without implementation of the above safeguards places an undue risk on patient care and is counter to current initiatives to improve patient care and safety. The position of FDA on importation and reimportation should serve as a key

indicator for the acceptability of this method of procuring products.

Providers are encouraged to consider these issues as they make decisions regarding sourcing of products. It is recommended that providers who are interested in accessing pharmaceuticals from outside of the U.S. distribution system should first become involved in advocating for the implementation of systems that facilitate an electronic pedigree to ensure the integrity of products. Anything short of this may be construed as placing financial considerations above patient care and safety.

Conclusion

The dilemma that health care providers face in these situations is the need to balance the relative risk with the need to provide the product for appropriate patient care. Providers should immediately report any concern about the integrity or questionable source of a product to the proper authorities. This is best accomplished by planning for the situation before it occurs.

Recent cases involving counterfeit products in both the retail and hospital markets have placed a new emphasis on the need for a secure pharmaceutical supply chain. Federal and state agencies are researching current supply chain dynamics in an effort to improve the security and integrity of pharmaceuticals. GPO pharmacy representatives are involved to varying degrees in many of these discussions and advocate on behalf of their membership and patients for a secure supply chain.

The key to increasing the security of the product is appropriate regulatory oversight combined with due diligence by purchasers when selecting primary and secondary suppliers. Technology and regulations currently under development or consideration should support an electronic pedigree, which will address many of the concerns outlined in this document. The suggestions in this document should assist the pur-

chaser in taking the steps necessary to improve the integrity and safety of pharmaceutical products. A key responsibility for purchasers is to properly evaluate potential alternative suppliers and to establish relationships, where necessary, using the recommendations above. There could be a significant risk to the public resulting from the entry into the United States of adulterated or counterfeit pharmaceuticals and other products, such as food. FDA and others have been evaluating the possibility of this risk should the medication and food supply chains become a target for terrorists. A secure supply chain with track-and-trace capability is essential, and the urgency for creating this capability is high.

Pharmacy leaders will continue to advocate for systems that increase the security and reliability of the pharmaceutical supply chain. Please contact your GPO representative or HIGPA for additional information or to provide comments regarding this document or the issues discussed herein.

^a*Secondary distributors or distribution channel* describes the movement of products purchased from an authorized distributor or source other than the manufacturer to another intermediary distributor. These products are then sold to the provider or end customer.

^b*Alternative or gray market* are terms used to describe a component of the secondary distribution channel. This component commonly markets via fax or other communication methods.

^c*Primary distribution channel* describes the normal process for distribution of product from the manufacturer to the provider (end customer). For most products this is through the authorized wholesaler or distributor channel. The other component of the primary distribution channel is the sale of products directly by the manufacturer to the provider. Products in the primary distribution channel are sold to the provider for use in the care of their patients, not for resale to other providers or reentry into the supply chain.

^dImportation refers to buying products from sources outside of the United States.

^eReimportation refers to importing products, which were originally exported from the United States, back to this country.

^f*Pedigree* is a statement that traces the drug from the point of manufacture and contains information about all transactions involving the product from origin until it reaches the end user. It may be in paper or electronic form.