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## Drug Shortages in the US – Causes, Impact, and Strategies

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### Introduction

Drug shortage in the United States is defined 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 user level".<sup>1</sup> A term rarely encountered decades ago, it was not until recent years that the magnitude and impact of drug shortage progressed to critical levels. While the annual new drug shortages list remained fairly stable prior to 2005, a rapid, steady increase has been observed over the second half of the past decade. In 2010, there were 211 newly reported drug shortages, tripling the amount in 2006 (Figure 1), with almost 75% being sterile injectables.<sup>2</sup> The shortage is present in all healthcare practice settings and affects nearly all drug classes, with critical therapeutic areas such as oncology and antimicrobials being affected the most.<sup>3</sup> As of October 2011, 232 shortages have been reported from multiple resources, exceeding the records in 2010, and it is estimated that 360 products will be in shortage by the end of 2011.<sup>4, 5, 6, 7</sup>

In October 2011, President Obama signed an executive order guiding the Food and Drug Administration (FDA) to set up efforts to relieve shortages.<sup>7</sup> The latest White House initiative that does not require congressional approval, the order directs the FDA to enforce reporting obligations for manufacturers on impending drug withdrawals, expedites review progress of new prescription drugs and forges collaboration with the Justice Department to prosecute price gouging from the gray market. However, these approaches do not directly tackle the fundamental causes of drug shortages, and the initiative is unlikely to have an immediate impact on the situation.<sup>8</sup>

### Causes of Drug Shortages

The causes of drug shortages are complicated and rooted in every phase of a drug's life cycle. Yet to be systematically studied, many trends contribute to the shortage, comprising shortage of raw materials, issues related to manufacturers (pharmaceutical mergers and acquisitions, decisions based on projected profit), regulatory and legislative factors, and labor disruption. It is worth noting that approximately 27% of the shortages are unexplained.<sup>9</sup>

#### 1. Unavailability of Raw Materials

Suboptimal quality of raw materials may have a profound impact on drug shortages. Raw material shortage can result from a number of factors, including a sole source

manufacturer that ceases operation, suboptimal quality of the raw material, and wars that disrupts importation. In 2010, nearly half of drug shortages resulted from quality issues of raw materials, including impurities, microbial contamination, and chemical instability.<sup>3</sup> Currently, eighty percent of the raw materials come from foreign markets, which imposes challenges to quality control of the raw materials.<sup>10</sup> For example, the market for Chinese active pharmaceutical ingredients (APIs) was reduced by nearly 50% in 2010, partly attributable to concerns over quality issues with Chinese APIs, exemplified by heparin contamination in 2008.<sup>11</sup> The shortages can be especially problematic when a major or sole-source supplier ceases production of raw materials, affecting all of the producers of finished product.<sup>12</sup>

#### 2. Manufacturer Decisions, Merger, and Acquisition

A number of factors can lead to manufacturer's decision to discontinue the production of certain drugs. These may include: discontinuing API due to investments required for new quality requirements imposed by FDA, diminishing demand, negligible profitability, for liability reasons, to utilize resources elsewhere, etc. For example, GlaxoSmithKline pulled its Lymerix vaccine off the market due to diminishing demand and increasing consumer criticism.<sup>13</sup> Nearly 20% of injectable drug shortages were consequences of product discontinuations. Unfortunately, manufacturers are not obligated to inform FDA about product discontinuation plans unless their product is the only medication to treat a life-threatening condition or debilitating disease. In addition, there is no legal requirement for a firm to continue producing any drug, even one that is deemed medically necessary.<sup>3</sup> Consolidations and mergers among manufacturers can result in decisions to consolidate product lines or decisions to discontinue the manufacture of certain drugs, particularly if companies have two similar products.

#### 3. Regulatory Issues, Noncompliance with Current Good Manufacturing Practices (cGMPs)

Another significant contributor to drug shortages results from regulatory barriers and ambiguities, including lack of sufficient communications between FDA and manufacturers. Specific cases include a lengthy period for FDA review of Abbreviated New Drug Applications (ANDAs) and supplemental applications, which are necessary steps for a change in source for API and change in manufacturer. Some manufacturers view the process of completing a New Drug

Application (NDA) to be costly, lengthy and complicated, and this has been a disincentive for entering a market.

The FDA requires manufacturers to comply with the Good Manufacturing Practices (cGMP) Act. Although the cGMP requirements were established to be flexible in order to allow each manufacturer to use individualized approaches, the cGMP change over time. The shortage of immune globulin intravenous pentelate, an injectable drug for enhancing the immune system, resulted from a manufacturer's failure to meet regulatory standards. Manufacturers that are in compliance and produce the same drug tend to operate close to their production capacity, and they may be unable to meet greater demand.<sup>14</sup> They plan to produce the quantity they expect to sell.

#### 4. Unexpected Demand

An outbreak of a rare disease can quickly disrupt the regular supply chain. In 2009, when the H1N1 pandemic came on the scene, FDA amended the original Emergency Use Authorizations (EUAs) for both Tamiflu and Relenza as part of the federal government's responses to the public health emergency.<sup>15</sup> Subsequently, the shortages of Tamiflu were reported everywhere, particularly in pediatric practices.<sup>16</sup>

#### 5. Natural Disasters

Natural disasters may result in a shortage by affecting the raw materials needed by the sole producer of a drug and impose unexpected impairment to manufacturing facilities. Hurricane George (1998) caused major damage in Puerto Rico. As a consequence, several drug shortages occurred as the many pharmaceutical manufacturing facilities on the island were severely disrupted.<sup>14</sup>

#### 6. Labor Disruptions

Labor disruptions attribute to drug shortages by diminishing the productivity of the manufacturing sector.

Other causes include voluntary recalls from manufacturers, changes in clinical practice patterns, and restricted distribution. The above reasons are not mutually exclusive and in many cases, shortages may result from a combination of factors. The above possibilities may be aggravated by a number of factors. If a drug is a sole product in a therapeutic area, then any dislocation in supply can result in unavailability of the drug. However, even if the drug is not a sole source, but manufactured by a small number of companies a decrease in supply by one manufacturer can lead to shortages if the other manufacturers are unable to increase production to compensate for the shortfall.

### Consequences of Drug Shortages

#### 1. Impact of Drug Shortages on Healthcare Quality

According to the report by the Drug Information Services of the University of Utah, the five drug classes in 2010 that encountered the most drug shortages were CNS (28 shortages, mainly anesthesiology), antineoplastics (20 shortages), antimicrobials (19 shortages), electrolytes (17 shortages), cardiovascular (17 shortages) and autonomic (13 shortages).<sup>17</sup> These products are essential for treating most critical health conditions and shortages in any of them inevitably caused disruptions in patient safety and quality of health care.

In situations where a drug in shortage is the sole treatment option for a life-threatening condition or appropriate alternative agents are difficult to obtain, patients' lives can be immediately placed at risk. Incidences of shortage-related patient deaths have been reported in all healthcare practice settings in the past 15 months and at least 15 deaths have been attributed to the shortages.<sup>18</sup> Even when alternative drugs are available, prescription errors due to unfamiliarity with the new regimen, adverse events caused by unexpected drug-drug interactions and suboptimal treatment outcomes associated with alternative agents can place severe distress to healthcare practices. For example, prochlorperazine was used in combination with droperidol to treat Chemotherapy Induced Nausea and Vomiting (CINV). After the shortage of prochlorperazine occurred at the University of Pittsburgh Medical Center, promethazine was selected for therapeutic interchange. The adverse events related to the use of promethazine had increased by over 3.3 fold in the subsequent year, due to unexpected drug-drug interactions.<sup>19</sup> A national survey conducted last year among 1,800 healthcare practitioners revealed that 80% of the participants expressed difficulty in obtaining a suitable alternative medication and 64% encountered risk of related adverse events.<sup>20</sup> In June 2011, the shortage of paclitaxel, the generic version of Taxol, has threatened lives and may have shortened survival of cancer patients, due to the lack of equally effective substitutes.<sup>21</sup> Shortages of drugs for attention deficit hyperactivity disorder (ADHD) led consumers to seek pricey alternatives that are less effective.<sup>22</sup> According to a recent report, drug shortage has also caused a barrier for patient enrollment in clinical trials. More than 300 NIH-funded clinical trials involve a drug that is in shortage.<sup>23</sup>

#### 2. Financial Impact of Drug Shortages

The results of drug shortage, particularly the rapid increase in its magnitude, have imposed substantial financial burdens on hospitals and to the healthcare system as a whole. To respond to shortages, health care organizations have taken various approaches, which can divert resources away from

routine care. According to a survey conducted by Premier, a hospital buying group, the annual financial impact of drug shortages on Premier alliance members alone exceeds \$78 million. More than \$66 million (or 85 percent) of the impact is felt by Premier's 2,500 hospital members, with the remaining amount within Premier's non-acute care sites.<sup>3</sup>

### 3. Gray Market Distributors

The gray market, also known as a parallel market, is a trade of products through supply channels which, while legal, is unintended, unofficial, unauthorized by the original manufacturer. Gray market distributors buy available drug supplies and sell them to providers or end purchasers at markups of several hundred percent. During times of drug shortages, this supply chain diversion may threaten drug integrity in addition to fleecing payers. According to a recent investigation led by Congressman Elijah Cummings<sup>24</sup>, in the event of shortage for some critically needed medications, gray market vendors can raise the product price by more than 80 times a typical contract price. For example, Cytarabine, a chemotherapy agent used to treat Acute Myeloid Leukemia (AML) and non-Hodgkin Lymphoma (NHL) in children and adults, was typically priced at approximately \$12 per vial but was sold at over \$900 per vial by a distributor from Southern Florida. The activities from gray market distributors have been wide-spread and aggressive. In July and August this year, the Institute for Safe Medication Practices (ISMP) conducted a survey regarding gray market activities and drug shortages which included healthcare providers from 549 hospitals across the nation. Over half (56%) of all participants reported receiving daily solicitations from vendors offering pharmaceutical products no longer available through authorized channels. It is also suggested by more than 10% of respondents that gray market vendors may have also purchased vital medications with impending shortages from hospitals, presumably to sell to other healthcare providers at inflated prices.<sup>25</sup> Further investigations revealed deeper rooted issues in the multilayered nature in the gray market. Many distributors reported buying the medications at already highly inflated prices and selling them at a normally increased rate, thus they considered generated profits to be "reasonable".<sup>26</sup>

## Responses from Government, Health Care Organizations, and Pharmaceutical Markets

### 1. FDA's Drug Shortage Program (DSP)

Currently, FDA has limited regulatory authority in the battle against drug shortages. Established in 1999, under the Center for Drug Evaluation and Research (CDER), one of the FDA's five centers, the DSP is aimed at resolving all issues related to shortages of the products reviewed by the CDER and release information about these drugs to the public. The DSP

primarily uses tools of communication, facilitation, and negotiation to formulate and implement effective plans for preventing and managing drug shortages.<sup>28</sup>

DSP maintains a partnership with the American Society of Health-System Pharmacists (ASHP), with the latter regularly sharing available data with the DSP. The DSP assesses the severity and duration of the shortage, as well as determines if the drug is medically necessary, currently defined as "...any drug used to treat or prevent a serious disease for which no appropriate substitute is adequately available".<sup>27</sup> A shortage involving medically necessary products is likely to cause significant disruption in patient care. FDA has established a website for posting information related to shortages of medically necessary products.<sup>28</sup> In addition to posting news on the webpage, the DSP staff answers each e-mail inquiry that it receives at its Drug Shortage email account.

When shortages of medically necessary products occur, the DSP determines the cause and works with manufacturers and appropriate FDA components to develop short-term and long-term management plans.

### 2. The American Society of Health-System Pharmacists (ASHP)

In November 2010, a Drug Shortage Summit was held jointly by the ASHP, the American Society of Anesthesiologists, American Society of Clinical Oncology, and Institute for Safe Medication Practices (ISMP).<sup>29</sup> Participants included pharmaceutical manufacturers, wholesalers and distributors, the FDA, the University of Utah Drug Information Services, Premier and others. The goals were to: 1) Discuss the causes of drug shortages; 2) Examine the impact of drug shortage on healthcare quality; 3) Identify the need and feasibility for changes in public policy to relieve and eradicate the detrimental impact of drug shortage; 4) Develop an action plan based on the recommendations of stakeholders.

Summit participants provided extensive recommendations to minimize the impact of drug shortages, including improving communication among stakeholders in the pharmaceutical supply chain and health care providers, and removing barriers faced by the FDA and drug manufacturers. With regard to handling regulatory and legislative factors that contributed to the shortage of drugs, it was recommended that greater authority should be given to FDA for requiring manufacturer advance notification of impending market withdrawals. Participants also proposed a revision of FDA's current definition of medically necessary.

The FDA will facilitate their communications with manufacturers to relieve shortages with the hope to mitigate patient risk. Furthermore, an approval process for alternative

products is subject to acceleration, based on reviewing the potential impact on healthcare quality and patient safety.<sup>29</sup>

### 3. *The Preserving Access to Life-Saving Medications Act*

In February 2011, Senator Amy Klobuchar introduced a bill, S. 296, the Preserving Access to Life-Saving Medications Act, that would provide FDA with key strategies to prevent drug shortages. These approaches include imposing a minimum of 6 months in advance for manufacturers to report to FDA of an impending market exit or product discontinuation. The legislation also requires FDA to perform expedited re-inspections of manufacturers in the case of a drug shortage.<sup>30</sup> The bill granted the FDA authority to impose penalties on noncompliant manufacturers.

#### Proposed Actions

##### 1. *Strengthen FDA's roles*

Currently, FDA has limited authority in forecasting, preventing, and controlling drug shortages. The Drug Shortage Program (DSP), under Drug Evaluation and Research (CDER), one of the five centers within the FDA, receives information about drug shortages mainly from the public e-mail account maintained by DSP.<sup>31</sup> Report of shortages to the FDA is not an obligation of manufacturers, except for medically necessary products.<sup>32</sup> Furthermore, FDA is not granted authority to regulate product discontinuation, a decision usually made by manufacturers. Senator Klobuchar's bill, S. 296, would require all pharmaceutical manufacturers to report to FDA at least 6 months before planned market exit.<sup>33</sup> The legislation also would provide feasibility for FDA to know the reasons for such discontinuations (e.g. whether it is caused by raw material shortage or lack of projected profits) and work with manufacturers to establish a continuity of operations plan to address drug shortages. While a 6-month period would leave considerable leeway for FDA to seek alternative solutions, a prolonged length should be recommended to accommodate additional procedures required for other manufacturers to increase production of drugs in short supply, or for re-importation of such products.

It may also be necessary to consider specific elements for revision of the current definition of medically necessary. For example, what would be the qualification standards for a "serious disease"? Is there a threshold for its prevalence, incidence, and survival period? Would it be feasible for FDA to define a list of "serious diseases" for which any disruption in treatment would cause detrimental impact to the population? A standardized and more precisely defined terminology for the indispensable pharmaceutical products can facilitate the process of empowering the FDA to regulate manufacturers' behavior for the continued production of drugs that are deemed medically necessary.

##### 2. *Regulations to halt gray market activities in short supply*

Stronger regulatory actions are needed to control and monitor distribution channels for pharmaceutical products. Regulatory engagements will focus on two aspects: a national pedigree law that restricts the distribution of pharmaceutical products to authorized wholesalers (Verified-Accredited Wholesale Distributor, VAWD) and with enhanced monitoring systems; and standardized pricing from distributors that prohibits price gouging, even during drug shortages. A coalition from all major stakeholders in the pharmaceutical manufacturing-supply chain: manufacturers, authorized distributors, pharmacies, healthcare providers and consumers. Healthcare providers can take advantage of the gray market solicitation and gain insight into potential drug shortages, which can lead to optimized planning for the allocation of remaining supplies in the practice setting, as well as potential exchange of products with other hospitals to avoid utilizing gray market vendors. In event of an impending shortage, direct ordering from manufacturers should be considered, if a situation warrants. Ultimately, FDA is entitled to greatly enhanced authorities for its pivotal role in the battle against drug shortages. When manufacturers know their products will soon be in shortage, FDA should be informed a minimum of six-month before the shortage occurs. To prevent potential purchases from gray market vendors during the reporting window, regulations should be made to requiring manufactures to stop deliveries to distributors and wholesalers after the impending shortage is reported to FDA and access to products will be only granted only to healthcare practices (e.g. hospitals, clinics, and pharmacies).

##### 3. *Grant temporary authorization to foreign markets and approve pharmaceutical products from Western European countries*

Drug purchases over the internet from foreign countries is not a new term. Although studies have shown that generic drugs in Canada or western Europe were generally more expensive than the same products in the US market, without even taking shipping cost into consideration, temporary regulatory adjustment process to allow larger scale drug importation from countries with more established drug quality management systems (primarily western European countries, Canada, Japan and Australia) can provide relief to the current crisis of massive drug shortages. In Europe, the majority of drugs are authorized through the European Medicines Agency (EMA), a scientific agency that is roughly parallel to the US FDA. A centralized procedure allows manufacturers to submit a single application to EMA to obtain from the European Commission a centralized (or 'Community') marketing authorization valid in all EU member states. A more collaborative relationship between FDA and

EMA has been cultivated in recent years. Earlier this year, The U.S. FDA and the EMA have launched a 3-year pilot program that will allow parallel evaluation of new drug marketing applications that are submitted to both agencies.<sup>34</sup> By imposing regular communication and consultation between the two agencies throughout the process, the programs will provide further space for FDA and EMA reviewers to share full knowledge about the application and harmonize regulatory decisions to the greatest extent possible.

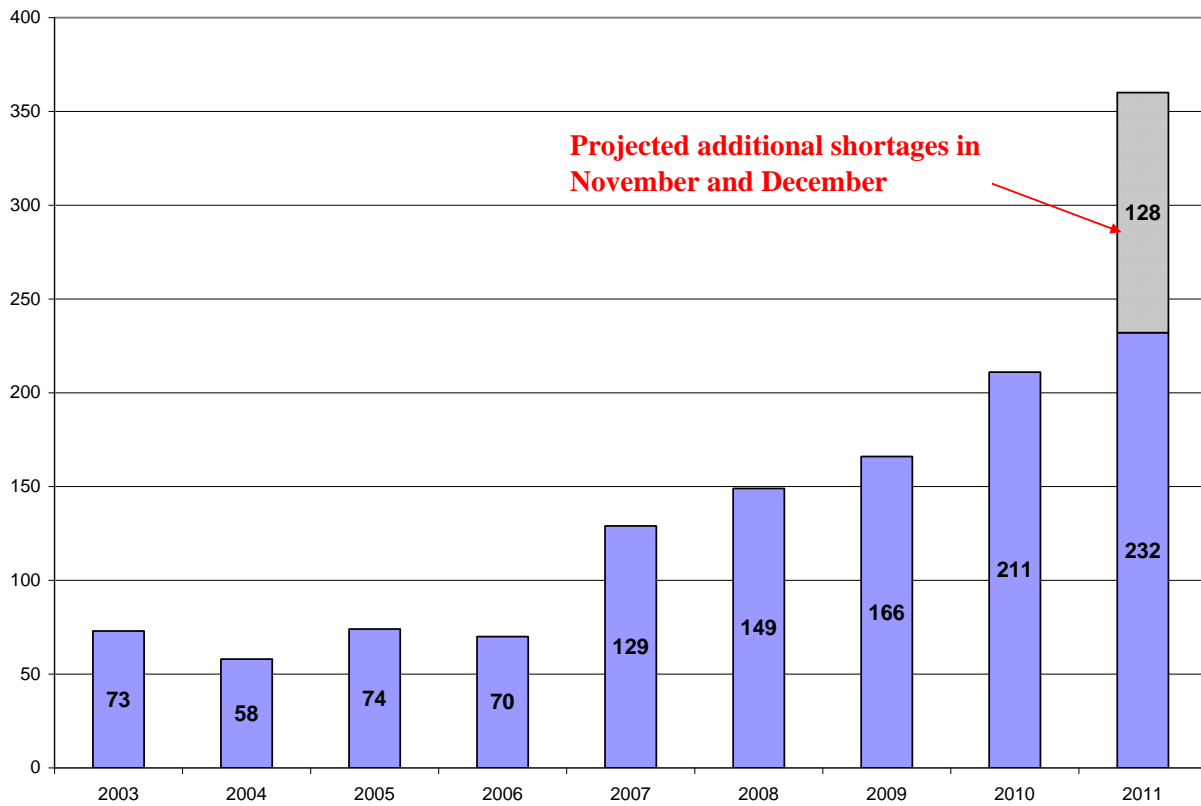
While still far away from a unified market, US and Western Europe share the commonality in many ways as they pertain to drug approval, regulation, quality inspection and monitoring. With the amount of foreign produced drugs approved in the US increasing steadily over the past decade, the FDA's regulatory actions has expanded across Europe, Asia and Latin America to ensure the safety of imported products.<sup>35</sup> While criticisms were raised against FDA's delayed approval of foreign pharmaceutical products to protect domestic manufactures and actions have been taken to expedite approval of critically needed drugs from foreign markets,<sup>36</sup> FDA's approval procedure for foreign drugs is heavily based on clinical trial data coming from overseas sites. Currently, there are no regulatory procedures to grant

FDA with sufficient authority to monitor these trials. It is encouraged that sponsors of foreign clinical trials voluntarily consult with FDA on their trial protocols or submit Investigational New Drugs (INDs) to the agency.<sup>37</sup>

### Conclusion

The escalating increase in the shortage of drugs has compromised patient quality of care and imposed a tremendous burden on our health care system. In response to the crisis, healthcare and government organizations have taken numerous initiatives, aiming to find rapid solutions. Nevertheless, the battle against drug shortage is likely to be long-term and requires joint efforts from all sectors of the health care system, as well as consumers, pharmaceutical traders and legal entities. New bills have been proposed to prevent or mitigate supply issues, but it will take efforts in lobbying for their incorporation into law, and their ultimate effect is unclear. Key elements to a successful program for managing drug shortages include a good understanding of the causes for the shortages, a clear channel for international communication and collaboration, and plans with all parties involved, and proven strategies for involving the entire health care system.

Figure 1. Annual New Drug Shortages (2003-2011)



Sources: Drug Information Service, University of Utah, 2010; The Washington Post, October 30, 2011.



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