

A Review of FDA's Approach to Medical Product Shortages



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. FOOD AND DRUG ADMINISTRATION

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EXECUTIVE SUMMARY

Despite the fact that the U.S. Food and Drug Administration (FDA) has successfully prevented 137 shortages since the beginning of 2010, drug shortages have been increasing in frequency and severity in recent years and adversely affecting patient care. Some recent shortages have involved drugs for life-threatening conditions and, in some cases, the product in shortage has been the only product for the patient's condition. While most drugs do not experience shortages, this is a significant public health problem, one that deserves the concerted attention of government and industry.

To that end, FDA conducted a review of medical product shortage activities in four product Centers in FDA and talked to external stakeholders in the drug arena to understand their perspectives on the current problem.¹ Based on these conversations, a review of published and unpublished information on drug shortages, and analyses of existing or newly created databases, this report concludes that the problem of medical product shortages is complex and stems from economic, legal, regulatory, policy, and clinical decisions that are deeply interconnected. Many parties along the entire supply chain, including essential raw ingredient suppliers, Active Pharmaceutical Ingredient manufacturers, final drug product manufacturers, wholesalers, group purchasing organizations, clinicians, and, ultimately, patients are affected. While FDA has taken on the task of working with manufacturers to help prevent and mitigate these shortages, many of the root causes and potential solutions to the shortage problem lie beyond its purview. The Agency is also limited in its current authorities as it formulates a response to the problem.

In addition, the U.S. Department of Health and Human Services' Office of the Assistant Secretary for Planning and Evaluation conducted an analysis of underlying economic factors that lead to periods of prescription drug shortages, particularly market factors that have contributed to shortages of sterile injectable oncology drugs. The report finds that growth in demand has occurred while the capacity of manufacturing facilities has remained stable, leading to a very high rate of capacity utilization. This analysis can be found at <http://aspe.hhs.gov/sp/reports/2011/DrugShortages/ib.shtml>.

Key Facts about Drug Shortages

- The number of drug shortages annually has tripled from 61 in 2005 to 178 in 2010.
- Of the 127 studied² drug shortages in 2010-11, sterile injectables accounted for the majority (80%). The major therapeutic classes of drugs in shortage included oncology drugs (28%), antibiotics (13%), and electrolyte/nutrition drugs (11%).

¹ In this report, the term "drug shortages" refers to shortages specifically pertaining to human drugs. "Medical product shortages" refers to all shortages, including human drugs, biologics, medical devices, and veterinary drugs.

² This represents a subset of drug shortages that occurred during 2010 and 2011. These shortages tended to be larger, of longer duration, and of greater public health impact than shortages not studied (see "Characteristics of Drug Shortages" in the text).

- The leading primary reasons for the shortages reported to FDA were problems at the manufacturing facility (43%), delays in manufacturing or shipping (15%), and active pharmaceutical ingredient shortages (10%).
- Manufacturing quality problems that have resulted in shortages can be serious, including findings of glass shards, metal filings, and fungal or other contamination in products meant for injection into patients.

FDA Actions to Prevent Drug Shortages

FDA helped to prevent 38 drug shortages in 2010 and 99 to date in 2011, an increase DSP staff attribute, at least in part, to improved notification by manufacturers.³ The most common FDA actions to prevent a drug shortage were:

- Expediting review of new manufacturing sites, new suppliers, and specification changes (71%),
- Exercising regulatory flexibility and discretion (20%),
- Asking other firms to increase production (7%).

FDA Actions in Response to Drug Shortages

In the shortages studied, the Agency's three most common actions were:

- Asking other firms to increase production (31%),
- Working with manufacturers to identify means to mitigate the dangers of products with quality issues (28%; e.g., work with a firm to include a filter with a product containing particulates), and
- Expediting review of regulatory submissions (26%).

FDA also exercised regulatory discretion regarding controlled importation of similar products approved abroad but not approved in the United States in 5% of cases.

Unique Manufacturing and Market Features of Sterile Injectables

- Manufacturing such products is complex and can more easily lead to problems that affect safety.
- Dedicated manufacturing lines are often required.
- The top three generic injectable manufacturers hold 71% of the market by volume.
- Most sterile injectables have one manufacturer that produces at least 90% of the drug (innovator and generic combined).

³ Cox E. Drug shortages: FDA's strategies and role. Presented at CDER Drug Shortage Workshop, Silver Spring, MD, September 26, 2011.

- “Just in time” manufacturing and inventorying practices leave little margin for error.

Together, these factors make shortages of sterile injectables more likely to occur and harder to prevent or mitigate.

Actions and Recommendations

There is no single or simple solution that can resolve the medical product shortage problem. Efforts to address the problem will need to be multifaceted, sustained over the long-term, and will require the engagement of all parties involved in the manufacture and distribution of medical products. Nonetheless, this report has identified a number of respects in which FDA’s internal processes might be improved, so that FDA is maximizing its contribution to the prevention and mitigation of shortages.

Immediate Actions

- Write a letter to drug manufacturers reminding them of their current legal obligations to notify FDA in advance of the discontinuation of certain drugs and urging them to voluntarily notify FDA of other potential disruptions to the supply of drugs that are not currently required, as soon as they become aware of them
- Develop guidance and regulations that clarify and enhance the information on potential drug shortages that is submitted by industry
- Provide additional staffing resources for FDA’s efforts to prevent and mitigate shortages
- Support legislation that requires early notification by manufacturers for drug shortages and provides new authority to FDA to enforce these requirements
- Implement and maintain a database that can analyze the characteristics of drug shortages

Longer-term Actions

- Identify factors that contribute to success or failure in preventing drug shortages and continue exploring new approaches to preventing drug shortages under existing authorities
- Identify the quality issues in manufacturing practices that have contributed to severe drug shortages and develop approaches to address them
- Encourage product manufacturers to develop and maintain a plan for back up manufacturing and sources of Active Pharmaceutical Ingredients and other essential product components
- Explore development of a sentinel reporting network (e.g., major healthcare systems, wholesalers, physician specialty societies) to facilitate early warning of drug shortages
- Encourage wholesalers to develop and publicize their procedures for distributing medical products in shortage
- Continue to maximize public disclosure of information regarding medical product shortages in FDA’s possession, within the bounds of what must remain confidential
- Continue improving communication between FDA’s field investigators and the Center for Drug Evaluation and Research’s Office of Compliance and Drug Shortage Program staff

- Improve the Drug Shortage Program's web site as a communications tool for health-care providers and other members of the public
- Explore the feasibility of developing a model based on available data on drug shortages, manufacturer characteristics, and market factors with the goal of assessing the probability of future shortages

Abbreviations Used in This Report

AHA:	American Hospital Association
ANDA:	Abbreviated New Drug Application
API:	Active Pharmaceutical Ingredient
ASA:	American Society of Anesthesiologists
ASCO:	American Society of Clinical Oncology
ASHP:	American Society of Health-System Pharmacists
ASPE:	Assistant Secretary for Planning and Evaluation
BLA:	Biologics License Application
CBER:	Center for Biologics Evaluation and Research
CDER:	Center for Drug Evaluation and Research
CDRH:	Center for Devices and Radiological Health
CVM:	Center for Veterinary Medicine
DHHS:	Department of Health and Human Services
DSP:	Drug Shortage Program
FDA:	Food and Drug Administration
FD&C Act:	Food, Drug, and Cosmetic Act
GAO:	Government Accountability Office
GMP:	Good Manufacturing Practice
GPO:	Group Purchasing Organization
ISMP:	Institute for Safe Medical Practices
MAPP:	Manual of Policies and Procedures
NDA:	New Drug Application
OAI:	Official Action Indicated
OCBQ:	Office of Compliance and Biologics Quality, CBER
OMPQ:	Office of Manufacturing and Product Quality, CDER
ORA:	Office of Regulatory Affairs
OSC:	Office of Surveillance and Compliance, CVM
OSE:	Office of Surveillance and Epidemiology, CDER
OTC:	over-the-counter
SOP (SOPP):	Standard Operating Procedures (and Policies)
UDI:	Unapproved Drugs Initiative

INTRODUCTION AND BACKGROUND

The Food and Drug Administration (FDA or the Agency) is responsible for protecting the public health by assuring that human drugs, biological products (including vaccines), veterinary drugs, and medical devices intended for human use are safe and effective. Drug shortages have been defined by 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.”⁴

While many of the root causes of medical product shortages lie outside the purview of FDA (the accompanying issue brief by the Assistant Secretary for Planning and Evaluation (ASPE) entitled “[Economic Analysis of the Causes of Drug Shortages](#)” provides additional analysis of the root causes of drug shortages), the Agency has taken on the task of working with manufacturers to prevent and mitigate such shortages. This report examines efforts being undertaken by FDA and other stakeholders in response to medical product shortages in four of the seven Centers within FDA: the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Center for Veterinary Medicine (CVM). It also examines data related to all medical product shortages and issues certain recommendations that, in a number of instances, can be applied to all product categories. However, many other recommendations apply to products regulated by CDER alone. In this report, the term “drug shortages” refers to shortages specifically pertaining to human drugs.⁵ “Medical product shortages” refers to all shortages, including human drugs, biologics, medical devices, and veterinary drugs.

Frequency of Drug Shortages

Only limited epidemiological data exist for drug shortages. Three hundred and eleven pharmacy experts representing 228 hospitals and other health-care sites responded to a survey by the group purchasing organization (GPO) Premier Healthcare Alliance that covered the second half of 2010 (response rate not calculable). Eighty-nine percent of respondents reported drug shortages that may have caused a safety issue or medical error and 80% reported that a shortage had resulted in the delay or cancellation of a patient care intervention.⁶

In April 2011, the American Society of Anesthesiologists (ASA) conducted an online survey of 1373 anesthesiologists (response rate not calculable) in which over 90% of respondents reported currently

⁴ Center for Drug Evaluation and Research, Food and Drug Administration. Manual of Policies and Procedures (MAPP), 6003.1. Available at: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079936.pdf> (accessed September 28, 2011).

⁵ In addition to small molecule drugs, CDER regulates certain larger molecule products, including certain biological products. For more information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm> (accessed September 28, 2010).

⁶ Cherici C, Frazier J, Feldman M, et al., Premier Healthcare Alliance. Navigating Drug Shortages in American Healthcare. March 2011. Available at: <http://www.premierinc.com/about/news/11-mar/drug-shortage-white-paper-3-28-11.pdf> (accessed September 28, 2011).

experiencing a shortage of one or more anesthetics and 98% reported ever experiencing an anesthetic shortage. Ninety-one percent of respondents reported switching to an alternative anesthetic and about 10% reported postponing or cancelling a procedure.⁷

A recent survey of community hospitals by the American Hospital Association (AHA) generated 820 responses (response rate: 16.4%).⁸ In the previous six months, 99.5% of respondents indicated they had experienced at least one drug shortage, with 44% reporting more than 20 shortages.⁹ Similar findings were reported in a survey of Canadian pharmacists, indicating that the drug shortage problem is not confined to the United States.¹⁰ Indeed, staff in CDER's Drug Shortage Program (DSP) report that some countries in Europe and Canada are experiencing similar shortages to the United States. Canada and the United States often depend upon the same manufacturers.

Based on data generated by CDER, the number of drug shortages has been rising steadily over the last five years. While there were only 61 shortages reported by CDER in 2005, in 2010 there were 178; data for 2011 are unavailable (See Figure 1). Some of this increase is likely due to FDA's efforts to encourage notifications, particularly in the later years. The American Society of Health-System Pharmacists (ASHP) typically reports larger numbers of shortages (for an explanation, see "FDA Communication" under the Review and Discussion of Key Issues section below), but their data confirm an increase in shortages of approximately the same magnitude starting at the same time.¹¹

⁷ American Society of Anesthesiologists. Survey Reveals 90 Percent of Anesthesiologists Experiencing Drug Shortage of Anesthetics. Press release, May 9, 2011. Available at: <http://www.asahq.org/For-the-Public-and-Media/Press-Room/ASA-News/Survey-Reveals-90-Percent-of-Anesthesiologists-Experiencing-Drug-Shortages-of-Anesthetics.aspx> (accessed September 28, 2011).

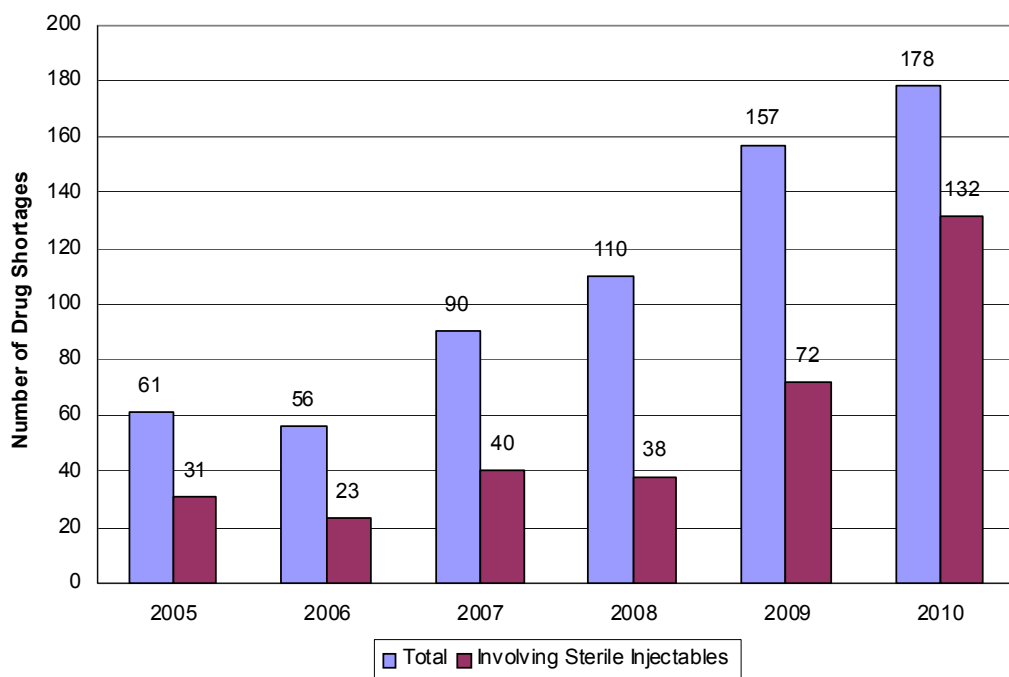
⁸ The survey report states that it was sent to all U.S. community hospitals. According to the American Hospital Association, there are 5008 such hospitals. See: <http://www.aha.org/aha/resource-center/Statistics-and-Studies/fast-facts.html> (accessed September 28, 2011).

⁹ American Hospital Association. AHA Survey on Drug Shortages. Available at: <http://www.aha.org/aha/content/2011/pdf/drugshortagesurvey.pdf>. Updated July 12, 2011 (accessed September 28, 2011).

¹⁰ Eggertson L. Continuing drug shortages affect North American patients. *Canadian Medical Association Journal* 2010;182:E811-2.

¹¹ Fox E. Update on the status of drug shortages, causes, and significant trends. Presented at CDER Drug Shortage Workshop, Silver Spring, MD, September 26, 2011.

Figure 1: Number of U.S. Drug Shortages FDA's Drug Shortage Program Helped Address, 2005-2010



(Source: CDER Drug Shortage Program)

Growing Attention to Drug Shortages

The rising number of drug shortages has generated increased attention from health-care providers, patients, legislators, and journalists. In recognition of the expanding problem, ASHP, ASA, the American Society of Clinical Oncology (ASCO), and the Institute for Safe Medication Practices (ISMP) convened a meeting of key stakeholders to discuss the problem and potential solutions in November 2010. More recently, CDER held an open, solutions-oriented meeting with manufacturers, providers, and the public on September 26, 2011.

Congress has also become concerned about drug shortages, after hearing growing concerns from patients and providers who have been unable to obtain critical drugs. On September 23, 2011, the Health Subcommittee of the House of Representatives Energy and Commerce Committee held a hearing entitled "Examining the Increase in Drug Shortages." Legislation has been introduced by Senator Amy Klobuchar (D-MN) and cosponsors and Representative Diana DeGette (D-CO) and cosponsors. (For more detail, see "Reporting of Supply Disruptions" in the Review and Discussion of Key Issues section below). In addition, the Government Accountability Office (GAO) is conducting an examination of FDA's response to drug shortages at the request of Senators Bob Casey (D-PA), Tom Harkin (D-IA), and Richard Blumenthal (D-CT), who are members of the Senate Committee on Health, Education, Labor, and Pensions. This report is expected in the fall of 2011.

The number of published medical journal articles on drug shortages and the growing number of news reports also reflect the rising awareness of drug shortages. A search of PubMed on July 19, 2011, using the search terms “drug shortage(s)” and “medication shortage(s),” revealed a clear increase in the number of articles over time, mostly in the form of commentaries.¹² In 2011, there have already been 17 such articles, up from one to two per year from 2006 to 2008. Three of the more prominent articles on drug shortages are an article describing ASHP guidelines for managing drug shortages¹³ and two articles by DSP, one describing FDA’s general approach to drug shortages¹⁴ and another focused on the recent propofol shortage.¹⁵ News articles on drug shortages in prominent newspapers are appearing with great frequency as well.^{16,17,18,19,20}

Impact of Drug Shortages

As the frequency of drug shortages has risen, there have been shortages of many commonly used drugs, including succinylcholine, naloxone, furosemide, epinephrine, and norepinephrine. Other drugs that have been in shortage, such as the cancer drug cytarabine, are important not only because they treat a critical disease, but also because they lack an effective alternative. In the past year, public attention to the drug shortage problem has shifted rapidly among an array of drug categories. During that period, anesthetics, “crash cart” drugs, intravenous nutritional supplements, and, most recently, cancer drugs have all at times been the focus of media articles.

While most drugs do not experience shortages, the impact of drug shortages on patients can be significant and even life-threatening. Certain drugs that have recently been in shortage, such as “crash cart” drugs, can literally be life-saving in the acute setting, while others, such as outpatient chemotherapy drugs, must be administered within days or weeks in order to provide maximum benefit.

¹² Articles on vaccines and foreign drug shortages were excluded.

¹³ Fox ER, Birt A, James KB, Kokko H, Salverson S, Soflin DL. ASHP guidelines on managing drug product shortages in hospitals and health systems. *American Journal of Health-System Pharmacy* 2009;66:1399-406.

¹⁴ Jensen V, Kimzey LM, Goldberger MJ. FDA’s role in responding to drug shortages. *American Journal of Health-System Pharmacy* 2002;59:1432-5.

¹⁵ Jensen V, Rappaport BA. The reality of drug shortages – the case of the injectable agent propofol. *New England Journal of Medicine* 2010;363:806-7.

¹⁶ Stein R. Shortages of key drugs endanger patients. *Washington Post*, May 1, 2011. Available at: http://www.washingtonpost.com/national/shortages-of-key-drugs-endanger-patients/2011/04/26/AF1aJJVF_story.html (accessed September 28, 2011).

¹⁷ Corben J. Drug shortages distress hospitals. *Wall Street Journal*, February 1, 2011. Available at: <http://online.wsj.com/article/SB10001424052748704680604576110613604195324.html> (accessed September 28, 2011).

¹⁸ Emanuel EJ. Shortchanging cancer patients. *New York Times*, August 6, 2011. Available at: <http://www.nytimes.com/2011/08/07/opinion/sunday/ezekiel-emanuel-cancer-patients.html> (accessed September 28, 2011).

¹⁹ Harris G. U.S. scrambling to ease shortage of vital medicine. *New York Times*, August 18, 2011. Available at: <http://www.nytimes.com/2011/08/20/health/policy/20drug.html?pagewanted=all> (accessed September 28, 2011).

²⁰ Szabo L. Drug shortages set to reach record levels. *USA Today*, August 15, 2011. Available at: <http://yourlife.usatoday.com/health/story/2011/08/Drug-shortages-set-to-reach-record-levels/49984446/1> (accessed September 28, 2011).

In one instance, a shortage of generic propofol led clinicians to substitute etomidate, resulting in eight patient reports of suspected phlebitis in a single hospital system.²¹ Awareness of these potential clinical consequences increases the urgency of the Agency to take additional steps to aid in the prevention and resolution of shortages.

However, while media and anecdotal reports of the adverse effects of shortages abound, there are no satisfactory systematic studies of the impact of shortages on patient care. An informal Internet survey of health-care practitioners (n = “more than 1800”; response rate not calculable) conducted by the ISMP between July and September 2010 provided examples of drug shortages and their impact on patient care. Thirty-five percent of respondents indicated they experienced a “near miss” as a result of a drug being in shortage in the previous year, with about one in four reporting a medication error and one in five reporting an adverse event.²² Adverse consequences were reportedly related to less effective alternative medications, delays in surgical procedures, delays in clinical trials, and lack of familiarity with alternative drugs. The impact upon National Institutes of Health clinical trials has been underlined specifically.²³ In the AHA study cited above, 82% of respondents reported delays in treatment, 69% said a patient had received a less effective drug, and 35% reported that a patient had experienced an adverse outcome. Seventy-eight percent reported rationing or restricting drugs and 92% said they had experienced increased drug costs as a result of shortages.²⁴ These reports are difficult to evaluate in view of the studies’ limitations.

Some studies have also estimated the costs of drug shortages to the health-care system. ASHP recently surveyed 1322 of its U.S. member pharmacy directors, of whom 353 responded (response rate: 27%). Pharmacists and pharmacy technicians reported spending on average nine and eight hours each week, respectively, dealing with medication shortages, a work load that translated into estimated labor costs of \$216 million per year.²⁵ The Premier survey reported above tallied \$78 million in drug shortage-

²¹ Kosarek L, Hart SR, Schultz L, DiGiovanni N. Increase in venous complications associated with etomidate use during a propofol shortage: an example of clinically important adverse effects related to drug substitution. *Ochsner Journal* 2011;11:143-6.

²² Institute for Safe Medication Practices. Drug Shortages: National Survey Reveals High Level of Frustration, Low Level of Safety. ISMP Medication Safety Alert. Sept 23, 2010. Available at: <http://www.ismp.org/newsletters/acutecare/articles/20100923.asp> (accessed September 28, 2011).

²³ Koh H. Testimony before the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health, September 23, 2011. Available at: http://www.hhs.gov/ash/news/testimony_koh_drugshortages_20110923.pdf (accessed October 10, 2011).

²⁴ American Hospital Association. AHA Survey on Drug Shortages. Available at: <http://www.aha.org/aha/content/2011/pdf/drugshortagesurvey.pdf>. Updated July 12, 2011 (accessed September 28, 2011).

²⁵ Kaakeh R, Sweet B, Reilly C. Impact of drug shortages on U.S. health systems. *American Journal of Health-System Pharmacy* 2011;68:e13-e21.

related costs to its members in 2010.²⁶ Four months of a shortage of selegiline was estimated to cost \$75,000 because an innovator product had to be substituted for a generic in shortage.²⁷

Characteristics of Drug Shortages

According to information from FDA's medical product Centers, the great majority of the medical product shortages reported to FDA pertains to prescription drug products intended for human use. Most of the drug shortages involve generic, sterile injectables; in 2010, these accounted for 74% of all reported drug shortages. As Figure 1 demonstrates, in recent years sterile injectables have accounted for a rising number and percentage of drug shortages managed by CDER's DSP. The impact of sterile injectables appears disproportionate. According to sales data from the pharmaceutical market analysis company IMS Health analyzed for this report by the Office of Surveillance and Epidemiology (OSE) in CDER, such products accounted for only 29% of generic drug product volume in terms of packages/bottles/vials of products sold in 2010. Among the approximately 80 manufacturers making generic injectables, about 40 experienced a shortage in 2010.

Compared to oral drugs, sterile injectables are more complex and require more specialized processes and equipment to manufacture, leading to a higher likelihood of manufacturing problems. Perhaps as a result, there are relatively few companies that produce sterile injectable drugs and thus a still smaller number that will manufacture any particular injectable. Because of considerably more complex manufacturing processes, shortages of sterile injectables typically last months; those of oral drugs are generally resolved more rapidly. Economic issues are discussed in greater detail below in the portion of the Review and Discussion of Key Issues section entitled "Market Conditions" and the accompanying [ASPE Issue Brief](#) provides economic analysis of this issue, particularly for the sterile injectable market.

Information previously collected by DSP²⁸ was entered into a new database covering the period January 1, 2010 to August 26, 2011. After excluding shortages prevented by DSP, 127 unique shortages reported to FDA were available for analysis, including several drugs that were in shortage more than once. Sixty-five of these shortages started in 2010 and 62 started in 2011. This represents 37% of the shortages identified by DSP in 2010 (data from DSP for 2011 were unavailable). According to DSP, the shortages available for analysis tended to be larger, of longer duration, and of greater public health impact than shortages not analyzed, a factor that must be taken into account if extrapolating from the data presented below to the larger universe of drug shortages.

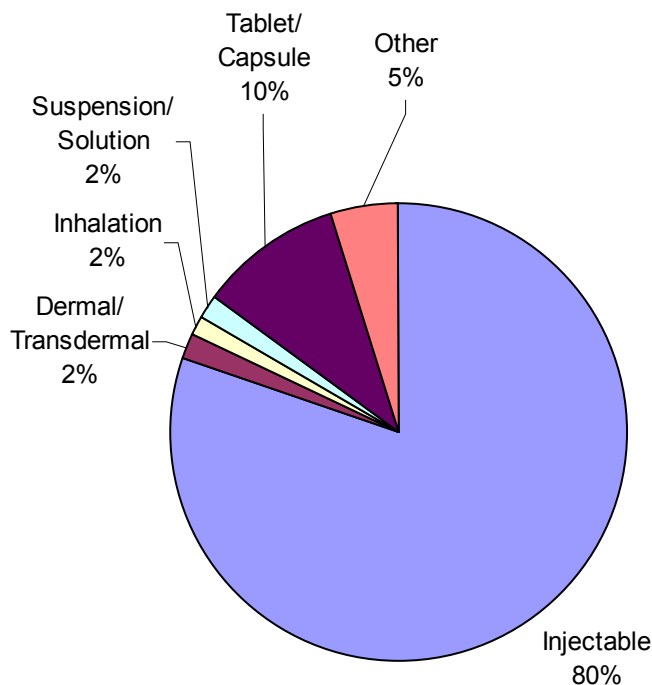
²⁶ Cherici C, Frazier J, Feldman M, et al., Premier Healthcare Alliance. Navigating Drug Shortages in American Healthcare. March 2011. Available at: <http://www.premierinc.com/about/news/11-mar/drug-shortage-white-paper-3-28-11.pdf> (accessed September 28, 2011).

²⁷ Dorsey ER, Thompson JP, Dayoub EJ, George B, Saubermann LA, Holloway RG. Selegiline shortage: causes and costs of a generic drug shortage. *Neurology* 2009;21;73:213-7.

²⁸ This information only contains a subset of ongoing shortages, but also includes some shortages DSP is working to prevent.

Of the 127 shortages studied, 50% were generic or unapproved²⁹ drugs, 43% were innovator drugs, and 7% had both categories in shortage. Unapproved drugs are generally older drugs marketed without required FDA approval; these represented fourteen of the 127 shortages (11%). Injectable medications accounted for 102 (80%) of drugs in shortage (92% of generic or unapproved drug shortages vs. 70% of innovator drugs³⁰), followed by oral tablets/capsules (10%). Dermal preparations, inhalation products, and oral liquids each accounted for less than 2% of shortages (see Figure 2).

Figure 2: Drug Shortages by Route of Administration, 2010-2011



(Based on 127 drug shortages beginning between January 1, 2010 and August 26, 2011)

Of 171 companies mentioned in the 127 drug shortages (some shortages involved more than one manufacturer), three companies accounted for 40% of mentions: one company was involved in 27 shortages, another in 23 shortages, and a third in 19 shortages.

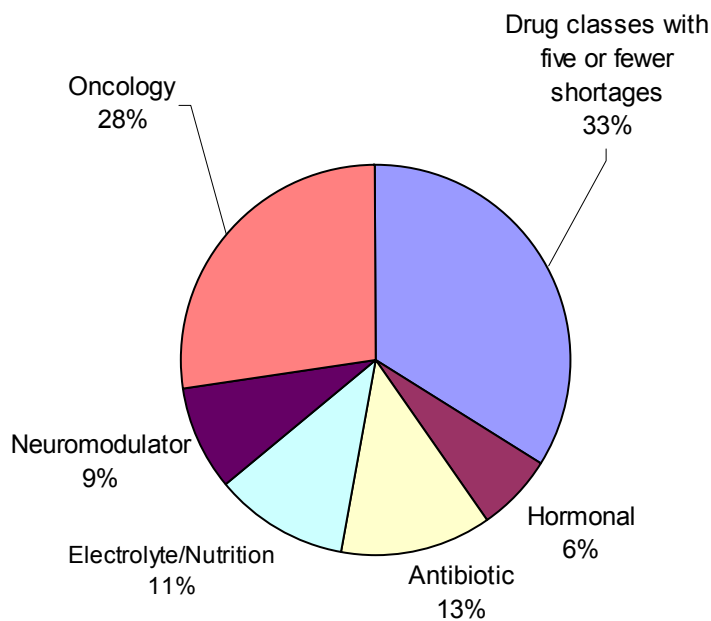
Shortages occurred among a large number of drug classes, with oncology drugs accounting for 28% of shortages (see Figure 3), followed by antibacterial drugs (13%). One hundred and eighteen shortages

²⁹ There are several thousand prescription drugs currently being marketed in the United States that have never been approved by FDA. Some of these drugs were on the market prior to the 1962 amendments to the FD&C Act, which required manufacturers to provide evidence of a new drug's effectiveness before it could be approved for marketing to the public.

³⁰ Nine shortages that included both generic/unapproved and innovator drugs were excluded from this analysis.

(93%) involved so-called “medically necessary” drugs (see discussion of this term under “Legal Framework” below) and 52 (41%) were both medically necessary and sole-source drugs.

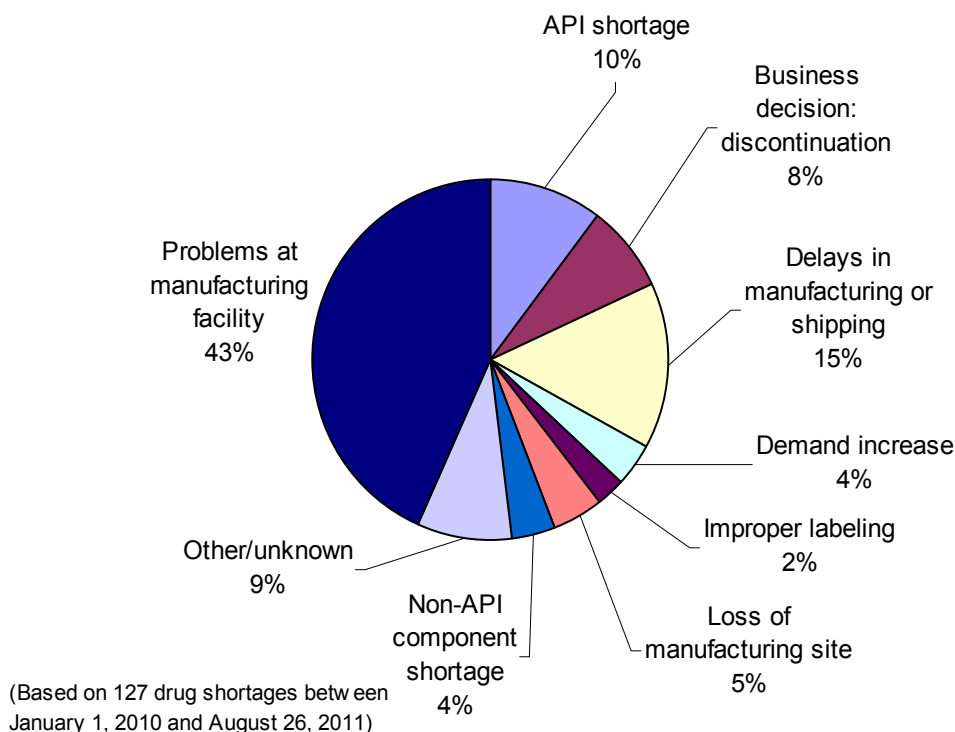
Figure 3: Drug Shortages by Drug Class, 2010-2011



(Based on 127 drug shortages between January 1, 2010 and August 26, 2011)

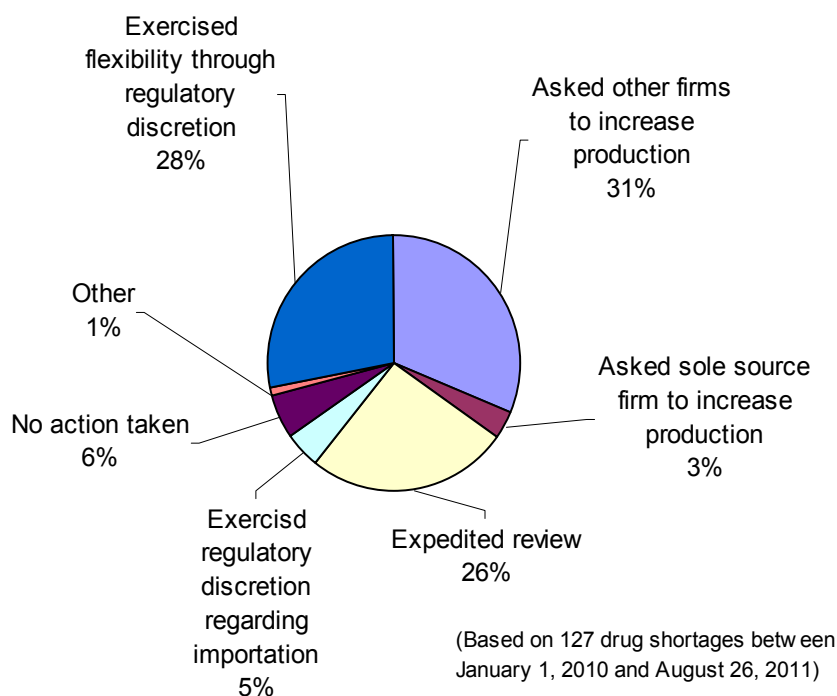
Quality problems at the drug manufacturing facility resulting in disruptions in supply were the leading cause of drug shortages (see Figure 4), accounting for 43% of all shortages, followed by other delays in manufacturing or shipping (15%) and a shortage of the Active Pharmaceutical Ingredient (API; 10%). In general, inspection findings that have been followed by shortages have been serious in nature: glass shards, metal filings, and fungal or other contamination in injectable products that must be sterile and pure to be safe for patients. Importantly, even though the majority of APIs are now produced abroad and imported into the United States, the manufacturing problems with shortages are, for the most part, being detected in domestic facilities in which the final product is assembled. In 8% of cases, the manufacturer made a business decision to discontinue production; in other cases, manufacturers responded to a serious problem at the manufacturing facility by discontinuing production. Innovator and generic or unapproved drugs had similar breakdowns by cause, except generic or unapproved drugs had relatively more shortages due to delays in manufacturing and shipping (23% vs. 6%). The main differences between injectable and non-injectable drugs were that injectables were more likely to have had a quality issue (45% vs. 32%) and less likely to have had an API shortage (8% vs. 20%).

Figure 4: Drug Shortages by Primary Reason for Disruption in Production and Supply, 2010-2011



CDER’s options for mitigating a drug shortage include notifying and encouraging manufacturers of the same or similar products to increase their production, finding another manufacturer to begin production of the product, using regulatory discretion with regard to selective release of product when accompanied by appropriate warnings or remedies (e.g., filters for products contaminated with particulates), expedited review of an Abbreviated New Drug Application (ANDA), expedited review of new manufacturing lines or raw material sources to help firms increase production, and regulatory discretion with regard to controlled importation of equivalent products approved abroad but not in the United States. Overall, FDA’s most common primary responses to drug shortage problems were to ask other companies to increase production (31%), exercise flexibility through regulatory discretion (28%), and expedite regulatory reviews (26%; see Figure 5). Regulatory discretion with regard to the controlled importation of similar products approved abroad but not in the United States was the primary response in 5% of cases.

Figure 5: Drug Shortages by Primary FDA Action Taken, 2010-2011



The most common primary FDA response to a generic or unapproved drug shortage was asking another firm to increase production (43%), while for shortages of innovator drugs it was expediting regulatory reviews (37%), followed by exercising flexibility and discretion (35%). For injectable drugs, the leading primary FDA responses were asking other firms to step up production (33%) and exercising regulatory discretion (30%), while for non-injectables it was expediting regulatory review (40%). For shortages that began and ended during the study period ($n = 64$), the median shortage duration was 62.5 days (mean 105 days; median for innovator drugs: 57 days; median for generic/unapproved drugs: 71.5 days³¹). In an alternative analysis, shortages that had not been resolved during the study period were also included. Fifty-five percent of such shortages lasted over 120 days (innovator 47% vs. generic or unapproved 64%).³²

³¹ Five shortages that included both generic/unapproved and innovator drugs were excluded from this analysis.

³² The overall analysis included 98 drugs. For the subanalysis by innovator status, six shortages that included both generic/unapproved and innovator drugs were excluded. To be included in this analysis, shortages had to begin at least 120 days before the database closed.

Legal Framework for FDA Medical Product Shortage Efforts

The federal Food, Drug, and Cosmetic Act (FD&C Act) does not grant the Agency legal authority to require companies to continue manufacturing medications that are in shortage. However, manufacturers of certain drugs are required to provide advance notification to FDA of a discontinuance in manufacture under section 506C of the FD&C Act³³ and in the implementing section of the Code of Federal Regulations.³⁴ Specifically, the statute provides that sole-source manufacturers of certain drugs that are life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition notify the agency at least six months prior to the date of discontinuation of the manufacture of such drugs. FD&C Act section 506C(b) provides certain criteria for the reduction in the notification period under certain circumstances. The advance notification provision in section 506C of the FD&C Act does not include explicit enforcement authority. However, FDA continues to explore new approaches to help prevent and mitigate shortages under existing statutory authorities.

This notification requirement applies to products approved under a New Drug Application (NDA) or ANDA, which encompasses most drugs regulated by CDER and a very small proportion of CBER-regulated products (e.g., anticoagulants that are part of blood collection bags and Hetastarch products). The bulk of CBER-regulated products (e.g., allergenics, blood and blood products, gene therapies, cellular products, and vaccines) and those therapeutic biologics regulated by CDER (e.g., monoclonal antibodies and therapeutic proteins), all devices, and all veterinary medications have no such reporting requirement related to shortages.

CDER's Manual of Policies and Procedures (MAPP) uses the term "medically necessary" for "Any drug product used to treat or prevent a serious disease or medical condition for which there is no other adequately available drug product that is judged by medical staff to be an appropriate substitute. Off-label uses and Investigational New Drug products can be considered medically necessary. Patient inconvenience alone is an insufficient reason to classify a drug product as medically necessary."³⁵ A given drug may be considered medically necessary at one point in time, but not at another, depending on prevailing evidence and/or clinical practice guidelines. CDER uses this definition exclusively to prioritize drug shortages.

Other Centers have also implemented programs to identify and aid in the prevention and mitigation of product shortages. CVM prioritizes shortages of drugs that are needed to treat or prevent serious diseases or conditions, or that are required to assure the availability of safe food products of animal origin for which CVM staff have determined there is no available source of that product or adequate alternative drug product.³⁶ While animal drug manufacturers are not required to report impending

³³ 21 U.S.C. 356c.

³⁴ 21 C.F.R. 314.81(b)(3)(iii).

³⁵ Center for Drug Evaluation and Research, Food and Drug Administration. Manual of Policies and Procedures (MAPP), 6003.1. Available at: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079936.pdf> (accessed September 28, 2011).

³⁶ Center for Veterinary Medicine, Food and Drug Administration. Program Policy and Procedures Manual 1240.4170.

shortages, they are required to submit annual reports for each medicine marketed detailing how much product was sold or distributed.³⁷ This information can be used by CVM to see whether a drug has had decreased market volume over the past year, possibly signifying a shortage. However, these data are not likely to be detailed or timely enough to identify or manage a shortage. CDRH has additional complexities because generics do not exist in the device field and similar devices may not be interchangeable. CBER also engages in activities intended to aid in the identification, prevention, and mitigation of product shortages such as encouraging manufacturers to increase production, expediting inspections of manufacturing facilities, and expediting application reviews. If a biological product that is in shortage is used to treat, cure, mitigate, prevent, or diagnose a serious disease or medical condition for which there is no adequate alternative product, the shortage is posted on the CBER Biologic Product Shortages web site.

FDA ACTIVITIES WORKING WITH MANUFACTURERS TO HELP PREVENT AND MITIGATE MEDICAL PRODUCT SHORTAGES

As each medical product Center at FDA addresses shortage problems, each brings its own perspectives, needs, and authorities to bear. Currently, medical product shortages are heavily concentrated in drugs, with CDER's DSP managing 30 to 40 drug shortages at any given time, while the other Centers experience only a handful of other medical product shortages each year. The information gathered for this report was generated through meetings with medical product shortage staff in CDER, CBER, CDRH, and CVM. Additional meetings involved CDER's Office of Compliance and FDA's Office of Regulatory Affairs (ORA). The authors also met with external stakeholders who have been affected by drug shortages. These external stakeholders included manufacturers' associations (innovator and generic), manufacturers of intravenous generics, wholesalers, GPOs, professional associations (medical and pharmacy), non-governmental organizations, and academics. The meetings occurred between January and June 2011.

Center for Drug Evaluation and Research

Of the FDA Centers, CDER has been most significantly affected by medical product shortages. CDER's DSP estimates that, at any point in time, it is working on 30-40 ongoing shortages. As mentioned, the reported number of shortages has increased significantly over the past decade from 61 in 2005 to 178 in 2010 (see Figure 1). CDER tracks shortages in both prescription and over-the-counter (OTC) medications, but, because they may be less likely to be "medically necessary," most shortages tracked by FDA involve prescription products.

CDER's DSP receives notification of shortages from manufacturers, ASHP, health-care providers, wholesalers, GPOs, and the public. As noted, manufacturers are only required to report to FDA the expected discontinuation of certain sole-source drugs. DSP staff state that more often than not manufacturers fail to provide notification of actual or potential shortages. Again, the advance notification provision in section 506C of the FD&C Act does not include explicit enforcement authority.

³⁷ 21 C.F.R 514.80; 21 U.S.C 360b(1)(3).

Although CDER evaluates all drug shortage reports it receives, higher priority is afforded those it considers medically necessary. Accordingly, upon receiving notification of an actual or potential drug shortage, DSP staff confirm the shortage with the manufacturer and request a determination of medical necessity from CDER's clinical division. In some circumstances, it seeks input on the medical necessity determination from outside stakeholders such as specialty societies. It also obtains data from IMS Health, a company that tracks pharmaceutical sales from manufacturers to retail and non-retail channels of distribution in the United States, to establish the rate of consumption or "burn rate" for the product and thus when supplies will run out. The IMS Health, IMS National Sales Perspectives™ database provides each firm's market share in terms of dollars and units sold.

The medical necessity determination also informs the balance struck by DSP between the potential risks associated with a particular quality defect and any benefit to patients of exercising regulatory discretion with regard to continuing drug availability. As part of the drug shortage process outlined in CDER's MAPP,³⁸ DSP staff seek an explanation for the shortage from the manufacturer, and inform the public of the existence of the shortage via communications with ASHP and other professional organizations, and via its own web site.³⁹

As noted previously, once a shortage has been confirmed, CDER has a number of means at its disposal to mitigate the problem. These include notifying and encouraging manufacturers of the same or similar products to increase their production, finding another manufacturer to begin production of the product, using regulatory discretion with regard to selective release of product when accompanied by appropriate warnings or remedies (e.g., filters for products contaminated with particulates), expedited review of an ANDA, expedited review of new manufacturing lines or raw material sources to help firms increase production, and regulatory discretion with regard to controlled importation of similar products approved abroad but not in the United States, as long as the shortage persists. Although reinspection of manufacturing facilities is typically not necessary to restart production, in those cases where reinspection is needed, the agency will expedite it. DSP coordinates efforts across CDER to resolve shortages, including staff in the Office of Generic Drugs, the Office of New Drug Quality Assessment, Office of Compliance, and the relevant clinical divisions. However, FDA has no capacity or authority to manufacture medications nor any authority to force manufacturers to do so.

Nonetheless, data provided by DSP suggest that FDA helped to prevent 38 drug shortages in 2010 and 99 to date in 2011, an increase DSP staff attribute, at least in part, to improved notification by manufacturers.⁴⁰ The most common FDA action to prevent a drug shortage (see Figure 6) was expediting review of new manufacturing sites, new suppliers, and specification changes, followed by

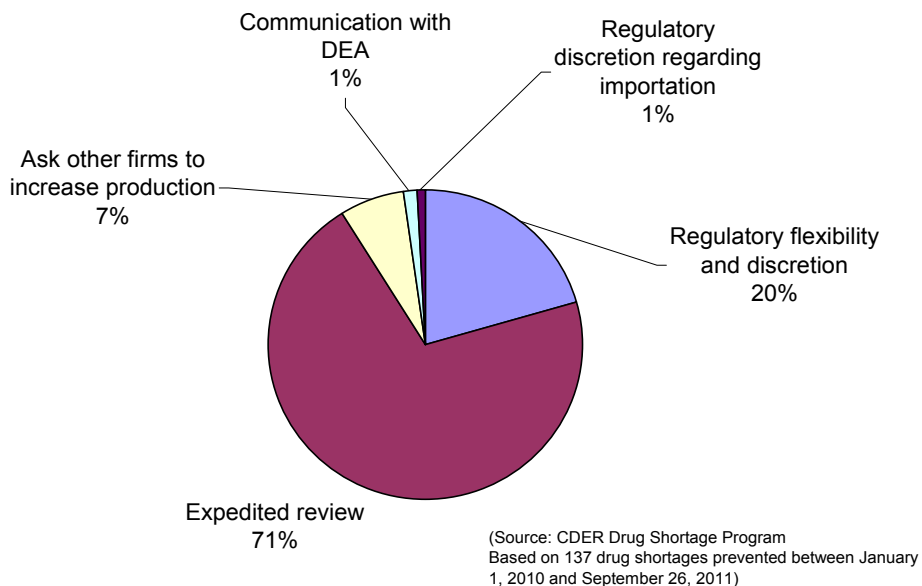
³⁸ Center for Drug Evaluation and Research, Food and Drug Administration. Manual of Policies and Procedures (MAPP), 6003.1. Available at: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079936.pdf> (accessed September 28, 2011).

³⁹ FDA. Drug Shortages. Available at <http://www.fda.gov/drugs/drugsafety/drugshortages/default.htm> (accessed September 28, 2011).

⁴⁰ Cox E. Drug shortages: FDA's strategies and role. Presented at CDER Drug Shortage Workshop, Silver Spring, MD, September 26, 2011.

exercising regulatory flexibility and discretion (the benefit of the drug was judged to outweigh the risk of the quality or manufacturing issue).

Figure 6: Prevented Drug Shortages by Primary FDA Action Taken, 2010-2011



DSP has recently added a fifth full-time employee; the DSP staffing level had remained essentially stable at four full-time equivalents over the previous six years. Many other offices within CDER also provide staff on a part-time basis to address drug shortages (see Appendix 1). For example, CDER’s Office of Compliance has a dedicated Recalls and Shortages Branch that helps manage shortages for the Office. When it becomes aware of a recall or impending recall, this branch will work with DSP to determine if the drug involved is a medically necessary drug and if the recall will result in or have an impact upon a shortage. If so, CDER’s Office of Manufacturing and Product Quality (OMPQ) works with the firm to determine the extent and risk of the product problem and works to prevent and mitigate a shortage.

Center for Biologics Evaluation and Research

CBER regulates allergenics, blood and blood products, certain devices specific to biological products, gene therapies, human tissues and cellular products, vaccines, and xenotransplantation products. CBER has been less significantly affected by medical product shortages than CDER. The number of shortages of products regulated by CBER has been fairly stable over the last several years, with sterile injectables, particularly vaccines, accounting for most.

Biologics are often complex and time-consuming for companies to develop. There are about 150 licensed biologic products in the United States, compared to thousands of approved drugs. Shortages of biological products can be difficult to foresee because most manufacturers engage in “just in time”

production and, as a result, many products that appear to be at risk for shortage never progress to an actual shortage. However, CBER product shortages can also take on national significance (e.g., influenza vaccine shortages).

Manufacturing problems are the most common cause of biological product shortages. These may be brought to the Agency's attention by the manufacturer itself or may be revealed during an inspection by FDA. Other causes of biological product shortages include corporate decisions to discontinue the product, distribution or production changes/disruptions, lack of availability of component materials, changes in release procedures, demand increases driven by new product indications or promotional campaigns, and catastrophic events/natural disasters.

Biological product shortages are closely monitored by staff within the Immediate Office of the Director of CBER's Office of Compliance and Biologics Quality (OCBQ). Actual or potential shortages may be reported to CBER by medical professionals, consumers/patients, manufacturers, other government offices, patient advocacy groups, media sources, and others. Reports may come to CBER through the CBER shortage email account and its shortage telephone number. The relative infrequency of biologics shortages has allowed CBER to manage the problem with a single employee. CBER has in place a Standard Operating Policy and Procedure (SOPP) 8506 titled Management of Biological Product Shortages. OCBQ is currently in the process of drafting SOPPs for use within its own office.

When a biological product shortage or discontinuation is reported (and CBER reports that manufacturers tend to do so promptly), CBER attempts to verify that an actual shortage or discontinuation exists through communications with manufacturers, other FDA offices, and external entities such as ASHP, as well as through market research data when available. All relevant files and databases are searched for information on the product in shortage and potential alternatives. This information is then shared widely within FDA and with other Department of Health and Human Services (DHHS) Agencies such as the Centers for Disease Control and Prevention. If the biological product is used to treat, cure, mitigate, prevent, or diagnose a serious or life-threatening condition and there is no other available source or alternative therapy, the shortage is posted on the CBER Biologic Product Shortages web site.⁴¹

Similar to CDER, CBER can draw from an array of policy options when addressing a shortage problem. These include encouraging manufacturers of the product to increase their production, encouraging other manufacturers of similar prescription drugs to increase production, expediting inspections of manufacturing facilities to begin or restart production, and expediting review of Biologics License Applications (BLAs), NDAs or ANDAs. In many instances, vaccine shortages can be ameliorated by delaying vaccination, building on the community levels of immunity that have developed in the population over time as a result of vaccination.

⁴¹ FDA. Biologic Product Shortages. Available at <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm> (accessed September 28, 2011).

Center for Devices and Radiological Health

CDRH measures and monitors medical product shortages differently from other FDA Centers. While therapeutically equivalent drugs are pharmacologically equivalent and bioequivalent and therefore substitutable, devices cleared as “substantially equivalent” under CDRH’s 510(k) provisions are generally not identical and may not be substitutable; even different models of the same device from a single manufacturer may not be interchangeable. Accessories and consumables, such as ventilator tubing and infusion sets, to particular devices are often brand- and version-specific, and shortages of either may result in a shortage of the device itself. Even if devices are theoretically substitutable, provider practices and preferences can contribute to shortages because physicians are often trained by manufacturers to use certain devices and may be unfamiliar with alternative devices.

CDRH identified a variety of causes of device shortages, including reliance on sole-source and/or foreign manufacturers, increasingly complex devices where a supply bottleneck of a single small component can jeopardize entire production lines, a shortage of a drug needed for the device to function, and the fragmentation of the device industry so that non-standardized and brand-specific technologies are produced. Device shortages may also occur if the firm conducts a recall or CDRH takes action against a firm due to manufacturing problems. In addition, the industry operates in a “just in time” production mode, so that production keeps pace with demand.

CDRH has formal procedures to determine if a shortage exists, in addition to procedures on how to address shortages. However, device manufacturers are not required to submit to FDA information regarding their manufacturing capacity and the number of products put into distribution, which hinders FDA’s ability to respond to the shortage. Even in cases where manufacturers voluntarily submit information to the Agency, FDA may not be authorized by manufacturers to disseminate that information, limiting public knowledge about the circumstances surrounding a shortage. Assessing the magnitude or impact of device shortages is difficult because the industry lacks databases to monitor the market share of specific devices, brands, and models.⁴²

Device manufacturers are not required to notify FDA of actual or potential shortages. CDRH acknowledges that it rarely receives notices of shortages from manufacturers themselves, more frequently learning of shortages through reports by user facilities or the media.

Device shortages are collaboratively managed by the staff of the Office of the CDRH Center Director and CDRH’s Office of Compliance. While CDRH does not have a position dedicated solely to handling device shortages, the Center’s point of contact for shortages is located in the Office of the Center Director. The shortage staff work closely with the Office of Compliance in performing risk and shortage assessments prior to taking any action that might reduce product availability. When addressing a shortage, Center staff typically request that manufacturers of similar devices increase production, but, due to the complexities of device production, there is typically a lag of up to six months before additional devices

⁴² The IMS Hospital Supply Index only captures data from hospitals, not from other sectors of the health-care system in which devices are also used.

are available. CDRH takes into account whether a shortage would result from a regulatory action and will typically allow a product to remain in distribution if the overall benefits outweigh the risks.

CDRH has developed a database listing devices susceptible to shortages in disaster and emergency settings. However, maintaining a database of timely manufacturing data is dependent upon voluntary cooperation from manufacturers, and is often limited because of the confidential and proprietary nature of such information. The information, therefore, cannot be released to the public and is used only for CDRH internal planning and response purposes. As part of its shortage evaluation process, CDRH also conducts investigations of affected manufacturers following recalls or natural catastrophic events to gather information to assess the potential for device shortages.

Center for Veterinary Medicine

CVM has generally experienced few veterinary drug shortages. Although CVM has received more reports of shortages of late, it is unclear whether this is a result of an actual increase in shortages, greater public awareness leading to increased reporting of shortages, or reduced public awareness of alternative products. The small numbers of past shortages make aiding in the prediction or prevention of potential shortages difficult.

Veterinary drug product manufacturers are not required to notify CVM of product shortages. However, such manufacturers are required to submit annual reports that include certain information about the distribution of each animal drug product, including the quantity of the drug distributed during the reporting period.⁴³ CVM receives notification of product shortages from manufacturers, the press, consumer groups, veterinarians, producer associations, the animal health industry, and through FDA surveillance and enforcement activities. CVM staff indicated that they would prefer more frequent reporting by manufacturers.

CVM takes action only in the event of a shortage of a veterinary drug that is needed to treat or prevent a serious disease or condition or that is required to assure the availability of safe human food products of animal origin. In addition, as in CDER and CBER, staff determine whether there is any other available source of that product or an adequate alternative.⁴⁴ When CVM is notified of a potential veterinary medicine shortage, the information is directed to the CVM shortage coordinator who is responsible for confirming that an actual shortage exists and establishing whether the drug meets these criteria. Internally, CVM maintains a list of drugs in shortage that meet these criteria, but does not post shortages on its web site.

CVM acts to resolve product shortages by encouraging other manufacturers of the same product or alternative products to increase their production, utilizing regulatory discretion with regard to the marketing of products that are not compliant with Good Manufacturing Practices (GMPs), and exercising enforcement discretion with regard to the importation of alternative products. The Center has found

⁴³ 21 C.F.R 514.80; 21 U.S.C 360b(1)(3).

⁴⁴ Center for Veterinary Medicine, Food and Drug Administration. Program Policy and Procedures Manual 1240.4170.

that many manufacturers who experience shortages are becoming less likely to return to production because products compounded from bulk APIs have addressed the need and manufacturers are likely to have difficulty regaining market share.

CVM's drug shortage program is located in its Office of Surveillance and Compliance (OSC). CVM staff believe that the Center currently has adequate resources to address and manage veterinary drug shortages. The Center is currently in the process of formalizing its protocol for monitoring and addressing shortages.

A Comparison of Medical Product Shortage Activities Across FDA Centers

Information gathered during meetings with CDER, CBER, CDRH, and CVM is summarized in Appendix 2, which reveals a number of respects in which the Centers' medical product shortage activities are similar and others where they are different. This is not to imply that all Centers need to develop identical programs. Rather, Appendix 2 is intended to serve as a starting point for the sharing of best practices between the Centers, with the clear understanding that different Centers face varying challenges in addressing shortages that could require dissimilar approaches and solutions, particularly given the Centers' varying medical product shortage experiences and statutory authorities.

Only CDER has employees working full-time on the shortage issue. Established plans and protocols for addressing drug and medical product shortages have been or are in the process of being developed for all Centers. CBER reports that manufacturers regularly report shortages, while other Centers report less reliable notification. Injectable drugs are most commonly affected in CDER, CBER, and CVM. **Although all Centers reported exercising regulatory discretion in attempting to resolve shortages, only CDER, CDRH, and CVM have used enforcement discretion with regard to importation to alleviate shortages, after carefully weighing the overall benefits and risks.**

REVIEW AND DISCUSSION OF KEY ISSUES

The following section synthesizes the information gathered during meetings with both FDA staff and external stakeholders, as well as additional research conducted for this report. Although the perspectives of numerous external stakeholders are described, doing so does not necessarily mean the authors endorse their perspectives.

Near-term Prospects

For a number of reasons, the nature of the drug shortage problem suggests that shortages are not likely to abate in the near-term and that the problem will not be resolved without concerted effort from many stakeholders. (For further discussion of some of these issues, see "Market Conditions" below.) The production capacity of generic manufacturers is expanding only slowly, the infrastructure requirements to produce these drugs safely are significant, and updating aging manufacturing facilities will require time and money. Companies operating at full capacity may not be able to manufacture a drug in shortage without dropping production of another product, potentially producing a secondary shortage.

In addition, industry concentration has made it difficult for smaller manufacturers to enter the marketplace, and wholesalers and GPOs are likely to continue to exert downward pressure on drug prices.

Performance of DSP in Preventing and Mitigating Drug Shortages

External stakeholders offered unanimous praise for the DSP staff. These stakeholders stated that the DSP team has been extremely responsive and works tirelessly to address drug shortages. Many also asserted that DSP seems under-resourced and could make use of additional assigned staff. According to data provided by DSP, the number of staff over the last several years has remained steady, even as the number of shortages has increased substantially.

DSP plays a valuable role within FDA: it acts essentially as a patient advocate ensuring that patient well-being is at the very center of Agency regulatory activities when drug shortages are an issue.

Data Collection

Most Centers reported maintaining a current list of drugs and other medical products in shortage in order to track and manage ongoing shortages. However, this information often lacks the specificity to allow for the analysis of the causes, durations, and FDA responses to shortages. The absence of readily analyzable data limits FDA's ability to assess the adequacy of its responses to shortages, to identify steps it can take to reduce the likelihood of shortages, and, potentially, to predict future shortages.

FDA Communication with External Stakeholders and the Public

Manufacturers and industry representatives assert that FDA lacks a firm definition of medically necessary, making it difficult to determine which drugs should be reported in the event of a shortage. They also believe that FDA should reach out to clinicians and other providers in determining whether a drug is considered medically necessary.

However, DSP does define medically necessary in its MAPP,⁴⁵ a document that was last revised in 2006. This document also outlines a procedure through which DSP consults with members of the relevant drug review division in FDA, as well as with experts outside of the Agency, including ASHP and other professional societies, as it determines whether a drug is medically necessary. The authors' discussions with professional associations confirm this practice. DSP welcomes suggestions from industry about how the consultation process could be improved.

ASHP and DSP web sites listing drugs in shortage are consistently cited as the definitive public references on current drug shortages. However, the lists are quite different, at times leading to confusion. ASHP's

⁴⁵ Center for Drug Evaluation and Research, Food and Drug Administration. Manual of Policies and Procedures (MAPP), 6003.1. Available at: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079936.pdf> (accessed September 28, 2011).

list is targeted toward its pharmacy clients and the information they require, while DSP's list takes a more public health-oriented approach.

Generally, ASHP's list of drugs is larger because it lists all known and confirmed drug shortages, including regional shortages. ASHP's web site is viewed by many external stakeholders as more informative because it includes recommendations for alternative drugs, while CDER's does not. In contrast, FDA's list is limited to national shortages and it mostly consists of medically necessary drugs. DSP does list some drugs that are not medically necessary if it receives repeated inquiries about them from the public. Some stakeholders recommended that CDER more often list non-medically necessary drugs in shortage. Others who are familiar with both lists stated that to do so would simply duplicate ASHP's efforts, but that assumes a user, perhaps encountering a shortage for the first time, would be aware of the ASHP list.

A 2010 ASHP survey of pharmacy directors found that the ASHP web site was used by 89% of respondents and DSP's web site was used by 72%. On a 5-point Likert scale, respondents preferred the ASHP's web site by a small margin for timeliness (ASHP: 4.0; DSP: 3.4), reason provided for shortage (ASHP: 3.8; DSP: 3.2), and alternatives provided (ASHP: 4.0; DSP: 2.7).⁴⁶

For this report, the authors compared the DSP and ASHP web sites on September 9, 2011. At that time, the DSP web site listed 62 active drug shortages, primarily of medically necessary drugs, compared to 181 drug shortages on the ASHP web site. Fifty-eight shortages appeared on both web sites. The ASHP web site listed 123 medications not listed on the DSP web site, whereas four medications appeared on the DSP web site but not on ASHP's.⁴⁷

The DSP web site lists drug shortages and manufacturers, the reason for the shortage (when manufacturers permit protected non-public information to be disclosed publicly), and often a brief explanation of current and future availability. The ASHP web site has more information regarding each medication (via links to pages for individual drugs), the reason for the shortage, a brief explanation of current and future availability, and a major section listing therapeutic alternatives to the drug in shortage. Both web sites provide instructions on reporting a shortage.

Most external stakeholders expressed a desire for greater transparency regarding the causes of shortages; they find this difficult to obtain from manufacturers. Most hospitals, pharmacists, and clinicians with whom the authors met believed that such disclosure would allow for greater preparation and planning in clinical care. Moreover, greater disclosure of the cause of a shortage would increase trust within the health-care team, with pharmacists reporting that their conversations with physicians "go better" when a reason for the shortage can be offered. If the Agency is aware of the reasons behind

⁴⁶ Kaakeh R, Sweet B, Reilly C. Impact of Drug Shortages on U.S. Health Systems. *American Journal of Health-System Pharmacy*. 2001;68:e13-e21.

⁴⁷ For this analysis, a drug shortage was included only if it did not involve a biologic and neither site considered the shortage resolved. Five shortages were counted twice on the DSP web site because they involved more than one formulation of the drug, but were only counted once on the ASHP web site. These were considered to be five shortages (not 10) for the purposes of this analysis.

a shortage, the information may be protected from public disclosure because it is confidential commercial or other information that cannot be disclosed without the permission of the manufacturer.

Communication within FDA

Several external stakeholders believed that better communication between FDA field investigators and DSP would be helpful in preventing and mitigating drug shortages. The Agency is cognizant that its inspection findings regarding quality problems may lead to a firm's shutdown even when FDA itself does not seek such a result. Facing potential costs to address issues identified during inspection, firms may make business decisions to discontinue manufacturing on a temporary or permanent basis. The Agency will often try to work closely with firms to prevent a full shutdown.

In addition, FDA assesses the impact of Agency actions prior to issuing a regulatory decision that could affect drug production. On numerous occasions, FDA has worked with a manufacturer to mitigate certain safety or quality concerns so that medically necessary drugs remain available.

There is an inherent tension between the Agency's compliance functions, which seek to ensure that industry produces quality products, and its desire to assure the availability of needed drugs. Significant communication and coordination between CDER's Office of Compliance, DSP, other CDER offices, and ORA is essential.

Communication between Manufacturers and from Manufacturers to Customers

Perhaps the major impediment to disclosure of impending shortages is manufacturers' concern that such disclosures would run counter to competitive business practices. However, from a public health perspective, advanced warning of an expected disruption or discontinuation of production by any party would prove useful to other manufacturers who might be able to increase production of similar products. Industry representatives pointed out that it could take many weeks for a manufacturer to find out that a competitor has discontinued a product. Often, it is only when GPOs can no longer secure a product through their typical purchasing channels and then contact alternative manufacturers that these manufacturers learn of the shortage. Through all of this, FDA may be unaware of the developing shortage.

Greater transparency in how wholesalers manage drug shortages would also be desirable. For example, one wholesaler reported that it fills orders for drugs in shortage in proportion to amounts requested previously by its regional offices. Some stakeholders claimed that other wholesalers distribute their remaining stock in the order in which requests were received. There is also concern that as soon as hospitals learn of a shortage, they might decide to hoard additional doses.⁴⁸ If the practices of the wholesalers were more consistent and transparent, purchasers and hospitals would be able to better manage shortages and forego hoarding.

⁴⁸ Thompson CA. Drug shortage broaches ethics of buying in excess. American Journal of Health-System Pharmacy 2009;66:610-1.

Gray Market Distributors

Following the manufacture of a finished product, drugs are typically further distributed by wholesalers, who then distribute the drugs to hospitals and pharmacies, often facilitated by GPOs. In some cases, a wholesaler will sell drugs to another wholesaler. Because of vulnerabilities in the drug distribution system in the U.S., drugs can be diverted and leave the legitimate supply chain. In such instances, the diverted drugs circulate in the “gray market” and, when the product is in shortage, they are often offered for sale at significantly higher prices.⁴⁹ It is unknown how these drugs are stored and handled or whether they are expired, counterfeit, or otherwise substandard.

Among the groups with whom the authors met, there were divergent opinions on how drugs in shortage are reaching these distributors. For example, GPOs and providers tend to see a segment of secondary wholesalers as responsible for drugs reaching the gray market. One wholesaler indicated that it had implemented policies designed to reduce leakage to the gray market by selling shortage drugs only to select purchasers and by cutting off purchasers that are selling their allotments in the gray market. Others point to retail pharmacies that sell their remaining inventory of shortage drugs at a marked-up price to gray market distributors. The actions of these retail pharmacies may not be legal if state law requires a wholesale drug license for resale.

External stakeholders with whom the authors met were in general agreement that gray market distributors were not likely to be the cause of the rise in drug shortages, but they do believe that some gray market distributors are taking advantage of the situation. Indeed, taking advantage of shortages has emerged as a new business model for some in this sector. A 2011 report by the ISMP examined gray market activities associated with drug shortages in an online survey of hospital purchasing agents and pharmacists. Of 549 respondents (response rate not calculable), 56% reported receiving daily solicitations from gray market vendors and 52% reported purchasing drugs from gray market vendors in the last two years. Many respondents provided examples of egregious price gouging, including propofol that was marked up by over 1500%.⁵⁰ Several stakeholders, including GPOs and hospitals, recommended that reports of price gouging should be monitored and investigated by appropriate federal agencies. FDA accepts reports of price gouging on its website.⁵¹

Market Conditions

While FDA can attempt to prevent and mitigate drug shortages, understanding the root causes of shortages requires an examination of broader market forces. Many recent drug shortages have occurred among generic drug manufacturers, for whom competition has contributed to the low prices

⁴⁹ Institute for Safe Medication Practices. Gray Market, Black Heart: Pharmaceutical Gray Market Finds a Disturbing Niche During the Drug Shortage Crisis. ISMP Medication Safety Alert, August 25, 2011. Available at: <http://www.ismp.org/Newsletters/acute/acute/showarticle.asp?ID=3> (accessed September 28, 2011).

⁵⁰ Institute for Safe Medication Practices. Gray Market, Black Heart: Pharmaceutical Gray Market Finds a Disturbing Niche During the Drug Shortage Crisis. ISMP Medication Safety Alert, August 25, 2011. Available at: <http://www.ismp.org/Newsletters/acute/acute/showarticle.asp?ID=3> (accessed September 28, 2011).

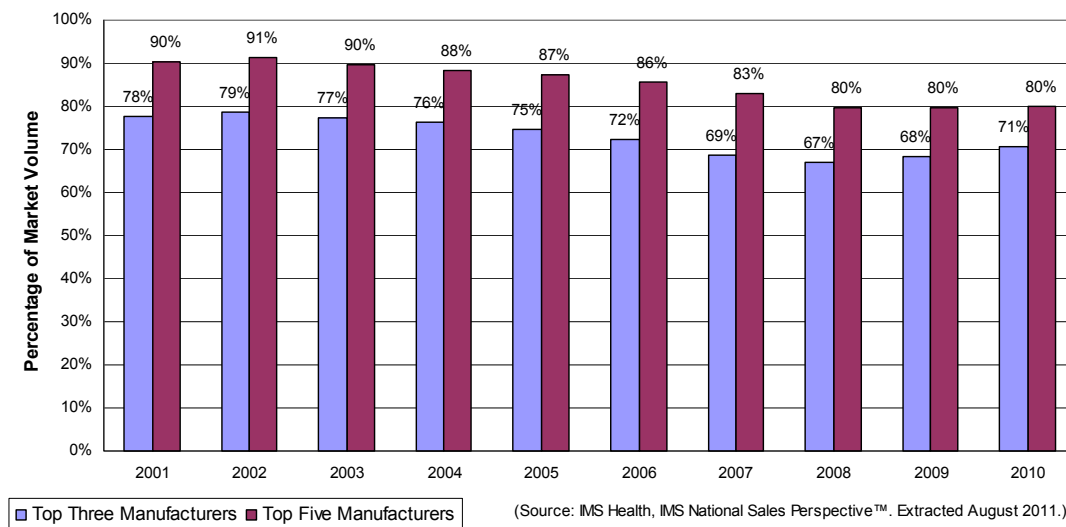
⁵¹ FDA Office of Criminal Investigation. Report Suspected Criminal Activity. Available at: <http://www.accessdata.fda.gov/scripts/email/oc/oci/contact.cfm> (accessed October 26, 2011).

associated with generic production. Purchasers of drugs and vaccines, including wholesalers and GPOs, put additional downward pressure on prices. In some instances, prices and profit margins may be so low that manufacturers may respond to GMP violations by simply terminating production.⁵²

According to an analysis of sales data from the IMS Health, IMS National Sales Perspective™ database conducted for the authors by CDER’s OSE, the total sales revenue for generic injectable products was \$1.492 billion in 2001 and \$4.622 billion in 2010, which is equivalent to \$3.752 billion in 2001 dollars,⁵³ a 251% increase. These data suggest that the overall market for generic injectables is robust, but do not shed light on the profitability of individual drugs.

The problem is exacerbated by market concentration in the generic injectable market (see Figure 7). According to data obtained from IMS Health and prepared for this report by OSE, in 2010, the top five generic injectable manufacturers accounted for 80% of the packages/bottles/vials sold in the U.S. market by volume (and 73% of the dollars in sales) and the top three manufacturers held 71% of the market. (These could be different top manufacturers each year.) However, the data do not support the oft-made claim that there is increasing concentration in the generic injectable market, as the percentage of the market (by volume) held by the top five manufacturers actually declined from 90% in 2001. It is noteworthy that all five of the top manufacturers in 2010 had drugs in shortage in 2011. These data do not establish whether market concentration differed for drugs that went into shortage compared to those that did not.

Figure 7: Percentage of Generic Injectable Market Held by Top Manufacturers, 2001-2010



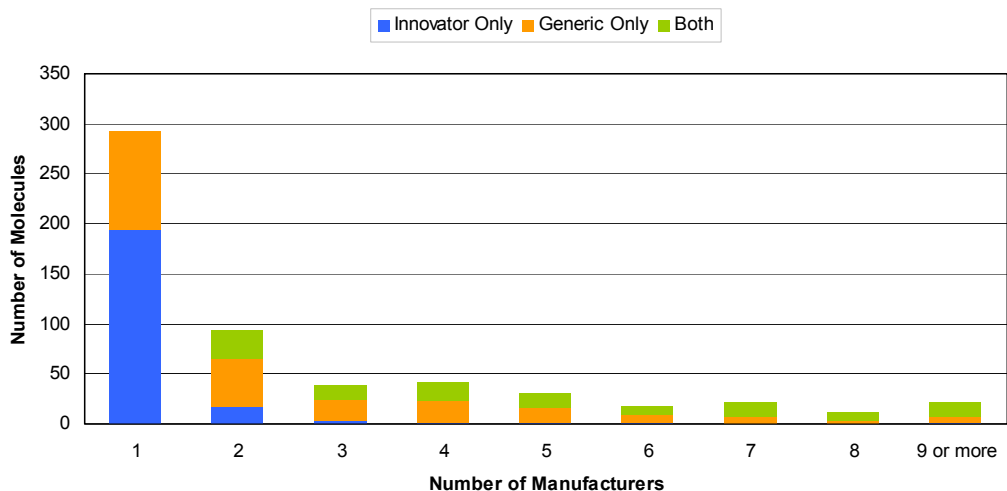
Additional forms of concentration occur at the product level, where only a limited number of companies may manufacture a given product. Figure 8 indicates that the great majority of sterile injectable

⁵² American Society of Health-System Pharmacists. ASHP guidelines on managing drug product shortages. American Journal of Health-System Pharmacy 2001;58:1445–50.

⁵³ Calculation performed at <http://www.usinflationcalculator.com>.

molecules have only one or two manufacturers. While innovator products comprise 66% of molecules that have only a single manufacturer, generics play a larger role when there is more than one manufacturer.

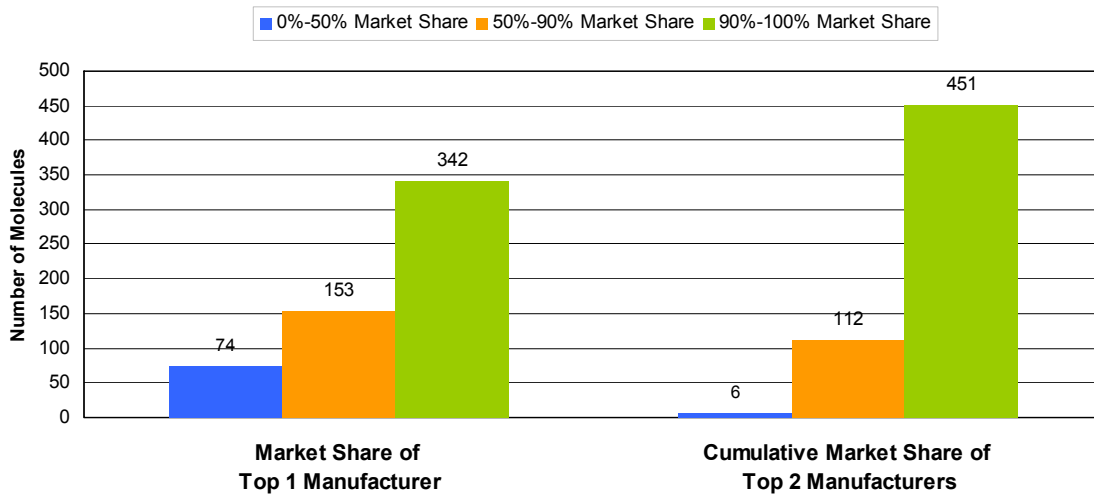
Figure 8: Number of Injectable Molecules by Number of Manufacturers, 2010



(Source: IMS Health, IMS National Sales Perspectives™, Extracted September 2011. Based on 569 sterile injectable molecules.)

Moreover, although a number of firms produce sterile injectables (there are approximately 80 generic injectable manufacturers), the production of any given molecule is commonly concentrated among a very small number of manufacturers. As indicated in Figure 9, 342 out of 569 (60%) sterile injectable molecules in 2010 were virtually sole-sourced (90% or more market share) and only 74 markets/molecules (13%) had a top producer with less than half of the market by volume. Many of these molecules are still under patent protection. However, even products with generic competitors have highly concentrated markets; in only six markets (1%) did the top two producers have less than 50% market share by volume between them. This kind of market concentration makes the supply system vulnerable to drug shortages because a large supply disruption is difficult to make up with alternative suppliers.

Figure 9: Injectable Molecules by Market Concentration, 2010



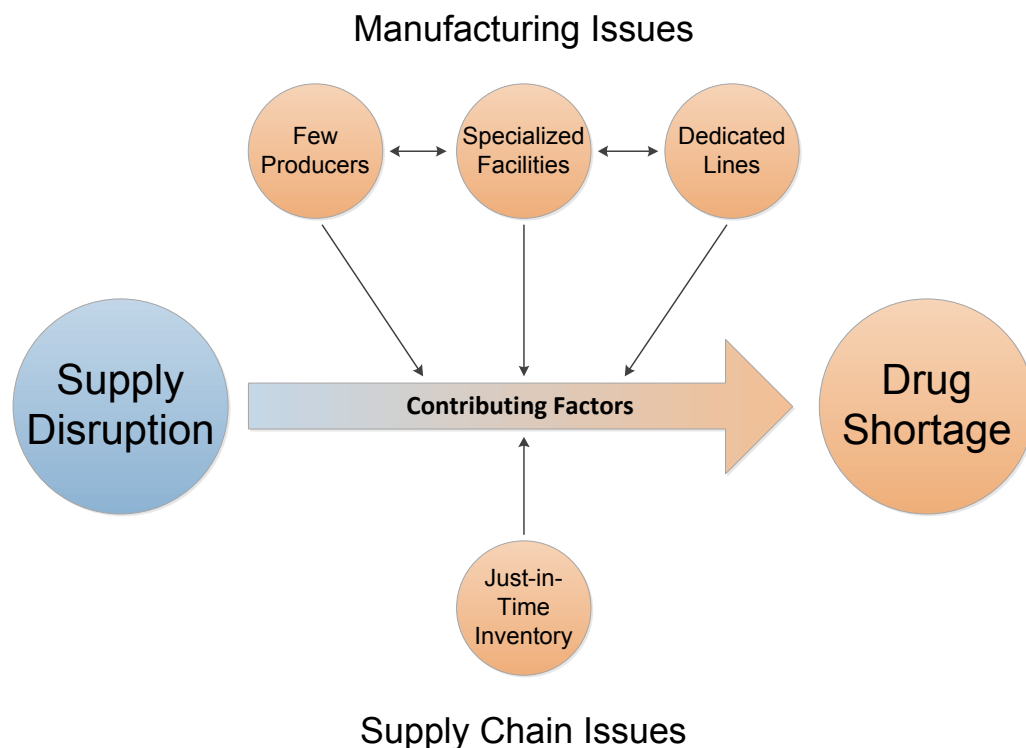
(Source: IMS Health, IMS National Sales Perspectives™, Extracted September 2011. Based on 569 sterile injectable molecules.)

Market concentration alone would not itself pose a problem if manufacturers could easily switch production to other facilities or production lines. However, such flexibility is limited because of the cost, expertise, and complexity associated with the maintenance of sterile injectable manufacturing facilities, limiting the number of facilities involved in the manufacturing of such products. In particular, sterile injectable products are manufactured with a well-defined manufacturing process and controls to assure product quality. These products must be sterile, free of particulate matter, and free of contamination from all pathogenic and nonpathogenic microorganisms. Furthermore, according to generally accepted industry practices, certain drug classes such as cytotoxics (cancer drugs) and cephalosporins (antibiotics) are made on dedicated equipment which then cannot be used to produce other types of injectable drugs. Because of considerably more complex manufacturing processes, supply disruptions of sterile injectable products not only are more likely to turn into drug shortages, but they also typically last months, while those of oral drugs are generally resolved more rapidly.

Partly because of this segmentation and specialization in production, even large firms will commonly have only one line dedicated to producing a particular type of product. Coupled with the limited number of producers, a supply disruption experienced on one dedicated production line can easily turn into drug shortages for multiple products when the lost production cannot be sufficiently supplemented by other manufacturers because of limitations in capacity available on their own limited lines. This results in clustering of shortages for co-produced drugs. Current oncology shortages can be traced to just three key cytotoxic lines operated by two separate manufacturers.

A final market factor is the shift to “just in time” manufacturing and inventorying practices. These practices reduce expenses by eliminating surpluses, but increase the risk that even a modest perturbation in the market can result in a shortage. Figure 10 captures how all these factors can convert a supply disruption into a full-fledged drug shortage.

Figure 10: Dynamics of Sterile Injectable Drug Shortages



Reporting Supply Disruptions or Product Discontinuations to FDA

There was broad consensus among all external stakeholders that S. 296 introduced by Senator Amy Klobuchar is an important step to remedy the problems associated with manufacturer non-reporting. If signed into law, S. 296 would require manufacturers of drugs and a small minority of products regulated by CBER to report to FDA all supply disruptions or product discontinuations that could lead to shortages (not just medically necessary ones) six months in advance or as soon as practicable after recognition of an impending shortage. The law would also enable the Agency to impose monetary penalties on manufacturers that fail to adhere to reporting requirements.⁵⁴ Representative Diana DeGette has introduced a similar bill, H.R. 2245, which has the added stipulation that fines for knowingly failing to adhere to reporting requirements would not exceed \$10,000 per day and a maximum of \$1,800,000, with the final fee schedule to be determined by the DHHS Secretary.⁵⁵ Most external stakeholders acknowledge that, while S. 296 will not completely prevent drug shortages, its requirements for expanded reporting and penalties for incomplete reporting would go a long way toward improving the current system.

⁵⁴ Preserving Access to Life-Saving Medications Act, S. 296, 112th Cong., (2011).

⁵⁵ Preserving Access to Life-Saving Medications Act of 2011, H.R. 2245, 112th Cong., (2011).

Any approach to drug shortages must, however, go beyond notification. Addressing shortages by improved notification can be considered secondary prevention and it requires resource-intensive efforts by DSP. In contrast, primary prevention (e.g., upgrading aging production facilities and expanding capacity) addresses the root causes of shortages and obviates at least some efforts at DSP. Finally, prevention of shortages will be enhanced if we have overlapping systems in place in case one system of prevention fails.

Importation

Importation of unapproved drugs manufactured for foreign markets is often seen by external stakeholders as a solution to alleviate domestic shortages, and FDA is sometimes accused of not exercising enforcement discretion in this regard frequently enough.⁵⁶

However, there are obstacles that prevent importation from being a satisfactory solution in many cases. The product may already be in shortage abroad or importation into the United States could trigger a shortage abroad. In either case, the manufacturer may be unwilling to divert drugs to the U.S. market. While there may be firms that manufacture the drug in shortage or alternatives for foreign markets, these suppliers are not FDA-approved and, accordingly, the manufacturing facilities may not have been inspected by FDA, among other issues. Furthermore, even if FDA uses enforcement discretion with regard to the importation of a drug manufactured for a foreign market, some pharmacist groups and providers contend that state laws and regulations concerning imported drugs have, at times, been impediments to importation. There also needs to be an entity (either the manufacturer or a distributor) willing to distribute the drug domestically. This process is often time-consuming because new contracts need to be developed by the manufacturer.

Nonetheless, in 2010, on three occasions, CDER utilized regulatory discretion with regard to the importation of drugs approved in other countries, after it had assured itself that the supplier was legitimate and relevant documentation had been reviewed by FDA. There had been an additional five such instances through mid-August 2011.

FDA Inspections and Enforcement Actions

Industry representatives often contend that FDA inspections and enforcement actions play a major role in drug shortages.^{57,58} They believe that FDA inspections have become more rigorous, leading to more frequent disruptions or delays in production that ultimately cause drug shortages.

⁵⁶ Greater New York Hospital Association. Drug shortages. Available at: <http://www.gnyha.org/10824/File.aspx> (accessed September 28, 2011).

⁵⁷ Stein R. Shortages of key drugs endanger patients. Washington Post, May 1, 2011. Available at: http://www.washingtonpost.com/national/shortages-of-key-drugs-endanger-patients/2011/04/26/AF1aJJVF_print.html (accessed September 28, 2011).

⁵⁸ Roy A. FDA-driven drug shortages: the new death panel? Forbes, June 24, 2011. Available at: <http://www.forbes.com/sites/aroy/2011/06/24/drug-shortages-the-new-death-panel/> (accessed September 28, 2011).

In fact, the primary cause of GMP citations is lapses in manufacturing protocols, equipment or practices, putting companies out of compliance with standards that are needed to provide patients with drugs that are safe and of high quality, and with which companies are legally obligated to comply. Manufacturing quality defects that produce substandard pharmaceuticals pose risks to patients and public health. In general, inspection findings that have been followed by shortages have been serious in nature: glass shards, metal filings, and fungal or other contamination in injectable products that must be sterile and pure to be safe for patients. (Less severe infractions are typically resolved quickly so any shortages are not lengthy.) The federal requirements for manufacturing quality have been in place for more than four decades and there have been no recent changes to these manufacturing standards.

FDA is committed to working with industry to prevent and mitigate shortages. When injectable drugs are contaminated or not sterile, the Agency must weigh the risks presented by the drugs against the risks posed by a potential shortage. Sometimes the manufacturer and the Agency can work together to address the immediate risks, such as by instructing health-care providers to filter injectable drugs before use. At other times, such measures are not available and, in order to protect public health, the Agency must prevent the contaminated or non-sterile products from being administered to patients. At the same time, the Agency works with the company to develop strategies to reduce the severity and length of any shortage that might ensue.

FDA's Unapproved Drugs Initiative

There are several thousand prescription drugs currently being marketed in the United States that have never been approved by FDA. Some of these drugs were on the market prior to the 1962 amendments to the FD&C Act, which required manufacturers to provide evidence of a new drug's effectiveness before it could be approved for marketing to the public.

In 2006, the Agency announced its Unapproved Drugs Initiative (UDI), an effort to use enforcement policies to increase the number of unapproved drugs that are tested and submitted for FDA approval.⁵⁹ The goal of the UDI is to ensure that all drugs marketed in the United States are evaluated for safety and effectiveness through the appropriate drug approval pathway. FDA is aware that there are drugs that have been marketed for many years that have not received FDA approval but are medically necessary. The goal of the UDI is to ensure continued availability of critical medications, while also encouraging companies to seek approval for these drugs. The UDI has resulted in many unapproved drugs being removed from the market, and, as a result, a number of pharmaceutical industry, purchaser, and provider organizations have asserted that it has been at the root of many recent drug shortages. Such assertions have found their way into the popular press.^{60,61,62}

⁵⁹ FDA's current Compliance Policy Guide on Marketed Unapproved Drugs (CPG) was issued in June 2006 as part of the Unapproved Drugs Initiative. The guidance emphasizes that marketed prescription drugs should obtain FDA approval and explains the Agency's enforcement priorities with regard to marketed unapproved drugs.

⁶⁰ de Rugy V. The FDA and drug shortages. National Review Online, June 14, 2011. Available at: <http://www.nationalreview.com/corner/269583/fda-and-drug-shortages-veronique-de-rugy> (accessed September 28, 2011).

However, prior to taking action to remove a particular unapproved product or class of drugs from the market, CDER's Office of Compliance works closely with DSP to prevent unnecessary disruption of the market or hardship to patients. In addition, FDA will meet with companies to provide guidance in helping them seek FDA approval for their product.

Moreover, data provided by DSP show that there were no shortages related to the UDI in 2010 or 2011. While a number of unapproved drugs, such as potassium phosphate and sodium chloride, have been in shortage (in the database developed for this report, 14 of 127 drugs in shortage were unapproved), the reasons for shortages of these and other unapproved drugs are similar to those of approved drugs and none was related to any action by the UDI itself.

The most recent shortage indirectly related to the UDI involved concentrated oral morphine sulfate, an unapproved product. In that instance, the drug was already in shortage due to GMP violations. In March 2009, the UDI issued a warning letter to the manufacturers of the concentrated form of the drug, believing that less-concentrated forms, which were FDA-approved, could satisfy market demand. The Agency reversed its action within days when providers pointed out that the concentrated form was medically necessary for some patients. As a result of this experience, it is now the policy of DSP to consult with outside professional societies and clinical reviewers when determining whether a drug is medically necessary.

ACTIONS AND RECOMMENDATIONS

This analysis has made clear that drug shortages are the result of a large number of overlapping causes. Accordingly, there is no single or simple solution that is likely to solve this problem; addressing it will require a multifaceted approach addressing many aspects of the problem simultaneously and involving multiple stakeholders including health-care professionals, industry, regulators, payers, Congress, and others. The Agency's primary role in this context is to work with manufacturers to aid in the mitigation and, whenever possible, the prevention of shortages.

These recommendations primarily focus on FDA. As in earlier sections of the report, most observations are directed toward drug shortages, but certain recommendations with relevance to other medical products are also included.

Immediate Actions

- 1. Write a letter to drug manufacturers reminding them of their current legal obligations to notify FDA in advance of the discontinuation of certain drugs and urging them to voluntarily notify FDA of other*

⁶¹ Ponnuru R. Too much FDA intervention equals too few drugs. Bloomberg, June 21, 2011. Available at: <http://www.bloomberg.com/news/2011-06-21/too-much-fda-intervention-equals-too-few-drugs-ramesh-ponnuru.html> (accessed September 28, 2011).

⁶² Cherici C, Frazier J, Feldman M, et al., Premier Healthcare Alliance. Navigating Drug Shortages in American Healthcare. March 2011. Available at: <http://www.premierinc.com/about/news/11-mar/drug-shortage-white-paper-3-28-11.pdf> (accessed September 28, 2011).

potential disruptions to the supply of drugs that are not currently required, as soon as they become aware of them

Currently, with certain exceptions, drug manufacturers are required to notify the Agency six months before discontinuing manufacturing only if they are the sole producer of a drug that is approved under section 505(b) or 505(j) of the FD&C Act and that is life-supporting, life-sustaining, or intended for use in the prevention of a debilitating disease or condition. It is apparent from the accounts of Agency staff that there are many instances in which manufacturers fail to notify FDA. This letter, combined with the recent national attention devoted to drug shortages, should lead to an improvement in notification with minimal cost and effort to the Agency and, as a consequence, an enhanced ability to prevent shortages.

2. Develop guidance and regulations that clarify and enhance the information on potential drug shortages that is submitted by industry

Together with the letter to industry in Immediate Action 1, these will expand notifications beyond what is currently required and help FDA work with industry to prevent and mitigate shortages.

3. Provide additional staffing resources for FDA's efforts to prevent and mitigate shortages

Despite the growing number of drug shortages, CDER's DSP has operated with essentially the same number of filled positions since 2004. Additional resources will be used to accommodate expected increases in notification and for such tasks as maintaining the newly developed database.

4. Support legislation that requires early notification by manufacturers for drug shortages and provides new authority to FDA to enforce these requirements

Additional explicit authorities for FDA to require and enforce early notification would be helpful. Therefore the Administration supports legislation before Congress, authored by Representatives DeGette and Rooney, and Senators Klobuchar and Casey, to provide these authorities. HHS and FDA will work with the sponsors to consider improvements to their bills and any other relevant legislation to maximize the impact for preventing and mitigating shortages and address this public health challenge. For example, some of these improvements would be designed to address the so-called "gray market," including requiring better tracking for medications.

5. Implement and maintain a database that can analyze the characteristics of drug shortages

Although DSP has retained information on past drug shortages in the form of weekly reports describing the current status of that week's most significant shortages and a library of emails, these data are not suitable for systematic analysis. In consultation with DSP staff, a new database containing information on drug shortages from January 1, 2010 onward has been developed. This new database captures various characteristics of each drug shortage, including drug class, reason for shortage, Agency action taken, and duration of shortage. The information captured in this database will allow the Agency to improve its tracking of drug shortages, to more consistently characterize each shortage, and to rapidly

identify and analyze new trends in shortages. The Agency will also use it to assess the effectiveness of any enhanced notification requirement enacted by Congress.

Longer-term Actions

6. Identify factors that contribute to success or failure in preventing drug shortages and continue exploring new approaches to preventing drug shortages under existing authorities

Despite the challenges described above, DSP reports that FDA prevented 38 drug shortages in 2010 and 99 in 2011 to date, an increase that DSP staff attribute, at least in part, to improved notification by manufacturers. Preventable shortages tend to be those where options include expedited reviews of changes in manufacturing practices, sites or suppliers, or discretion with regard to particular lots at ports of entry into the United States. A thorough examination of how FDA prevented specific shortages was beyond the scope of this report. However, FDA should conduct a comprehensive identification of the factors that have led to these successes so that lessons learned can be replicated, amplified, and disseminated. A similar examination of shortages that took place, including those that occurred despite FDA's efforts to prevent them, would also be worthwhile. In so doing, FDA should continue exploring and using new approaches to help prevent and mitigate shortages under existing statutory authorities.

7. Identify the quality issues in manufacturing practices that have contributed to severe drug shortages and develop approaches to addressing them

FDA should identify and examine the lapses in manufacturing protocols and non-compliance with current quality standards that have led to drug shortages and to recalls. This work should better focus industry's and FDA's attention on those manufacturing factors that will most help maintain the safety and quality of medical products and ensure their continued availability. It may also inform reviews of the agency's current regulatory requirements.

8. Encourage product manufacturers to develop and maintain a plan for back up manufacturing and sources of Active Pharmaceutical Ingredients and other essential product components

According to stakeholders with whom the authors met, APIs are increasingly being obtained from foreign sources that may be susceptible to supply disruptions. Although shortages of drug APIs have not been the predominant reason for the rising number of drug shortages (more commonly the problem occurs during manufacture of finished product at domestic plants), data on shortages handled by DSP that are generally among the more serious place this figure at 8% for injectable drugs and 20% for non-injectables. Drug API disruptions have even resulted in device shortages in the recent past (e.g., the heparin shortage resulted in shortages of devices using heparin to prevent clotting, such as oxygenators used in bypass machines). The Agency should explore having manufacturers submit to the Agency a plan, at approval and annually, to address potential disruption of their primary API supplies and other essential components to ensure that manufacturers are better prepared for supply interruptions. Similar requirements should be considered for manufacturing procedures as well. The burden of such requirements upon industry will need to be carefully considered before moving forward.

9. Explore development of a sentinel reporting network (e.g., major healthcare systems, wholesalers, physician specialty societies) to facilitate early warning of drug shortages

As noted elsewhere in this report, FDA does not always learn promptly about product shortages. Any system that increases reporting must ensure that, in the pursuit of more “signal,” DSP is not overwhelmed with “noise.” FDA should therefore explore the feasibility of creating sentinel reporting sites (e.g., major healthcare systems, wholesalers, and physician specialty societies) to facilitate the expeditious reporting of high quality information on drug shortages.

10. Encourage wholesalers to develop and publicize their procedures for distributing medical products in shortage

The wholesaler interviewed for this report described a system whereby drugs in shortage were distributed to its regional offices in proportion to previous orders. Other wholesalers may operate on a first-come, first-serve basis. Regardless, the lack of transparency contributes to a climate in which distrust between the various links in the supply chain can be rife. This is compounded by “leakage” of products to gray market suppliers.

The adoption and publication by wholesalers of a uniform, industry-wide policy on the distribution of shortage drugs could reduce confusion among recipients, allow for more consistent distribution, and reduce leakage to gray market distributors.

11. Continue to maximize public disclosure of information regarding medical product shortages in FDA’s possession, within the bounds of what must remain confidential

Many pharmacists and clinicians would like to know the reasons behind a particular shortage because it allows them to gauge the likely duration of a shortage based on their prior experience and to adjust their clinical decisions accordingly. It would also facilitate communications with patients if a drug were scarce. The Agency is often aware of the reasons behind a shortage, but if the information is protected from public disclosure because it is confidential commercial information, generally the Agency cannot disclose this information without the permission of the manufacturer. The Agency should continue to carefully consider what information can be publicly disclosed and when disclosure is not permitted without sponsor consent. The Agency should also attempt to persuade manufacturers to voluntarily allow broader dissemination of the reasons behind their shortages. The Agency should consider working with all stakeholders to maximize disclosure of information provided to the public about shortages, including the reason for a particular shortage and alternative therapies, if they have the same FDA-approved indications.

12. Continue improving communication between FDA’s field investigators and the Center for Drug Evaluation and Research’s Office of Compliance and Drug Shortage Program staff

Communication is essential for the Agency to efficiently and effectively prevent and mitigate shortages. Information that might be relevant should be shared on a timely basis with all FDA stakeholders. There currently appears to be an informal process for communication between ORA field investigators and

CDER's Office of Compliance and DSP staff. Interviews with Agency staff indicate that, while this consultation process appears to be occurring, it could be streamlined and formalized so that the roles and responsibilities of Agency offices in addressing shortages are clarified and strengthened.

CDER's Office of Compliance has multiple SOPs that require the Office to communicate with DSP staff when a potential recall or action is to be taken. FDA should undertake a thorough review of CDER-ORA interactions and determine whether similar SOPs can be developed in other areas, among other potential improvements.

13. Improve the Drug Shortage Program's web site as a communications tool for health-care providers and other members of the public

Many stakeholders, particularly pharmacists and clinicians, seem unclear on the differences between the lists of drug shortages maintained by DSP and ASHP. The differing inclusion criteria between the two lists (primarily that FDA lists, for the most part, shortages of medically necessary drugs and does not include regional shortages) should be better highlighted to raise public awareness and address criticism that DSP's list is shorter than ASHP's. Although the Frequently Asked Questions document⁶³ on FDA's drug shortage web page does mention the differences in the two lists, it might be preferable to highlight this distinction at the very top of the list of FDA's current shortages.

DSP should also consider maintaining a "dashboard" of metrics that would allow the public and the media to better monitor the overall status of drug shortages and enhance public accountability (see Appendix 3). These potential metrics would have to be assessed for feasibility of collection, usefulness of the data for month-to-month comparisons, among other factors.

14. Explore the feasibility of developing a model based on available data on drug shortages, manufacturer characteristics, and market factors with the goal of assessing the probability of future shortages

The ability to assess the risk of a particular medical product going into shortage could allow for more focused and potentially more effective prevention efforts. However, little research has been done on this question, at least in the drug area. Such research would face significant challenges, but has the theoretical potential to alter how shortages are managed or even prevented.

While it seems clear that a large proportion of recent drug shortages involve injectable generics, this does not establish how much more frequent shortages among injectable generics are compared to other products. Even that is quite different from predicting whether a particular drug is likely to go into shortage in a given period of time, or the kind of information that would be necessary to identify particular drugs as prevention targets. There are a number of inherent challenges to such an approach, one of which is the large number of unique injectable products available in the United States. Data from IMS National Sales PerspectiveTM, an audit that tracks national sales estimates of product packages into

⁶³ Center for Drug Evaluation and Research, Food and Drug Administration. Frequently Asked Questions about Drug Shortages. Available at: <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm> (accessed September 28, 2011).

retail drugstores, hospitals, clinics, and other non-retail type outlets, provided to the authors of this report by the Office of Planning and Informatics in CDER, suggest that there were an estimated 1468 injectable products sold in 2010, where products are defined by unique combined molecule, dosage form, and strength combinations. One thousand and twelve products (69%) have at least one generic product.

However, DSP only has data on actual drug shortages and, to a more limited extent, prevented shortages. To develop a model that might predict drug shortages would require extensive model development and validation and the identification of a control group of drugs not in shortage. Presumably FDA could assemble such a control group from other FDA and external databases. The Agency would have to incorporate market information on products and manufacturers into the model. While the feasibility of developing a model that could accurately assess the likelihood of a shortage is unclear at this point, the Agency should give such efforts full consideration because of the inherent public health value of preventing shortages before they occur.

CONCLUSION

Medical product shortages are harmful to nearly all parties involved. This shared experience can help motivate stakeholders to collaborate in developing approaches that might serve to prevent, ameliorate, and resolve this significant public health problem.

However, the problem of medical product shortages is complex and stems from economic, legal, regulatory, policy, and clinical decisions that are deeply interconnected. Many parties along the entire supply chain, including essential raw ingredient suppliers, API manufacturers, final drug product manufacturers, wholesalers, GPOs, clinicians, and ultimately, patients, are affected. While FDA has taken on the task of working with manufacturers to help prevent and mitigate these shortages, preventing 38 drug shortages in 2010 and 99 to date in 2011, many of the root causes and potential solutions lie beyond its purview. The Agency is also limited in its authorities as it formulates a response to the problem. Nonetheless, this report has identified a number of respects in which FDA's internal processes might be improved, so that FDA is maximizing its contribution to the prevention and mitigation of shortages.

There is no single or simple solution that can resolve the medical product shortage problem. Efforts to address the problem will need to be multifaceted, sustained over the long-term, and will require the engagement of all parties involved in the manufacture and distribution of medical products.

Appendix 1: FDA Offices Engaged in Mitigating Drug Shortages

Center for Drug Evaluation and Research

Drug Shortage Program: Facilitates prevention and resolution of shortages by collaborating with stakeholders involved in or affected by drug shortages, including FDA experts, industry, and external stakeholders. Also provides drug shortage information to the public and conducts outreach to health-care professional organizations, patient groups, and other stakeholders.

Office of New Drugs: Assesses whether a particular drug is medically necessary and assesses the risks associated with continued distribution if there are quality concerns.

Office of Pharmaceutical Science (Office of Generic Drugs) and Office of New Drug Quality Assurance: Expedites review and pre-approval inspections of applications for new manufacturing sites, suppliers, production lines, and other changes related to addressing or preventing a shortage of a medically necessary drug. Facilitates resolution of regulatory and scientific issues related to the drugs in shortage, including issues that involve Chemistry, Manufacturing, and Controls issues.

Office of Compliance: A dedicated Recalls Coordination Branch functions as coordinator between the Office of Compliance and DSP. OMPQ in the Office of Compliance works with firms to help resolve manufacturing/quality issues. May utilize flexibility through regulatory discretion to address shortages and mitigate risks to patients. Can also facilitate expedited inspections or develop options related to inspections and reinspections, and initiate, facilitate, and monitor importation plans.

Office of the Commissioner

Office of Regulatory Affairs: As the lead office for FDA field activities, provides FDA leadership on imports, inspections, and enforcement policy. ORA inspects regulated products and manufacturers, conducts sample analysis on regulated products, and reviews imported products offered for entry into the United States.

Appendix 2: Comparison of Medical Product Shortage Activities in Selected FDA Centers

	CDER	CBER	CDRH	CVM
Product shortage reporting requirement	Required to provide up to 6 months notification of discontinuation of certain sole-source drugs	Similar to CDER for a small proportion of CBER-regulated products	No reporting requirement	No reporting requirement
Frequency of industry reporting on shortages	Staff estimate under 50% of product discontinuations are properly reported to CDER	Good cooperation and early notification received from manufacturers	Rarely, if ever. CDRH often finds out about shortages from the media. To obtain information, CDRH must contact the manufacturer directly	Rarely
Description of shortage problem	About 30-40 shortages currently. Number of shortages has increased significantly over last several years	Very few shortages (last reported in 1/2010)	Limited information	6 active shortages currently. Has been experiencing an increase in shortages
Product most often involved in shortage	Sterile injectables	IVIG, vaccines	Unknown	Sterile injectables
Database of shortages that have occurred?	Yes	No; Access database in development	No	Consolidated internal list of shortages
List of shortages publicly available? Does it include reason for shortage?	Yes; List includes company/product, reason (general), and related information	Yes. List includes product name, reason for shortage (general), and status	No	No
Is there a shortage plan in place?	Yes: MAPP	Yes; SOPP 8506. SOPPs for use within OCBQ currently being developed	CDRH has Standard Operating Procedures to address device shortages	No. In process of updating written procedures
Have you used regulatory discretion in attempting to resolve shortages?	Yes. Through expedited review, discretion with regard to distribution of particular lots, and importation	Yes. Through expedited review and/or inspection of a facility	Yes	Yes, temporary regulatory discretion is considered, but extent of use is unclear
Have you used importation as a solution to resolving shortages?	Yes; 3 new instances of importation in 2010 and 5 new instances to date in 2011	No	Yes	Yes. While the supplemental approval process is being reviewed

Appendix 3: Potential Metrics to Include in Dashboard on Drug Shortage Program Web Site

Number of drug shortages in previous calendar year

Number of drug shortages currently active

Number of drug shortages resolved in previous calendar year

Number of drug shortages prevented in previous calendar year

Dosage forms of drugs currently in shortage

Causes of current drug shortages

Number of drug shortages related to the Unapproved Drugs Initiative in previous calendar year

Number of shortages addressed through importation in the previous calendar year

Median duration of shortages