

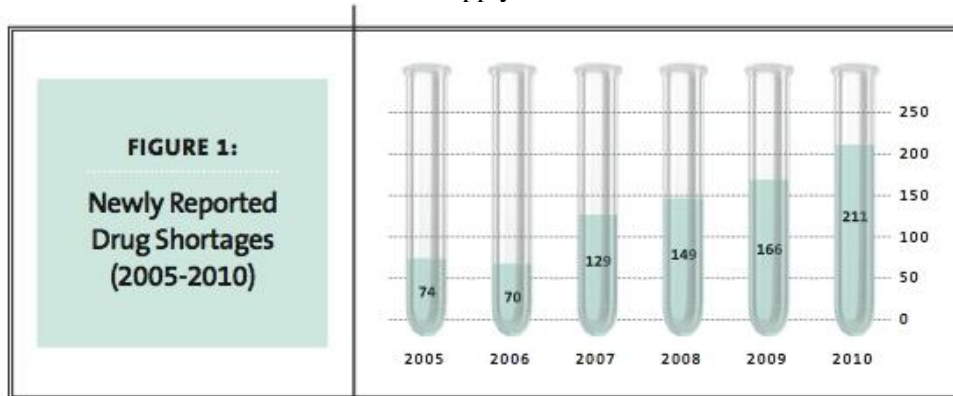
# Navigating Drug Shortages in American Healthcare: *A Premier healthcare alliance analysis*

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## **I. What is the nature of the problem?**

The frequency and impact of drug shortages have risen to critical levels, more than tripling since 2005, and affecting all segments of healthcare (Figure 1).<sup>1</sup> In 2010, over 240 drugs were either in short supply or completely unavailable and more than 400 generic equivalents were backordered for greater than five days.<sup>2,3</sup> In most instances, these did not progress to critical shortages, but point to instabilities in the supply chain that cause national concern. Many of the drugs identified in 2010 remain unavailable or in short supply in 2011.<sup>2,4,5</sup>



Source: Drug Information Service, University of Utah, 2010

Seventy-seven percent of drugs in short supply in 2010 were sterile injectable products, critical in the acute care setting.<sup>6</sup> Recent media coverage highlights the plight of patients and physicians faced with shortages for cancer drugs, anesthetic agents, and critical care medications that have contributed to delays in treatment and surgery, or changes in care plans. Drug backorders cause patients to receive substitute therapies that add expense to patient care.

## **II. Why are these shortages occurring?**

Many trends contribute to the situation, including quality of active pharmaceutical ingredients (APIs), drug recalls, industry consolidation, offshore production, and just-in-time inventories, among others. Recent regulatory and financial pressures further compound the problem.

### ***Raw material quality situations***

At least 42 percent of sterile injectable drug shortages in 2010 were due to product quality situations such as presence of particulates, microbial contamination, newly identified impurities, and stability changes. Nine percent were due to situations with raw materials and 5 percent were attributed to the shutdown of a manufacturing site.<sup>6</sup> Foreign markets are the source for as much as 80 percent of the raw materials required to manufacture pharmaceuticals. The market for Chinese APIs halved to \$16 billion in 2010 due in part to global pharma's wariness over quality problems with Chinese APIs, exemplified by contamination of the heparin supply in 2008.<sup>11</sup> Disruptions in the manufacturing processes increase financial burdens placed on manufacturers to ensure the quality and integrity of product ingredients.

### ***Manufacturer financial decisions***

Pressures are mounting to offset profit reductions resulting from patent expirations, healthcare reform, and investments related to FDA regulatory compliance for older products. Manufacturers are delaying or discontinuing investments, thereby impacting product availability. At least 18 percent of sterile injectable shortages in 2010 were due to product discontinuations. Manufacturers are not required to report plans for product discontinuations to the FDA unless they are

the sole manufacturer of a life-supporting or life-sustaining medication or a medication used to prevent a debilitating disease or condition. Early notification, even with these limited requirements, prevented at least 24 product shortages in 2010.<sup>6</sup>

#### ***Enforcement of FDA standards and regulations***

The FDA requires manufacturers to abide by good manufacturing processes (cGMPs) to avoid regulatory action. The cGMPs change over time.<sup>12</sup> Although the FDA reserves the right to inspect all manufacturing plants, insufficient resources have resulted in the FDA's risk-based approach in deciding which factories are inspected in a given year.<sup>13</sup> Furthermore, the FDA's Unapproved Drug Initiative, launched in 2006, mandates submission of a New Drug Application containing clinical trial data to prove the safety and efficacy of products that were brought to market prior to more stringent approval processes.<sup>14</sup> Many of these products are now generic. High costs have led some manufacturers to cease production rather than invest to meet requirements and regulatory user fees inherent in the drug approval process. Other suppliers of the generic entities may not be able to respond to the increased market demand. While the FDA's vigilance of cGMPs and actions against unapproved drugs help keep medications safe and effective for the public, new regulations may have a downstream impact on the entire marketplace.

#### ***Leaner inventory levels***

In recent years, a "just-in-time" inventory trend has become popular in many segments of the supply chain. Stocking leaner quantities of raw materials and finished products improves capital efficiency.<sup>15</sup> The reduction in onshore stockpiles of APIs, inactive product ingredients, and manufactured drugs creates some risk of instability in the pharmaceutical market.<sup>16</sup>

#### ***Gray market distributors (price gouging)***

During times of shortages, "gray market" distributors buy up available supplies and offer to sell them to end purchasers at significantly higher prices, creating huge profits for themselves. Premier members report "gray market" prices as much as 335 percent more for a shortage drug. A recent *Kaiser Daily Health Policy Report* highlighted how the chain of custody in the gray market may pass from one distributor to another, creating a string of transactions that lead to higher prices and drug integrity concerns.<sup>17</sup>

#### ***Stockpiling by end-users***

Drug shortages have been exacerbated by stockpiling on the part of providers. Artificial shortages can result from end-users who attempt to protect themselves from the instability of the drug supply chain by placing orders that exceed normal requirements.

#### ***Changes in clinical practice and emergency situations***

Manufacturers may discontinue older products as their clinical demand decreases and profitability drops. One drug product shortage can increase demand for a therapeutically similar product that is not normally produced in quantities sufficient to meet unanticipated market needs. This scenario occurred in 2010 with the morphine and subsequent hydromorphone shortages.<sup>18</sup> At least 4 percent of sterile injectable shortages in 2010 were due to increase in demand from another drug shortage.<sup>6</sup>

### **III. What is the impact on patient safety and quality of care?**

Some antibiotic and antiviral medication shortages contributed to patient mortality because specific bacteria and viruses were not sensitive to other available medications. The factors that may lead to errors when drug shortages occur include tactics that pharmacy directors and key stakeholders are beginning to incorporate into their failure mode analysis (Table 1).

**TABLE 1 | DRUG SHORTAGE FACTORS THAT MAY LEAD TO ADVERSE PATIENT SAFETY EVENTS**

- Absence of early warning for drug shortage
- Poor communication between suppliers and end users
- Poor communication between pharmacy and end users
- Incomplete information on cause, duration, and expected resolution
- Labor challenges that limit ability to adopt proactive strategies

The American Society of Health-System Pharmacists (ASHP) provides a detailed algorithm which may be used to improve the organizational response to drug shortages.<sup>20</sup> The ISMP recommends a rigorous action plan to reduce the risk of drug errors when a shortage occurs (Table 2).<sup>21,22</sup>

**TABLE 2 | ISMP RECOMMENDATIONS WHEN A DRUG SHORTAGE OCCURS**

- Identify and learn more about drug shortages
- Assess inventory of drugs available in pharmacy
- Research uses and optimal doses for drugs in short supply
- Conduct DUEs if necessary and decrease waste and unnecessary orders
- Identify potential therapeutic alternatives early
- Prioritize and place limitations on use with ethics committee consultation
- Conduct a failure analysis and take action
- Do not hoard medications
- Establish ongoing communications on possible alternatives and potential adverse events
- Establish a shortage network with other healthcare providers to obtain needed supplies
- Determine position regarding alternative suppliers
- Remove supplies from floor stock when able and have pharmacy dispense the drug
- Institute strategies to avoid errors with substitutes
- Proactively monitor adverse events and report to risk management
- Monitor and report drug shortages

Clinicians should work prospectively as a team, and use a Failure Mode Effects Analysis model, to identify potential safety hazards with alternatives to the unavailable drug and then effectively communicate such concerns to all pertinent practice areas.

### **Premier Drug Shortage Survey**

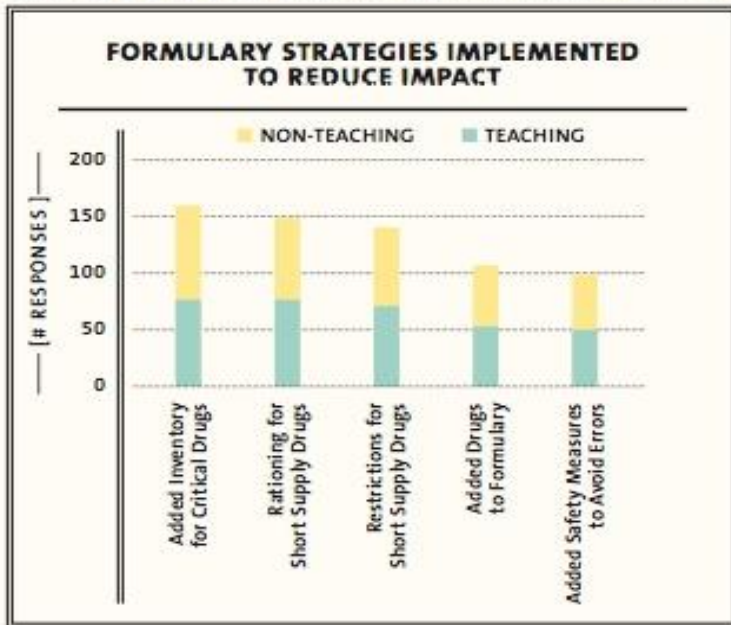
According to a Premier healthcare alliance survey of 311 pharmacy experts representing 228 hospitals and multiple other healthcare sites (infusion, oncology and surgery centers; outpatient and retail pharmacies; and long-term care facilities), over the course of six-month period July-December 2010:

- 89 percent experienced shortages that may have caused a medication safety issue or error in patient care.
  - 53 percent suggested occurrence 6+ times.
- 80 percent experienced shortages that resulted in a delay or cancellation of a patient care intervention.
  - 34 percent suggested occurrence 6+ times.
- 98 percent experienced shortages that resulted in an increase in costs.
  - 88 percent suggested occurrence 6+ times.
  - 41 percent suggested occurrence 21+ times.

The survey identified a number of innovative strategies that members have implemented to reduce the negative impact resulting from drug shortages; they include adding management procedures, changing standard processes and modifying normal communication strategies.

Formulary changes identified by members were directed toward changes in key tactics for how drugs are allocated during these times to reduce patient care impact:

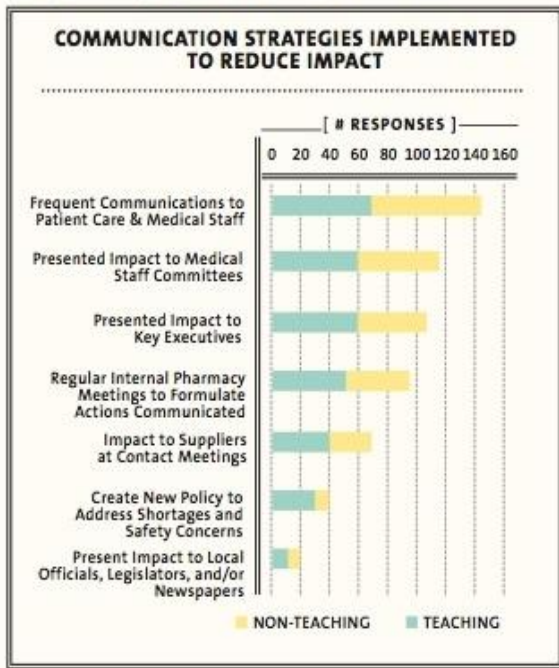
Formulary changes identified by members were directed toward changes in key tactics for how drugs are allocated during these times to reduce patient care impact:



Respondents checked all of the above that applied. Results: Added inventory - 164; Rationing - 140; Restrictions - 136; Added drugs - 103; Added safety measures – 102.

Hospitals focus on specific communication strategies designed to navigate through the challenges of the situation that are important for success:

Members' focus on specific communication strategies designed to navigate through the challenges of the crisis that are important for success:

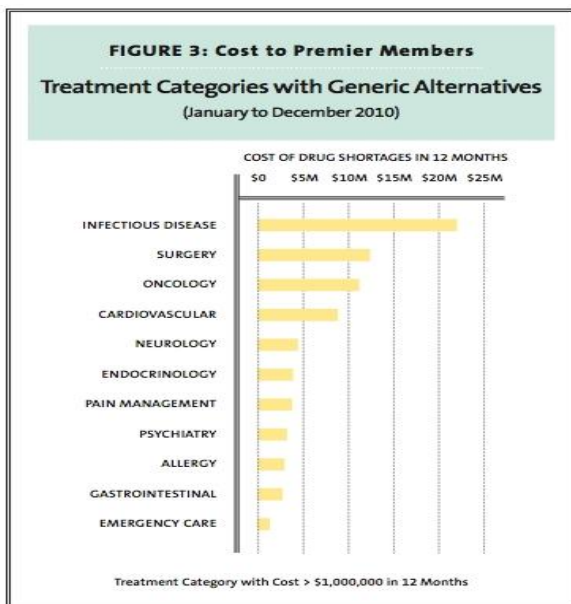


Respondents checked all of the above that applied. Results: Communications to staff - 146; Presented impact to medical staff - 110; Presented impact to execs - 106; Regular internal meetings - 94; Impact to suppliers - 70; Create new policy - 43; Present impact to locals - 19.

#### **IV. What is the impact on the cost of healthcare?**

##### **Premier research**

Premier's ability to analyze the expansive pharmaceutical supply chain data of our members has enabled us to provide financial impact snapshots of drug shortages. Based on Premier's current membership of hospitals and other non-acute care sites, using Premier's Purchasing Partners services, the annualized financial impact of drug shortages *where generic equivalent alternatives are available* exceeds \$78 million, with the highest approximate cost impacts (Figure 3) to infectious disease (\$22.5 million), surgery (\$12 million), oncology (\$10.5 million), and cardiovascular therapies (\$8.5 million). More than \$66 million (or 85 percent) of this estimated financial impact in 2010 is being felt within the acute care sector alone.



From a national standpoint, the analysis suggests the shortage could cost U.S. hospitals at least \$200 million annually through the purchase of more expensive generic or therapeutic substitutes. Providers are paying an average of 11 percent more for shortage products, although the total economic impact is likely much higher, since research excludes drugs purchased on the “gray market,” or those with therapeutic alternatives. The research also does not include indirect costs such as added labor needed to manage shortages and secure alternative supplies, as data on these areas does not exist.

## **V. What are the FDA and professional organizations doing about the problem?**

The ASHP in conjunction with the American Society of Anesthesiologists, American Society of Clinical Oncology, and the ISMP hosted a Drug Shortage Summit on November 5, 2010. Pharmaceutical manufacturers, wholesalers and distributors, the FDA, the University of Utah Drug Information Service, Premier, and others participated in the summit.<sup>1</sup> The goals were to:

- Discuss the scope and causes of drug shortages
- Investigate the impact on quality and safety of patient care
- Identify the potential need for changes in public policy to prevent patient harm
- Develop an action plan that reflects the recommendations of stakeholders

At the summit, the FDA provided their perspective on statutory and regulatory authority and limitations related to drug shortages. The FDA will work with manufacturers to address shortages while trying to minimize patient risk. The extent to which the FDA can mitigate the impact of a shortage depends on whether it meets “medical necessity” criteria. If there is a shortage of a medically necessary product, they may engage in discussions with manufacturers to encourage additional sources of the product, provide technical assistance to manufacturers experiencing difficulties with cGMPs, or expedite reviews of product marketing applications or manufacturing processes. Additionally, the FDA accelerates the approval process after reviewing the potential impact on drug safety and drug authenticity.<sup>5</sup>

Summit participants provided 21 recommendations for improving communication among stakeholders and removing barriers faced by the FDA and drug manufacturers.<sup>1</sup> Participants are meeting with legislators to ensure inclusion of key drug shortage situations in federal legislation.<sup>23</sup> Senator Amy Klobuchar’s legislation provides the FDA authority to require early notification from pharmaceutical manufacturers at least 6 months in advance if there is a planned decision to limit or discontinue production of prescription drugs, or as soon as possible in the case of an unexpected interruption or adjustment. The legislation would also direct FDA to establish a criteria to identify drugs vulnerable to a shortage and work with manufacturers to establish a continuity of operations plan to address drug shortage. It also requires FDA to perform expedited re-inspections of manufacturers in the case of a drug shortage. If a manufacturer is forced to alter or suspend production due to an FDA initiated review, the FDA must perform a re-inspection of the site within 90 days once the manufacturer has addressed the underlying situation.

The ASHP and FDA maintain websites regarding drug shortages.<sup>4,5</sup> The ASHP Drug Shortage Resource Center provides very comprehensive, up-to-date information and suggests clinically relevant alternatives to consider when a shortage occurs.<sup>1</sup> The website also provides position papers on managing drug shortages and a sample policy and procedure that hospitals can use as a template. The ASHP and the FDA encourage reporting of drug shortages.<sup>25,26</sup>

## **V. What is Premier’s response to the drug shortage situation?**

Premier believes that new measures and accelerated efforts are needed to address situations with prescription drug shortages and is prepared to help members navigate the ongoing situation.

We are working aggressively to diminish shortage-related costs to member hospitals. Our expansive supply chain data repository provides unique opportunities to source drugs from suppliers that demonstrate the ability to safely meet member market demands.

We encourage communication from both suppliers and providers about product releases through professional networking via our *PharmacyConnect*<sup>®</sup> portal.<sup>28</sup> We regularly communicate this information to the FDA to make them aware of what is being shorted. In collaboration with our members, we have developed toolkits, programs, and professional advisories to help members manage drug shortages.

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