

# **Medication Shortages**

*an Information Paper*

*Developed by Members of the  
Emergency Medicine Practice Committee*

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### **Introduction**

A drug shortage is defined by the US Food and Drug Administration (FDA) as “a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the patient level.”<sup>1</sup> While a rarity before the year 2000, with three reports in 1996, there were at least 232 reported drug shortages in 2011. These shortages primarily affect sterile injectable drugs which represent approximately 75% of drug shortages in 2010.<sup>1</sup> In recent years shortages have affected commonly used medications. An executive order by President Obama in 2011 provided the FDA broader latitude to prevent drug shortages. However, to date, the pharmaceutical industry is neither legally required to report on potential drug shortages (unless they are sole source suppliers or suppliers of ‘medically necessary products’) nor obligated to manufacture drugs that are already in short supply.<sup>2</sup>

### **Causes of drug shortages**

#### *Business decisions*

Manufacturers may simply cease production of medications, especially generics, when profit margins are small. Consolidation of manufacturers, such as through merger or acquisition practices, can lead to decreased production, particularly if both companies manufactured the same medication prior to consolidation. Liability concerns may lead to market withdrawals.

#### *Supply chain disruption*

Raw materials may become limited when a sole source supplier ceases operation, or quality is compromised (eg, presence of particulates, impurities, chemical instability, microbial contamination, and crystallization). Areas of conflict, natural disasters, and labor disputes can disrupt importation, as 80 percent of raw materials come from abroad.<sup>3</sup>

#### *Unexpected demand increase*

Manufacturers tend to operate at demand levels and a shortage may occur when demand suddenly increases. Recent examples include shortages of flu vaccine and oseltamivir during influenza outbreaks. There has been a recent trend to maintain ‘just-in-time’ inventories to decrease waste, which diminishes the ability to respond quickly to demand increase.

#### *Distribution*

Purchasers of large quantities of medications, for example group purchasing organizations (GPO), can adversely affect the supply available to small and rural facilities. Additionally, manufacturers that fail to obtain GPO contracts may have little to no incentive to manufacture certain medications. Gray market (as opposed to black market) or parallel market distributors are known to accumulate medications and resell them at significant markup.

#### *FDA oversight*

A New Drug Application (NDA) to the FDA can be burdensome and prohibitive, preventing manufacturers from entering existing markets or maintaining market share. Even abbreviated NDAs, required for changes to FDA-approved drugs (eg, change in active pharmaceutical ingredients [API]) can be cost prohibitive due to the duration and unpredictability of the process.<sup>3</sup> Compliance with the Good Manufacturing Practices (GMP) Act may lead to disruptions if a manufacturer cannot meet regulatory standards. A 2012 staff report from the Committee on Oversight and Government Reform asserts that part of the problem is the Medicare Modernization Act (MMA), which decreased Medicare reimbursements for injectable medications, reimbursements which are often already below manufacturing costs. It also

asserts that due to a 2009 FDA policy to force manufacturers to upgrade facilities, many manufacturers upgraded simultaneously, resulting in a 30% loss of manufacturing capacity.<sup>4</sup>

#### *Other*

Of unclear significance are recalls, changes in clinical practice patterns, and patent challenges.

### **Effect on facilities and patients**

According to a 2010 Premier Healthcare Alliance survey (including hospitals; infusion, oncology and surgery centers; outpatient and retail pharmacies; and long-term care facilities), 89% of healthcare facilities experienced shortages that may have caused a medication safety issue or error in patient care 80% experienced shortages that resulted in a delay or cancellation of a patient care intervention, and 98% experienced a delay that resulted in an increase in costs.<sup>3</sup>

In order to address shortages, some health care facilities have divided medications intended for single-use into multiple doses. Anecdotally, it is reported that prehospital care has been adversely affected and use of medications beyond their expiration date may occur. The FDA FAQs state, “When a shortage occurs and a firm has inventory that is close to expiry or already expired, if the company has data to support extension of the expiration dating for that inventory, FDA is able to review this and approve the extended dating to help increase supplies until new production is available.”

The Associated Press reported at least 15 deaths attributable to drug shortages over a 15-month span.<sup>5</sup> When less desirable medications are used, adverse events may include medication error due to unfamiliarity, unanticipated side effects and drug-drug interactions, and less than optimal treatment outcomes. Numerous adverse outcomes reported in 2010 by the Institute for Safe Medication Practices<sup>6</sup> include:

- absence of sedation in a paralyzed, ventilated patient when propofol was unavailable and a substitute not ordered;
- self-extubation by patient when inadequate amount of benzodiazepine was administered;
- wrong doses of paralytics administered when providers forgot that alternative was used, or used protocol to prepare medication intended for another medication;
- hydromorphone administered at morphine doses, resulting in patient deaths;
- hoarded bags of heparin accidentally dispensed to nursing unit instead of plain intravenous solutions;
- phenytoin, used in place of fosphenytoin, administered too rapidly resulting in thrombophlebitis, arrhythmia, and cardiac arrest;
- patient death when amikacin is unavailable to treat pseudomonas infection sensitive only to this antimicrobial.

### **Proposed solutions**

Drug manufacturers must provide early notification to the FDA when a shortage is anticipated. For proprietary reasons, as well as to avoid the appearance of collusion, this will likely be a confidential process. Legislation has been introduced unsuccessfully to make this mandatory. The FDA maintains a website with information on current drug shortages and discontinuations.<sup>7</sup>

Much like disaster planning, the American Society of Health-System Pharmacists recommends facilities have a defined process to anticipate and deal with shortages. They recommend a plan divided into assessment, preparation, and contingency phases, which is available online.<sup>8</sup>

The FDA should review which medications qualify as medically necessary, in order to require manufacturers to report shortages in a timely manner, and in order to expedite the review process for

those entering the market to manufacture drugs in short supply. Regulations should be put in place to limit or stop gray market suppliers. Consideration should be given to approve the importation of drugs manufactured in other countries with quality control standards that approach those of the FDA. Manufacturers should be incentivized to produce generic medications, possibly through exclusive licensing or increasing reimbursement. The safety of dividing single-use medications, and using expired ones, should be determined.

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