Drug Shortages


Food and Drug Administration workshop on drug shortages, September 26, 2011. Materials and full-day meeting may be reviewed online: http://www.fda.gov/Drugs/NewsEvents/ucm265968.htm.


Kantarjian HM: When the drug you need to cure a cancer is nowhere to be found. Washington Post, April 18, 2011.


Text and summary of S. 296 (Klobuchar and Casey), Preserving Access to Life-Saving Medications Act.

Text and summary of H.R. 2245 (DeGette and Rooney), Preserving Access to Life-Saving Medications Act.

Bompey N: Generic drug makers want distribution communication added to shortage bills. Inside Health Policy, September 29, 2011.

Bompey N. Drug shortages put clinical trial data, future research in jeopardy. Inside Health Policy, September 29, 2011.
U.S. Drug Shortages

Overview

- Background on CDER Drug Shortage Program
- U.S. Drug Shortage Trends
- Reasons for Drug Shortages
- Industry’s Role
- CDER’s Approach to Prevention/Mitigation of Drug Shortages (includes, drugs, therapeutic proteins, monoclonal antibodies)

Drug Shortage Program History

- Drug Shortage Program (DSP) began in 1999
- Mission: to address potential and actual drug shortages
- Currently 4 full time staff and Coordinator
  - Facilitate prevention and resolution of shortages by collaborating with FDA experts, industry, and external stakeholders
  - Provide drug shortage information to the public
  - Outreach to healthcare professional organizations, patient groups and other stakeholders

Current Relevant Authorities

- Very limited authorities directly related to drug shortages
- Limited notification requirement
  - Only requirement is notification of sole source discontinuation
  - No consequence for failure to notify
- Manufacturing capacity - FDA cannot dictate the production quantity
- Program operates largely based on voluntary participation of industry
DISCONTINUANCE OF A LIFE SAVING PRODUCT


(a) IN GENERAL.—A manufacturer that is the sole manufacturer of a drug—

(1) that is—

(A) life-supporting;

(B) life-sustaining; or

(C) intended for use in the prevention of a debilitating disease or condition;

(2) for which an application has been approved under section 505(b) or 505(j); and

(3) that is not a product that was originally derived from human tissue and was replaced by a recombinant product, shall notify the Secretary of a discontinuance of the manufacture of the drug at least 6 months prior to the date of the discontinuance.

• See also 21CFR 314.81(b)(3)(iii)

Shortage Trends Injectables-- 2010

• 54% - Due to Product Quality/significant CGMP issues (e.g., particulate, contamination, impurities)

• 21% - Due to Delays/Capacity issues

• 11% - Due to Discontinuations

• 5% - Due to raw material (API) issues

• 4% - Increase in demand due to another shortage

• 3% - Due to loss of manufacturing site

• 2% - Due to component problems/shortage

Reasons for Shortages – Older Sterile Injectables

When a firm has manufacturing/quality problem with older injectables or discontinues a product, a shortage usually occurs

• Not enough manufacturing capacity

• Industry consolidation
  – Fewer firms making these products
  – Seven (7) manufacturers make up large percentage of this market
  – Contract manufacturers – firms contract out manufacturing as well as acting as contract manufacturers

• Lack of redundancy
  – Multiple products made on existing manufacturing lines

• Complex manufacturing process

• Generally not economically attractive
  – e.g., propofol 20ml sells for $0.48/vial
FDA’s Approach to Shortage Prevention/Mitigation - 1

• Consider medical necessity
• Risk/Benefit of the drug always considered
• FDA does everything possible within our authority to continue availability while minimizing risk to patients.
• For manufacturing/quality problems – work with the firm to address the issues.
• Flexibility may be employed to address shortages to mitigate any significant risk to patients (e.g., Cytarabine injection)

Medical Necessity

• A medically necessary drug product is a product that is used to treat or prevent a serious disease or medical condition for which there is no other alternative drug, available in adequate supply, that is judged by medical staff to be an adequate substitute

CDER Manual of Policies and Procedures on Drug Shortage Management 6003.1

FDA’s Approach to Shortage Prevention/Mitigation - 2

• Encourage remaining firms to ramp up if others manufacturing.
• FDA can and does expedite issues related to addressing shortages (e.g. new manufacturers, increased expiry, increased capacity, new raw material source, changes in specifications).
• In rare cases, temporary importation from unapproved sources
  – 2010 temporary importation of propofol
  – 2011 temporary importation of foscarinet, ethiodol, thiotepa, norepinephrine, Xeloda, levoLeucovorin, Leucovorin

Prevented Shortages - 2010

• In 2010, 38 shortages were prevented due to early notification from firms
  – 16 prevented through regulatory discretion (risk of quality/manufacturing issue able to be mitigated and was outweighed by benefit of the drug)
  – 13 prevented through expedited review (new manufacturing sites, suppliers, changes in specification or other changes)
  – 8 prevented through encouraging other firms to ramp up
  – 1 prevented through communication with DEA regarding firm’s report to FDA regarding need for quota increase
Prevented Shortages – 2011 (to date)

• In 2011, have seen increased reporting by manufacturers of potential shortages.
• 99 shortages have been prevented so far due to early notification from firms
  – 84 prevented through expedited review (new manufacturing sites, suppliers, changes in specification or other changes)
  – 12 prevented through regulatory discretion (risk of quality/manufacturing issue outweighed by benefit of the drug)
  – 1 prevented through encouraging others to ramp up
  – 1 prevented through communication with DEA regarding firm’s report to FDA regarding need for quota increase
  – 1 prevented through assisting a firm with an import delay

Within FDA/CDER

• DSP works with
  – Review division(s) in OND that regulates the therapeutic areas for the drug
  – Office of Generic Drug Products
  – Office of New Drug Quality Assessment
  – Office of Biotechnology Products
  – Office of Compliance
    • Office of Regulatory Affairs
  – Others

Important to Note:

• FDA plays a key role working with manufacturers to facilitate responses to prevent or mitigate a drug shortage
  – This is a secondary response to mitigate a problem that has already happened
• Manufacturers play a key role in responding to shortages as they make the products that doctors and patients use
• It is important to consider the root cause of a shortage
• If the root cause that leads to a shortage can be prevented, one can get to primary prevention
• Some shortages can be prevented – others cannot be prevented
  – Some shortages involve unforeseen (unanticipated) problems such as a manufacturing line breakdown or other event that causes an unavoidable shortage
  – Manufacturer(s) may not be able to make up production shortfall
  – In some cases risks are significant and would cause patient harm (e.g. sterility problems)

Examples of Recent Quality and Manufacturing Issues Involving Sterile Injectables - 1

• Significant quality issues that have occurred
  – Sterility problems – including bacterial and mold contamination
  – Particles of foreign matter (glass, metal and fibers) in vials
  – Crystallization of the active ingredient
  – Precipitate formation (due to reaction with raw materials or container/stopper with the drug)
  – Newly identified impurities or degradants
Examples of Recent Quality and Manufacturing Issues Involving Sterile Injectables - 2

- Issues that are more easily able to be addressed
  - Errors in labeling or packaging
  - Slightly out of specification results that do not unfavorably alter benefit / risk
- Unforeseen/ Unanticipated issues
  - Manufacturing equipment breakdown
  - Natural disasters or other events causing loss of manufacturing time and in some cases loss of inventory
    - Fire at raw material or finished product manufacturing site
    - Japan earthquake caused several potential shortages
    - Icelandic volcano caused transportation delays

Flexibility - examples

- Allow release of medically necessary products with extra testing and third party oversight
- Build in exemptions for medically necessary products into enforcement actions (e.g., consent decrees)
- Allow distribution of product with filters and alerts to health care providers

Industry’s Role - Potential solutions

- Plan ahead by adding redundancy to manufacturing & raw material supply to prevent shortages of medically necessary drugs (flexible regulatory approaches possible)
- Commitment to quality: proactively identify & promptly correct issues
- Prevent sudden lack of lifesaving medications for consumer
- Notify FDA as soon as aware of an issue that could impact supply. Contact Drug Shortage Program at drugshortages@fda.hhs.gov
  - 38 shortages prevented in 2010 due to early notification by firms
  - 99 shortages prevented in 2011 so far due to early notification

Continuing Role for CDER’s DSP

- Continue working with firms
- Encourage voluntary reporting
- Continue tracking number of shortages and reasons for shortages
- Outreach
  - Health care professionals
  - Consumers
  - Manufacturers
Thank You

• FDA drug shortage website is: http://www.fda.gov/Drugs/DrugSafety/default.htm

• To report shortages our e-mail account is Drugshortages@fda.hhs.gov

• FDA Webinar on Prescription Drug Shortages
  Sept. 30, 2011, 11:00 a.m.
  http://www.fda.gov/AboutFDA/Transparency/Basics/ucm272223.htm
The Drug Shortages Summit was co-convened by the American Society of Health-System Pharmacists (ASHP), the American Society of Anesthesiologists (ASA), the American Society of Clinical Oncology (ASCO), and the Institute for Safe Medication Practices (ISMP) on November 5, 2010 in Bethesda, Maryland. The goals of the summit were to:

- Discuss the scope and causes of drug shortages;
- Shed light on the harm to patients that is occurring due to drug shortages;
- Discuss the potential need for changes in public policy and stakeholder practices to prevent patient harm from shortages; and
- Develop an assertive action plan that reflects the recommendations and intent of stakeholders to work together to stop patient harm and disruptions in patient care caused by drug shortages.

Summit participants included representatives from health professional organizations, pharmaceutical manufacturers, and supply chain entities. Representatives of the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention also attended portions of the meeting as observers. A complete list of attendees is found in Appendix A.

This summary report reflects discussion at the Drug Shortages Summit, including recommended actions that will be further evaluated and implemented, if appropriate, based on an assessment of feasibility, impact, and resources required for implementation. Compliance with legal requirements (e.g., Federal Trade Commission regulations) and avoidance of unintended consequences (e.g., hoarding,
manufacturing disincentives) will also be factored into this evaluation. Next steps will focus on establishing workgroups to explore, prioritize, and develop detailed action plans to achieve summit recommendations that are selected for implementation based on these criteria. Additional information will be available from the co-conveners and at www.ashp.org/drugshortages as these plans are developed.

Introductory comments by Henri R. Manasse, Jr., Ph.D., Sc.D., Executive Vice President and Chief Executive Officer, ASHP; Mark A. Warner, M.D., President, ASA; and Michael P. Link, M.D., President-elect, ASCO illustrated the negative effect of drug shortages on patient care, including delayed care, inferior clinical outcomes, and patient injury or death. Participants were encouraged to collaborate to address what was described as a public health crisis. Presentations by Erin R. Fox, Pharm.D., Manager, Drug Information Service, University of Utah Hospitals & Clinics; Burgunda (Gundy) V. Sweet, Pharm.D., Director, Drug Information and Medication Use Policy, University of Michigan Health System; and Michael R. Cohen, R.Ph., M.S., Sc.D., President, ISMP described causes and current trends for drug shortages, resource utilization for managing drug shortages, and safety concerns associated with drug shortages), respectively. Details of these presentations are provided in appendices B and C; data from a survey on resource utilization are not provided due to pre-publication embargo. FDA staff, including CAPT Valerie Jensen, R.Ph., Associate Director, CDER Drug Shortage Program and CDR Jouhayna Saliba, Pharm.D., Senior Program Manager, Center for Drug Evaluation and Research (CDER) Drug Shortage Program, provided an overview (Appendix D) of Agency activities in this area, described current regulatory authority related to drug shortages, and responded to participant questions. Additional information on causes, impact, and proposed solutions for drug shortages and an antitrust statement are contained in the background documents provided to participants prior to the summit (Appendices E through H).

Outcomes of the Drug Shortages Summit included development of initial recommendations and participant agreement to continue collaborating to address issues associated with drug shortages. Broad areas of work will include exploring strategies to:

- Improve communication among stakeholders in the pharmaceutical supply chain and health care providers, and
- Remove barriers faced by the FDA and drug manufacturers to minimize the impact of drug shortages.
Regulatory and Legislative Factors

Summary of Causes: Regulatory barriers and ambiguities, including the lack of FDA authority to require notification and other actions, were considered significant contributors to drug shortages. Examples include the absence of a requirement for manufacturers to notify FDA of anticipated market withdrawal and no statutory authority for enforcing notification requirements for medically necessary drugs. Several drug shortages (e.g., concentrated morphine sulfate solution, levothyroxine injection) have been precipitated by actual or anticipated action by the FDA as part of the Unapproved Drugs Initiative, which is designed to increase enforcement against drugs that lack FDA approval to be marketed in the United States. (These drugs are commonly called pre-1938 drugs, referring to their availability prior to passage of the Food, Drug, and Cosmetic Act of that year.) Some participants noted that the cost and complexity of completing a New Drug Application (NDA) for those unapproved drugs is a disincentive for entering or maintaining a market presence. Other regulatory barriers include the time for FDA review of Abbreviated New Drug Applications (ANDA) and supplemental applications, which are required for changes to FDA-approved drug products (e.g., change in source for active pharmaceutical ingredients (API), change in manufacturer). Manufacturers described this approval process as lengthy and unpredictable, which limits their ability to develop reliable production schedules. Participants noted that some FDA activities are based on internal policies, not regulation. While this was perceived as allowing for flexibility and discretion, it may also result in unpredictable or delayed responses. Some participants believed that a perceived backlog of applications awaiting approval may be related to insufficient FDA resources. Another contributing cause to drug shortages may be the availability of improved assays and other technologies that have resulted in issuance of new product specifications (e.g., revised United States Pharmacopeia [USP] standards for assessing heparin potency). In addition, when one manufacturer submits revised standards that are accepted by USP, other companies are required to meet the new specifications. Shortages may be caused when companies are delayed in complying with these new requirements. For controlled substances, pre-established Drug Enforcement Agency (DEA) quotas can delay or prohibit manufacturers from obtaining API to increase production of these products when another manufacturer experiences a shortage or production issue. Other potential causes that were discussed, but considered less or not causative of drug shortages included evolving regulatory requirements for packaging (e.g., barcodes), Risk Evaluation and Mitigation Strategies, and inconsistencies in international drug approval processes that prevent use of foreign products when shortages occur.

Recommendations:

- Explore expanding FDA authority to require manufacturer notification of market withdrawals (e.g., notification required 9 to 12 months prior to planned market exit).
- Evaluate the current FDA definition of medically necessary, including the established criteria and responsible party for making this determination, to assess the need for increased FDA statutory authority in this area.
• Define and implement evidence-based and other criteria for identifying critical drug therapies that are vulnerable to drug shortages. Criteria might include factors such as availability of therapeutic alternatives, supply chain characteristics, and other elements that determine products’ vulnerability for shortages.

• Explore providing incentives (e.g., tax credits) to manufacturers that produce critical drug products or upgrade manufacturing plants to meet or exceed Good Manufacturing Practices (GMP) in exchange for guarantee of continued production of these therapies.

• **Require** confidential notification of FDA when there is a single API or manufacturing source. Notification would also apply to informing FDA of an interruption in the supply of raw materials, API, or manufacturing processes. *(This recommendation also listed under Raw Materials Sourcing and Manufacturing Factors as a voluntary action).*

• Explore reauthorization of Prescription Drug User Fee Act (PDUFA) as a mechanism to establish a modified/reduced user fee program for generic drugs, which would provide FDA additional resources to support prioritization and expedited review of supplemental applications and ANDA. Intent of user fee program would be to provide more timely approval of applications and incentivize manufacturers to enter market based on increased ability to plan production schedules.

• Establish an expedited approval pathway for those unapproved drugs (i.e., pre-1938 therapies) that are deemed critical therapies. In addition, reduce or eliminate the current NDA user fee that is required for these products. Incentives could also be considered.

• Assess the need to establish or enhance use of existing processes to expedite approval of ANDA, supplemental applications (e.g., alternate source API), and new or altered production lines for drugs in short supply. In addition, advocate for additional FDA resources to minimize wait time for approval of these applications.

• Evaluate processes for new product specifications (e.g., USP standards), including appropriateness of timeline for implementation. *(Note: Invite USP to participate in these discussions).*

• Increase collaboration with industry, DEA, and FDA to establish a process that would more readily modify API quotas in response to drug shortages of controlled substances.

• Establish improved processes to extend product stability for products in short supply.

• **Require** manufacturing redundancies (e.g., multiple manufacturing sites for a sole product or multiple API sources, when available) as part of the FDA approval process. *(This recommendation also listed under Raw Materials Sourcing and Manufacturing Factors as a voluntary action).*

Other proposed solutions discussed briefly by summit participants included harmonizing international drug approval processes in order to minimize barriers to importation (when desirable) and clarifying the definition of public health emergency to determine if this mechanism could facilitate allocation and other activities that avoid or minimize the effect of drug shortages.
Raw Materials Sourcing and Manufacturing Factors

**Summary of Causes:** Manufacturing-related causes that contribute to drug shortages are multifactorial. Inability to fully comply with GMP, which results in production stoppages or recalls, was considered a major cause. It was noted that FDA has increased inspections of injectable drug manufacturing processes based on the higher likelihood of harm should these processes be inconsistent with GMP. Manufacturers have also voluntarily increased their quality standards, which on occasion, has resulted in companies being temporarily unable to meet their own standards. Participants recognized that there is limited understanding of the complexity and inter-relatedness of drug production activities. For example, increased product demand in response to another drug product shortage may result in a secondary shortage. Manufacturers generally run production lines at full capacity and may be unable to quickly accommodate increased market demand or FDA requests to produce additional quantities of these alternative therapies. Unpredictable timelines for FDA approval of supplemental applications and ANDA for new-to-market generics also contribute to uncertainty in production planning processes. In addition, there are limited sources of API. Some API are sole source products, which increases a product’s vulnerability to drug shortages. Other causes that were discussed, but considered less or not causative of drug shortages included natural disasters and changes in product formulation.

**Recommendations:**

- **Encourage** confidential notification of FDA when there is a single API or manufacturing source. Notification would also apply to informing FDA of an interruption in the supply of raw materials, API, or manufacturing processes. *(This recommendation also listed under Regulatory/Legislative Factors as a proposed required action.)*
- **Encourage** manufacturing redundancies (e.g., multiple manufacturing sites for a sole product or multiple API sources, when available). *(This recommendation also listed under Regulatory/Legislative Factors as a proposed required action.)*
- Establish or improve mechanisms to communicate anticipated or actual manufacturing and inventory problems (e.g., standardize terminology for causes of shortages, eliminate causes being described as “reason unknown” or “not provided”). Some information may require privileged communication between FDA and manufacturers to avoid unintended consequences (e.g., hoarding, releasing business information that supports fair business competition). Other mechanisms should focus on improving communication and transparency among supply chain entities and health care providers. Ensuring that information on the reason for and anticipated duration of the shortage reaches frontline clinicians was considered key.
- Maintain/improve adherence to GMP to avoid quality issues and recalls.

**Business and Market Factors**

**Summary of Causes:** Several market factors were noted as contributing to drug shortages, including consolidation of firms that leads to fewer manufacturers for a given product, reassignment or
reallocated production lines, lack of transparency or communication about actual or possible product shortages, and lack of business incentives to enter a specific product market. Some participants believed that insufficient profit margins and product liability concerns are factors that lead to market withdrawals. However, manufacturers stated that these factors do not contribute to the decision to discontinue a product, which was described as being multifactorial (e.g., complexity of manufacturing newer drugs can necessitate shifting of manufacturing resources away from other products). Other causes that were discussed, but considered less or not causative of drug shortages were unpredictable fluctuations in product demand (i.e., changes in clinical practice) and patent challenges.

Recommendations:

- Improve communication to, among, and from product manufacturers and FDA, including detailed information on reason and anticipated duration of shortage. Also enhance communication to supply chain entities and health care providers (e.g., Dear Provider letters).
- Decrease barriers/disincentives to market entry (See recommendations under Regulatory/Legislative Factors).

Distribution Factors

Summary of Causes: Inventory practices by health care facilities (e.g., just-in-time inventory) and supply chain entities (e.g., sole source and bundled purchasing) were identified as a significant factor that contributes to the impact of drug shortages on patient care. This practice results in little or no inventory cushion to address short-term shortages. In addition, regional and local differences in product availability were described as resulting from contractual agreements with wholesalers and group purchasing organizations (GPOs). Current systems for product allocation are intended to address this, but are often imperfect based on a lack of reliable information on resumed product availability. Another system limitation is the inability of GPOs to determine competitive pricing that would facilitate establishing multiple contracts for a specific product. Drug procurement is especially challenging for ambulatory infusion centers and small and rural facilities, which generally lack the business relationships that can facilitate product availability for larger facilities or health systems. The grey market (i.e., distribution channels other than those authorized by the manufacturer) and price escalations for products in short supply were also discussed. The potential for hoarding and price gouging were described as a significant concerns related to drug shortages.

Recommendations:

- Enhance communication among manufacturers, health professional associations, and FDA to support product distribution.
• Consider distribution options for products in short supply (with increased information exchange among supply chain members).

Another proposed solution discussed briefly by summit participants was creation of a national “stockpile” for critical therapies. However, it was noted that this approach would require an initial expanded supply of products that already had limited availability. Direct manufacturer distribution of products in short supply was discussed, but not preferred, because of limitations in the current model. For all recommendations, participants were especially cautious of avoiding unintended consequences (e.g., hoarding) related to distribution practices.
When the drug you need to cure a cancer is nowhere to be found

By Hagop M. Kantarjian, Published: April 18

As a doctor I took an oath to do no harm, but I fear there will be more and more occasions when I can do no good.

In the United States this year, about 10,000 people will receive a diagnosis of acute myeloid leukemia (AML). Since mid-December, the most effective drug to treat this fatal disease has been in dangerously short supply.

The chemotherapy medication cytarabine was first approved by the Food and Drug Administration in 1969. For four decades, it has been the backbone of AML treatment. With cytarabine combination chemotherapy, the cure rate in AML is 40 percent to 50 percent. Without cytarabine, there is no cure.

In December, it was added to the FDA’s drug shortage list. There is no therapeutic equivalent to cytarabine, and optimal treatment starting on Day One is critical to the cure. Simply put: No cytarabine, no cure. Never in my 30 years of treating patients with leukemia has such a drug shortage occurred, resulting in inadequate therapeutic options for patients.

Take, for example, the 43-year-old Kentucky father who got a substandard dose of cytarabine because his doctor used all the doses he could find but still didn’t have enough. “I don’t know what I’ll do next,” the doctor told me.
Or the 45-year-old retired Air Force lieutenant colonel from Colorado, father of an incoming Air Force Academy cadet, whose leukemia came back after six months. His doctor looked all over the state for cytarabine with no luck and so was forced to give his patient second-line therapy.

Or the 15-year-old boy from Florida who is in remission but can’t get the therapy that will cure him.

Recently I sent out a plea on this national crisis to 8,000 oncologists who subscribe to a monthly e-mail newsletter published by the leukemia department at the MD Anderson Cancer Center. Within 12 hours, my in-box was jammed with replies from doctors in more than 25 states, each with his or her own horror story.

One works for a large California provider that cares for several million members. “As of this morning, the entire inventory of cytarabine in our system was 30 grams,” he wrote. “We are prioritizing the little remaining drug to go first to pediatric patients requiring cytarabine. … Patients will inevitably die as a result of this tragedy.”

A colleague from Wisconsin wrote, “We have been forced to form a panel of physicians, pharmacists and nurse practitioners to make difficult decisions regarding … this drug (i.e. who can receive it and who can’t).”

A doctor at a large center in Nebraska wrote, “We are completely out after the end of the week and no cytarabine in sight. It is like we live in a Third World country!”

Cytarabine used in the United States is manufactured by three companies: Bedford Laboratories, Hospira and APP Pharmaceuticals.

“We are currently facing manufacturing capacity constraints that are resulting in back orders of some products and we are working diligently to prioritize and expedite manufacturing for all current orders,” wrote Bedford spokesman Jason Kurtz in an e-mail in which he blamed Bedford’s shortage largely on increased demand as supplies from others were squeezed. He said Bedford expects to release more cytarabine in late May or early June. Hospira notified the FDA last week that it had begun releasing new supplies of the drug. And APP will begin releasing newly manufactured cytarabine this week, according to a company spokeswoman.

Along with cytarabine, dozens of other drugs are on the list, including such cancer-fighting workhorses as doxorubicin, cisplatin, etoposide and bleomycin. Shortages are not limited to cancer drugs; they also encompass categories such as antibiotics, heart medications and painkillers. Brand-name drugs rarely appear on the list.

All of these shortages can be critical for individual patients; none is more critical than the shortage of cytarabine.

Several of the concerned calls I received were from colleagues in Houston’s Texas Medical Center, the largest medical center in the world with 49 institutions that occupy an area the size of downtown Chicago. If these colleagues cannot get cytarabine, imagine how difficult it is for a solo practitioner in small-town America.

The drug-shortage problem has grown rapidly in this country in the past decade. The FDA reported a record 211 shortages in 2010, up from 58 six years ago, according to the American Society of Health-System Pharmacists. Eighty shortages were reported in the first quarter of 2011 alone. At this rate, the
year-end total will be more than double the number last year.

“This problem is not just a blip,” said ASHP spokeswoman Cynthia Reilly. “It is getting worse, not better.”

What is behind these shortages, and what can be done to prevent them?

The FDA has no authority to compel manufacturers to continue producing a drug, nor does it have the power to force companies to inform it about issues that might result in drug shortages. Sen. Amy Klobuchar (D-Minn.) and Sen. Robert Casey (D-Pa.) are attempting to address this issue with legislation that would compel manufacturers to notify the FDA when there are supply problems or when they plan to discontinue a product. This is a start.

Valerie Jensen, associate director of the FDA’s drug shortages program, says it’s not clear why the shortages are getting worse. “We really don’t know the reason, but it is a concerning trend,” she said. Asked whether financial considerations play a role in the shortages, Jensen said, “The older drugs are often not cost-effective for companies to make. Often we see products like [cytarabine] get discontinued. … We cannot require a company to manufacture a product.”

Jensen said that the FDA is working with the companies to make cytarabine widely available again. She said the FDA is examining the possibility of allowing temporary importation of the drug from foreign sources.

Why are these shortages almost unique to the United States? We pride ourselves on being the No. 1 nation in medical care, but today a patient with AML in an emerging nation, such as my native Lebanon, may be treated with more-effective therapy than a patient in the United States. No shortages of cytarabine have been reported in other countries. We urgently need to examine and address the reasons behind the increasing occurrence of shortages of generic drugs in the United States.

The most common explanations given for drugs’ presence on the FDA list are “manufacturer delays,” “increased demand” and shutdown of plants for manufacturing issues. Some generic drugs called “sterile injectables,” including cytarabine, are on the list because of their cost and complexity of manufacturing.

There is little financial incentive for any company to produce labor-intensive medications that are heavily regulated but offer a slim profit margin. The fewer companies that manufacture a drug, the more vulnerable the supply, though in the case of cytarabine three companies produce it, which Jensen said “is actually good for one of the older drugs.” The drug is very inexpensive. At my hospital, a two-gram vial costs $16.

Cytarabine is used to treat a leukemia affecting patients numbering in the thousands rather than the millions. Shortages of other drugs affect much larger groups. Why not offer tax incentives to companies willing to fill this need, or perhaps subsidies similar to those offered in the agricultural sector?

In a country as rich as ours, patients should not have the misfortune of contracting a fatal disease for which an unprofitable treatment is withdrawn or not available.

Shortages of sneakers, the latest electronic gizmos and toys around the holidays routinely make headlines with a notable public outcry and demand for more. Surely the shortages of lifesaving medicines demand more attention and more action.
“Sorry, we’re out of stock” is simply not acceptable.

Kantarjian is chairman of the department of leukemia at the University of Texas’s MD Anderson Cancer Center.

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Shortages of key drugs endanger patients

By Rob Stein, Published: May 1

Doctors, hospitals and federal regulators are struggling to cope with an unprecedented surge in drug shortages in the United States that is endangering cancer patients, heart attack victims, accident survivors and a host of other ill people.

A record 211 medications became scarce in 2010 — triple the number in 2006 — and at least 89 new shortages have been recorded through the end of March, putting the nation on track for far more scarcities.

The paucities are forcing some medical centers to ration drugs — including one urgently needed by leukemia patients — postpone surgeries and other care, and scramble for substitutes, often resorting to alternatives that may be less effective, have more side effects and boost the risk for overdoses and other sometimes-fatal errors.

“It’s a crisis,” said Erin R. Fox, manager of the drug information service at the University of Utah, who monitors drug shortages for the American Society of Health-System Pharmacists. “Patients are at risk.”

The causes vary from drug to drug, but experts cite a confluence of factors: Consolidation in the pharmaceutical industry has left only a few manufacturers for many older, less profitable products, meaning that when raw material runs short, equipment breaks down or government regulators crack down, the snags can quickly spiral into shortages.

“It seems like there were a lot of things happening with consolidations and quality issues and more...
things coming from overseas,” said Allen J. Vaida, executive director of the Institute for Safe Medicine Practices, a nonprofit group that helped organize a conference last fall to examine the issue. “It just reached a point where the number of shortages was slowly going up and up, and now we have a national crisis with this huge shortage of critical medications.”

While the dearth that has garnered the most public attention is — ironically — for a barbiturate that is hindering prisons trying to execute inmates, the scarcities are having a much broader impact on keeping people alive, especially in emergency rooms, oncology wards and intensive care units.

No one is systematically tracking the toll of the shortages, but reports are emerging of delayed treatments, anxious searches for desperately needed drugs, devastating injuries from mistakes and less-adequate drugs, and even possible deaths.

Federal regulators have been rushing to alleviate the shortages, sometimes helping firms resume production more quickly or approving emergency imports of supplies from overseas.

The Food and Drug Administration eased a shortage of the anesthetic propofol last year by allowing foreign importation, for example, and this year approved bringing in several other medications, including two cancer drugs.

“The types of products we’re seeing shortages of are really concerning,” said Valerie Jensen, who heads the FDA’s Drug Shortages Program. “This is affecting oncology drugs, critical-care drugs, emergency medicine drugs. We’re doing everything we can under our current authority to try to deal with this situation.”

In Congress, legislation has been introduced to address the problem. For example, a bill would require companies to notify the FDA in advance about anything that might cause a shortage and give the agency new powers to try to assuage them.

“We can’t put patients’ lives at risk simply because there’s some snafus in a process or a manufacturer decides it’s less profitable to make a certain drug,” said Sen. Amy Klobuchar (D-Minn.). “Patients deserve better than that.”

‘Very global supply chain’

Many of the shortages involve older, cheaper generic medications that are less profitable, causing many firms to stop producing them and leaving fewer sources. Most involve “sterile injectable” medications that are more complicated to produce and therefore are more prone to manufacturing problems.

In addition, drug companies increasingly rely on raw materials from other countries.

“We’ve certainly reached a very global supply chain for drug products, with the active ingredients typically made outside of the United States,” said Gordon Johnston, vice president for regulatory sciences at the Generic Pharmaceutical Association. “It could be Europe, India — some cases China. If there’s a problem at a facility in Italy or India, it leads to disruption of the drug supply in the United States.”

Some industry representatives blame part of the problem on increased oversight by the FDA, which has made drug safety a higher priority after coming under intense criticism for being too lax.
“As you know right now, FDA has taken a heightened approach towards drug safety,” said Maya Bermingham, senior assistant general counsel at the Pharmaceutical Research and Manufacturers of America. “FDA has stepped up inspections. The more you look, the more you may discover problems.”

While acknowledging that the industry needs to do a better job of coordination, some company officials said the agency should coordinate enforcement actions and drug shortage issues more closely to avoid administrative requirements that cause interruptions.

“We’re not sure how much of that is going on recently because we’ve seen more and more shortages in the industry. We think that maybe some of those coordination issues can be worked on,” said Joshua Gordon, vice president and general manager of specialty pharmaceuticals at Hospira, the largest producer of specialty generic sterile injectables.

Shortages of pre-loaded epinephrine syringes and propofol, for example, occurred when suppliers dropped out just as the FDA was demanding additional documentation, he said.

“They are very focused on taking quick and aggressive action,” Gordon said. “We applaud the agency’s role in assuring quality, but it can slow things down significantly.”

FDA officials dispute that greater government oversight is a major factor, saying manufacturing problems were the cause of most shortages.

“There has not been a significant increase in domestic enforcement actions (seizure or injunction) for this class of products in recent years,” Jensen wrote in an e-mail.

‘Too many … will die’

Whatever the causes, many of the affected drugs are mainstays of medical care, such as the potent painkiller morphine, norepinephrine, which is commonly used in emergency rooms, and electrolytes, which are often given to patients in intensive care.

But shortages have been reported in many categories of drugs, including antibiotics, and drugs central to the treatment of many cancers, forcing oncologists to delay or alter carefully timed chemotherapy regimens.

“We have heard some horror stories where patients are really begging to get the drugs from other sources and where practices or institutions are forced to kind of triage patients and save the drugs for those — quote — most curable, where they have the best prognosis and using substitutes where there isn’t a cure possibility,” Michael Link, president-elect of the American Society of Clinical Oncology.

The drug cytarabine has caused the most concern and gotten the most attention because it is highly effective for treating several forms of leukemia and lymphoma but must be administered as quickly as possible, especially to patients with acute myeloid leukemia.

“With this drug they can be cured and without this drug too many of them will certainly die. That’s the simplest way to put it,” said Deborah Banker, vice president for research communication at the Leukemia & Lymphoma Society. “The disease progresses so rapidly that untreated patients can sadly die within days. There is no time for delay and no certainty of a good outcome if you can’t get a full dose.”
Many hospitals are running low, and some have run out completely. That has required many facilities to ration the drug, giving priority to those who need it most urgently.

“It’s so unbelievable,” said Mary Collins, 57, of La Crosse, Wis., whose husband, Michael, 66, had problems obtaining cytarabine to fight lymphoma. “A cancer diagnosis is a long, very, very stressful circumstance. And then to learn that a particular drug is no longer available to you and that there seems to be no formalized mechanism in place to correct it just makes it worse.”

Cytarabine’s scarcity was caused by hitches that two out of the three manufacturers hit in obtaining raw materials, as well as the discovery of crystals in some shipments.

The third manufacturer was unable to make up for the shortfall. Some of the problems have been resolved, however, and the FDA is working on importing the drug.

The shortages are forcing hospital pharmacists to juggle supplies and hunt for new sources. Many hospitals, including several contacted in the Washington area, say they are usually able to patch together solutions.

But some resort to paying inflated prices or buying from unfamiliar suppliers, increasing the risk they may be getting counterfeits.

“When it becomes clear that some drug may be in short supply or going into a shortage, what happens is sometimes there are unsavory folks — small distributors — who buy up whatever is left and sell it back at exorbitant prices,” said Roslyne Shulman, director of policy development for the American Hospital Association.

‘Panic in the pharmacy’

When shortages occur, physicians turn to less optimal alternatives or find out too late that the drug they need is unavailable. Mark Warner, president of the American Society of Anesthesiologists, described two calamities that occurred in the past year because of shortages. In one, a 16-year-old boy suffered brain damage because doctors did not have one muscle relaxer needed to treat a complication from jaw surgery.

In another, a middle-aged woman was left in a permanent vegetative state because doctors did not have the drug epinephrine after she experienced complications from heart surgery.

“These are tragic cases,” Warner said. “It’s one of those things most anesthesiologists in the country think about when they are driving to work every day. We don’t know where the shortages are and they come on very quickly.”

Nurses and doctors responding to emergencies, meanwhile, are losing precious minutes when they must work with unfamiliar substitutes or recalculate dosages, increasing the chances of overdosing or under-dosing patients. One of the biggest problems is a shortage of syringes pre-filled with precisely measured doses.

“Grabbing the right medication out of a crash cart that’s already in a syringe is a big advantage over having to get out the syringe, get out the needle, get the medication and get the measurement right,” said Angela Gardner, an emergency medicine physician at the University of Texas Southwestern Medical Center in Dallas and immediate past president of the American College of Emergency Physicians.
“Those minutes are lives.”

Many hospitals are recalibrating electronic medication delivery systems or preparing the correct doses ahead of time, especially for the emergency room, to minimize mistakes.

“We’ve been extremely fortunate using strategies in cooperation with our medical staff,” said Jay Barbaccia, head pharmacist at the Washington Hospital Center. “We’ve had a lot of panic and inconvenience but minimal, if any, impact on our ability to provide care. It makes my life miserable — the panic is in the pharmacy when we’re scrambling around to find alternatives.”

Nevertheless, a long list of errors and near-misses have been reported, including incidents in which patients required emergency care to save them.

At least two patients reportedly died from overdoses of hydromorphone they received because of a morphine shortage.

At least 19 patients were sickened and nine died in Alabama this year after being infused with a solution through their feeding tubes that was apparently contaminated with bacteria by a pharmacy using an unfamiliar ingredient because of a shortage.

The shortage occurred because the manufacturer had trouble getting the product’s packaging.

“It’s horrible. It’s something that shouldn’t have happened,” said Donald J. Mottern of Alabaster, Ala., whose 71-year-old mother was one of the victims. “We lost the matriarch of our family. The loss to our family has left each of us very hollow.”

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DeGette on drug shortages: ‘It’s a problem that’s crept up on us.’

By Sarah Kliff, Published: August 22

The number of drug shortages in the United States has tripled since 2005, hitting treatments for rare cancers particularly hard. The shortages have federal officials “scrambling” to find a remedy, the New York Times reported over the weekend. Solutions could range from a national drug stockpile to an overhaul of how we price rare drugs. Rep. Diana DeGette (D-Colo.) has been a congressional leader on the issue, introducing a bill in June that would require drug companies to notify the FDA of impending shortages. The bill, introduced with Rep. Tom Rooney (R-Fla.), is a companion to a Senate proposal from Sen. Amy Klobuchar (D-Minn.)

I reached Rep. DeGette in this afternoon in Denver, part of her home district, to discuss why drug shortages have spiked and what Congress can - and can’t - do about it. What follows is a lightly edited transcript of our conversation.

Sarah Kliff: I was hoping you could start by walking me through the problem we’re facing with drug shortages right now and what can be done about it.

Rep. Diana DeGette: It’s a problem that’s crept up on us. All of a sudden we started hearing from hospitals and physicians that they were having drug shortages with a wide range of drugs, but in particular, drugs that are used to treat a narrow niche of childhood cancers. These providers weren’t finding out about the drug shortage until middle of treatment protocol, when suddenly they couldn’t get it anymore.
S.K.: FDA statistics show that the number of drug shortages has tripled recently. Do we know why that’s happening?

D.D.: It’s one of those situations where there seem to be a variety of factors [and] difficult to pinpoint what has caused drug shortages...I’ve read some of the different articles with drug companies. Some [explanations] sound like they might be reasonable but others sound like excuses.

S.K.: What sounds like an excuse to you?

D.D.: I can’t really say globally. It’s hard to put a finger on it. They say “well, there’s an increased demand” but there can’t possibly be an increased demand for all drugs. It might increase for some but not others. Some say it’s a cost issue, but I haven’t seen the data to support that. I don’t think there’s one clear answer and I don’t even know if the drug companies could give you clear data at this point.

As we’ve gone forward with our legislation we have worked with pharmaceutical companies and have worked with [the biotech industry’s association]. We don’t want to be punitive. We want to help them identify when they might have a drug shortage and help the providers find alternatives.

S.K.: Your legislation would require drug companies to report impending shortages to the FDA. How would that help address the problem?

D.D.: Right now, we don’t have any kind of early warning system. What would happen [with the new legislation] would be pharmaceutical companies anticipating a shortage would have to notify the FDA, and the FDA would notify providers. The intent is to allow the providers to find an other source of the drug or undertake a different course of treatment.

S.K.: I understand how that helps providers, but would that that reduce the number of shortages?

D.D.: The hope is ultimately that having an early warning system will allow drug companies to better identify where they need to beef up production.

S.K.: Do you get a sense that this legislation has potential to move in this Congress?

D.D.: The good news is it’s bicameral and bipartisan. This is a piece of legislation that might have a good chance. I’ve already spoken with both Chairman [Cliff Stearns (R-Fla.), chair of the Energy and Commerce Committee’s Investigations and Oversight Subcommittee] and [Rep. Fred Upton, chairman of the Energy and Commerce Committee] about the potential of doing hearings. It hadn’t been particularly on Cliff’s radar but Congressman Rooney, who is my Republican cosponsor, had told him about how it was a terrible problem for Florida hospitals.

S.K.: What do you think about some of the non-legislative proposals out there? There’s been a decent amount of discussion of creating a national drug stockpile to combat shortages.

D.D.: Frankly, I’ve been focused on this. The problem with doing a national stockpile is there are so many types of drugs and they’re changing all the time. I think it might be worth looking into, especially for drugs that are difficult to manufacture. But it’s not like a petroleum reserve. There are so many thousands, maybe millions of drugs, and they’re continually changing.

Related content:

Enzyme Drug Is in Short Supply

By ANDREW POLLACK

Genzyme’s flagship drug, Cerezyme, is in short supply again.

In a letter to health care providers sent Tuesday, Genzyme said adult patients would probably receive only one dose a month instead of the usual two, from October through January. The drug, which costs $200,000 a year or more, treats Gaucher disease, a rare inherited enzyme deficiency.

Genzyme attributed the new shortfall to “a temporary decrease in Cerezyme yields, combined with changes to our product release processes and procedures that lengthen the overall time it takes to release Cerezyme.” A spokeswoman said the yield has since been restored to normal.

The company was forced to temporarily close its main factory, in Boston’s Allston neighborhood, in June, 2009 because of viral contamination. It did not restore full supplies of Cerezyme until January of this year, much later than it initially expected.

The sales shortfall left Genzyme vulnerable to a takeover by Sanofi, which was completed earlier this year.

Patients with Gaucher disease, however, have it better than those with Fabry disease, another rare enzyme deficiency, who depend on another Genzyme drug, Fabrazyme.

While there is an alternative to Cerezyme on the market – Shire’s Vpriv – there is none yet for Fabrazyme in the United States. And supplies of Fabrazyme have been tighter than for Cerezyme. Fabrazyme doses for August were not delivered at all to American patients.

Some people with Fabry disease have suffered heart or kidney problems and one or more may have even died because of the shortage.

Fabry patients — there are probably about 1,000 in the United States being treated with Fabrazyme — have become more aggressive.

The National Fabry Disease Foundation wrote a letter to the Food and Drug Administration on Aug. 30 asking, among other things, that some Cerezyme production be converted to Fabrazyme and that the F.D.A. quickly approve Shire’s Replagal, a drug for Fabry disease that is approved in Europe.
About a dozen patients have sued Genzyme seeking damages. The suit also names Mount Sinai School of Medicine, which licensed patent rights related to Fabrazyme to Genzyme.

Some Fabry patients also tried to get the National Institutes of Health, which paid for some of the research at Mount Sinai, to exercise its “march-in” rights on the patents and allow another manufacturer to produce the drug. The N.I.H. declined to do this.

Genzyme is building a new factory in Framingham, Mass., that will produce Fabrazyme – and thereby also allow the Allston factory to concentrate on Cerezyme and increase production of that drug. But the expected start of shipments from the new factory has also been delayed until the first quarter of next year, rather than late this year.
In this Aug. 29, 2011 photo, Erin Fox, manager of the Drug Information Service at the University of Utah Hospital in Salt Lake City, stands by a board listing drugs in short supply. At hospitals across the country, "scoring drugs" has taken on a new meaning. Hundreds admit buying medicines at exorbitant prices from "gray market" dealers taking advantage of, and possibly exacerbating, a record shortage of life-saving prescription medicines. (AP Photo/Jim Urquhart)

TRENTON, N.J. (AP) — A drug for dangerously high blood pressure, normally priced at $25.90 per dose, offered to hospitals for $1,200. Fifteen deaths in 15 months blamed on shortages of life-saving medications.

A growing crisis in the availability of drugs for chemotherapy, infections and other serious ailments is endangering patients and forcing hospitals to buy from secondary suppliers at huge markups because they can't get the medications any other way.

An Associated Press review of industry reports and interviews with nearly two dozen experts found the shortages — mainly of injected generic drugs that ordinarily are cheap — have delayed surgeries and cancer treatments, left patients in unnecessary pain and caused hospitals to give less effective treatments. That's resulted in complications and longer hospital stays.

Just over half of the 549 U.S. hospitals responding to a survey this summer by the Institute for Safe Medication
Pfizer, pharmacy group warn on counterfeit drugs
Sep. 29, 2011

Practices, a patient safety group, said they had purchased one or more prescription drugs from so-called "gray market vendors" — companies other than their normal wholesalers.

Most also said they've had to do so more often of late, and 7 percent reported side effects or other problems with those drugs.

Hospital pharmacists "are really looking at this as a crisis. They are scrambling to find drugs," said Joseph Hill of the American Society of Health-System Pharmacists.

At a hearing Friday before the health subcommittee of the House Energy and Commerce Committee, hospital officials and other experts testified that the worsening shortages are preventing them from giving many patients the best care and are driving up costs.

"Considering the nation's budget crisis and our skyrocketing health care bill, these markups are nothing more than profiteering at the expense of patients and providers who are struggling to afford vital medicines," said Mike Alkire, chief operating officer of Premier Healthcare Alliance, a group that helps U.S. hospitals and other health providers improve their patient care and finances.

The shortages could cost hospitals at least $415 million a year, he said, citing data from health care providers across the nation. So far, hospitals have been absorbing the extra costs, but
they’ll soon have to start passing them on to insurers and patients, according to the American Hospital Association.

The scarcity of mainstay cancer drugs is not only hurting patients but is halting or disrupting clinical studies of potential new treatments, said Dr. Robert S. DiPaola, director of the Cancer Institute of New Jersey.

"The drug shortages of today can have a ripple effect on the availability of new drugs and treatment combinations tomorrow," he told the committee.

On Monday, the Food and Drug Administration is holding a meeting with medical and consumer groups, researchers and industry representatives to discuss the shortages and strategies to fight them.

The FDA says the primary cause of the shortages is production shutdowns because of manufacturing problems, such as contamination and metal particles that get into medicine.

Other reasons include theft of prescription drugs from warehouses or during shipment, as well as the "gray market" vendors who buy scarce drugs from small regional wholesalers, pharmacies or other sources and then sell them to hospitals at many times the normal price. These sellers may not be licensed, authorized distributors.

In addition, many companies have stopped making generic injected drugs because the profit margins are slim. Producing them is far more expensive than stamping out pills, and it takes about three weeks to produce a batch. Making things worse, companies don't have to notify customers or the FDA that they've stopped making a medicine. That means neither FDA nor competitors can fill the gap in time.

Only a half-dozen companies make the vast majority of injected generics. Even if other companies wanted to begin making a drug in short supply, they're discouraged by the lengthy, expensive process of setting up new manufacturing lines and getting FDA approval.

Hospitals that buy scarce medicines from the "gray market" are taking a gamble.

The drugs may be stolen and hospitals can't always tell whether a medicine was properly refrigerated — as required for many injectable drugs — or whether it's past the expiration date, said Michael R. Cohen, a pharmacist and president of the institute. The active ingredient might have degraded and the drug might not work well or could even harm the patient, he said.

Cohen attributes at least 15 recent deaths to drug shortages, either because the right drug wasn't available or because of dosing errors or other problems in administering or preparing alternative medications. But many deaths and injuries go unreported, he said.

In the worst known case, Alabama's public health department this spring reported nine deaths and 10 patients harmed due to bacterial contamination of a hand-mixed batch of liquid nutrition given via feeding tubes because the sterile pre-mixed liquid wasn't available.
So far this year, 210 drugs have been added to the list of those in short supply, one less than the total for all of last year, according to the University of Utah Drug Information Service, which tracks the shortages. That's triple the roughly 70 a year from 2003 to 2006, when shortages began to climb steadily.

"The shortages aren't resolving. They're piling up on top of existing ones," said Erin Fox, a pharmacist who manages the service. She said at least 55 drugs from shortages before this year are still unavailable or scarce.

The average price markup on drugs sold by secondary distributors was 650 percent, according to an Aug. 16 report by the Premier Healthcare Alliance. The figure is based on an analysis of 636 unsolicited sales offers that were faxed and emailed to hospitals from secondary distributors in April and May.

Virtually every offer was for at least double the normal price, the survey found. The drugs with the highest markups were for critically ill patients needing anesthesia or other medicines for surgery or for emergency care, cancer, infectious diseases and pain management.

In an extreme case, one vendor was offering a generic beta blocker for dangerously high blood pressure, normally priced at $25.90 per dose, for $1,200.

The FDA says it must uphold quality standards but also works hard to prevent shortages. "When FDA detects a contaminant, whether it be shards of glass or metal particles or an infectious agent, we have to take action to protect the public," said Dr. Peter Lurie, a senior adviser in the FDA commissioner's office.

When such problems force a company to shut down production, the FDA urges other manufacturers to boost their output and expedites any approvals needed, said Valerie Jensen, associate director of the agency's drug shortage program. When raw materials used to make drugs are in short supply, the FDA tries to find new sources.

The agency averted 38 shortages last year, Jensen added. Another 99 have been prevented so far this year, Howard K. Koh, assistant secretary for health in the Department of Health and Human Services, told the committee.

Legislation pending in the House and Senate would increase penalties for drug thefts from warehouses and tractor-trailers. Another proposal, which has bipartisan support, would require drug manufacturers anticipating a shortage to immediately notify the FDA.

The pitches hospitals get from secondary distributors generally say they have small batches of specific drugs that are hard or impossible to find. "Are you enjoying this crazy 'roller coaster ride' of pharmaceutical shortages? ... I utilize over 60 vendors to locate and procure needed pharmaceuticals to assist when you have shortage needs," one reads.
Several distributors who sent hospitals solicitations for scarce drugs didn't return calls from the AP. One representative said he wasn't authorized to discuss the issue.

Another company, Novis Pharmaceuticals, defended the higher prices, saying secondary distributors have to charge far more because they don’t get the big rebates manufacturers give primary distributors. They also have high costs to locate and transport batches of scarce drugs, although the company, which mainly distributes blood plasma, would not disclose its profit margin.

It's illegal for companies to collude to create a medicine shortage and raise prices, and there's no evidence of that. There's no federal law against price-gouging on prescription drugs, according to the FDA, but it does urge pharmacists to report cases to its Office of Criminal Investigation. An agency spokeswoman said she could not discuss whether any cases are being investigated.

The top three wholesalers say they try to alleviate problems by working with drug manufacturers, updating hospitals on shortages and rationing scarce supplies by giving their regular hospital customers a portion of their normal order. McKesson Corp. and Cardinal Health Inc. say they halt sales to any smaller distributors found to be diverting drugs or otherwise breaking rules. AmerisourceBergen Corp. does background checks on customers.

The hospital association and other groups urge hospitals not to buy from unaccredited vendors, to insist on documentation of the drug's source if they must, and to report price gouging to state authorities. But only three states — Kentucky, Maine and Texas — have price-gouging laws that specifically cover medicines.

"Something has to be done here," said pharmacist Michael O'Neal, head of drug procurement for Vanderbilt University Medical Center in Nashville, which has had to purchase medicines from secondary suppliers about 70 times over the past two years.

"This is unethical," he said. "We're talking about people's lives."

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Institute for Safe Medication Practices consumer site: http://www.consumermedsafety.org/
WASHINGTON—Cancer-drug shortages in the U.S. have caused hundreds of clinical trials to be stopped or delayed, threatening progress on new treatments, a top health official told Congress Friday.

Howard Koh, assistant secretary of health for the Department of Health and Human Services, said drug shortages are "dramatically affecting clinical trials." Dr. Koh testified Friday before the House Energy and Commerce Subcommittee on Health during a hearing on drug shortages.

"The inability to obtain adequate supplies of these cancer drugs for research has resulted in promising clinical trials being suspended indefinitely and patient enrollment being abruptly halted," Dr. Koh said in written testimony. More than 300 clinical studies being paid for by the National Cancer Institute involve a drug that is in short supply, according to the testimony.

While the drug shortages continue to be a problem for patients, doctors are concerned the delay in cancer clinical trials will affect new and future treatments.

"The next generation of cancer therapy is driven by today's clinical trials," said Robert DiPaola, director of the Cancer Institute of New Jersey, in testimony prepared for Friday's hearing.

He explained that experimental cancer drugs are often added to existing cancer treatments in clinical studies in order to test the new drug.

"During a clinical trial, a shortage of only a few weeks in an existing drug might mean delays of years for the development of new drugs," Dr. DiPaola said.

The FDA reported a record 178 drug shortages in 2010, and Dr. Koh said there is "an even greater" number of shortages this year.

Most of the shortages involve older drugs administered by injection or intravenously. Along with cancer drugs, they also include antibiotics to treat infections and nutritional drugs for patients who can't eat. They are mainly generic, not highly profitable and are now made by only one or two companies. Teva Pharmaceutical Industries Ltd. and Hospira Inc. are two of the bigger producers of generic drugs.

The shortages are growing more severe, in part because of industry consolidation and manufacturing problems in the past year. When one company runs into a manufacturing problem with a product or decides to quit making a drug, competing companies can't quickly fill the void. In April, Teva reopened a California plant that it had shut down voluntarily for about a year, in part to retool to meet Food and Drug Administration manufacturing guidelines.

The cancer-drug shortage involves chemotherapy drugs that were developed decades ago. They are still the backbone of cancer treatment as newer drugs are typically added to chemotherapy. Some of the drugs that have
been in short supply include doxorubicin, often used to treat breast cancer, and cytarabine, a leukemia drug that has no substitute.

The shortages of key cancer and other critical-care drugs used in emergency rooms and intensive-care units have caused the majority of hospitals to ration drugs this year, according to doctors and industry surveys. Hospitals and clinics have reported delaying cancer treatment or switching to an alternative drug that might not be as effective.

Write to Jennifer Corbett Dooren at jennifer.corbett-dooren@dowjones.com
TESTIMONY OF

DR. HOWARD K. KOH

ASSISTANT SECRETARY OF HEALTH

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

“EXAMINING THE INCREASE IN DRUG SHORTAGES”

SUBCOMMITTEE ON HEALTH

ENERGY & COMMERCE COMMITTEE

U.S. HOUSE OF REPRESENTATIVES

SEPTEMBER 23, 2011
Good Morning, Chairman Pitts, Ranking Member Pallone and distinguished members of the Committee. I am Dr. Howard K. Koh, the Assistant Secretary for Health at the United States Department of Health and Human Services. Thank you for inviting me here today to discuss the growing problem of drug shortages. This is a very troubling situation, and one that the Department, and the Secretary herself, take very seriously. The increasing number of drug shortages has the potential to have an impact on our entire health care system. But, as we discuss and debate this problem, we should bear in mind that the people affected most by these shortages are patients and their families. Although many of the root causes of drug shortages lie outside our purview, we at the Department are committed to confronting this problem, and are eager to work with others to help find substantive long-term, as well as short-term, solutions to the challenge of drug shortages.

**OVERVIEW: THE SCOPE OF THE DRUG SHORTAGE PROBLEM AND POTENTIAL UNDERLYING CAUSES**

The Food and Drug Administration (FDA) defines a drug shortage 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.

According to FDA’s Center for Drug Evaluation and Research (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. This trend has continued into 2011 with an even greater number of drug shortages. Although shortages can occur with any drug, shortages of generic sterile injectables currently make up a large and increasing share of these shortages, despite the fact that generic sterile injectable drugs comprise a small percentage of the overall prescription drug market. These include critical products such as oncology drugs, anesthetics, parenteral (intravenous) nutrition drugs, and many drugs used in emergency rooms. Oncology drugs account for 28 percent of shortages followed by antibiotics at 13 percent. During 2010 and 2011, one hundred eighteen shortages (93 percent) involved “medically-necessary” drugs and 52 of the shortages (41 percent) were both medically necessary and sole source drugs.
Figure 1 above shows the trend over the past six years in the total number of drug shortages as reported to the FDA, and the relative number of shortages attributable to sterile injectables. In 2010, 74 percent of the shortages involved older sterile injectables, and approximately 54 percent of these were due to product quality issues such as particulates, microbial contamination, impurities and stability changes resulting in crystallization. Approximately 21 percent of the shortages were due to production delays and capacity issues and 11 percent were due to manufacturer discontinuations, usually for business reasons. Some of the other trends that were seen to a lesser extent were raw material issues, increases in demand due to another shortage, loss of a manufacturing site and component problems.

There is no single reason that drug shortages occur. HHS has developed a number of hypotheses for the root causes of drug shortages, some of which I will discuss here. Ultimately, in any given drug shortage many factors are involved and underlying causes may operate alone or in combination to result in an individual shortage. These include, but are not limited to industry consolidation, shortages of underlying raw materials, changes to inventory and distribution practices, difficulty in producing a given drug, quality and manufacturing problems, production
delays, discontinuations for business reasons, and unanticipated increased demand. The majority of drug shortages occur with generic drugs (often ones that have been on the market for decades). The profit margins on generic drugs are quite small compared with brand name drugs, and over time, some companies may choose to discontinue production of generic drugs due to lack of profitability.

Classical economic theory suggests that a drug shortage should be corrected by the laws of supply and demand. However, drug markets do not operate according to these principles in every instance. A declining supply of a drug does not necessarily result in a price increase, and increased drug production to fill the shortage gap. Part of the reason for this is that the vast majority of drug prices are established in contracts and not subject to short-term fluctuations. Additionally, pharmacy benefit managers and other drug purchasers are ordering such large quantities of drugs, that they have the power to put downward pressure on drug prices. Finally, when a shortage does occur, the ability to expand revenues by either expanding sales or raising the drug price may be insufficient for existing producers to make the necessary capital investment to expand production, or for new companies to enter the market.

Industry consolidation has also contributed to the drug shortage problem. A majority of the injectable drugs classified as experiencing a shortage are produced by only seven manufacturers. Generally, when a firm has a manufacturing or quality problem they will often voluntarily suspend production so they can identify and address the root cause of the product quality problem. Some of these quality issues are complex and firms need to take significant time to correct the underlying cause of the problem. Such is the case with shortages of older sterile injectables, which entail a much more complex manufacturing process than solid dosage forms. Consolidation has led to fewer firms making these drugs and the firms have a limited number of manufacturing lines. When one firm experiences a quality problem which results in production holds or slowdowns, the remaining firms are usually not able to make up the shortfall due to capacity constraints.

Some reports in the media about drug shortages have focused on the lack of raw materials necessary to manufacture certain classes of drugs that are currently experiencing shortages. In
the past, some shortages of non-controlled substance drugs have been due to shortages of underlying raw materials, particularly of the active pharmaceutical ingredient (API) for a specific drug. However, this does not appear to be a significant contributor to the current shortages of sterile injectables. In fact, in both 2010 and 2011, unavailable API was cited by drug manufacturers as a factor in less than 10 percent of shortages.

Changes in inventory and distribution practices by manufacturers and distributors can alter the availability of drugs, often creating short-term shortages. Better technology for supply management may lead manufacturers or distributors to reduce the size of their inventories. This minimizes product loss from short expiration times and carrying costs. However, smaller inventories mean that there are fewer reserves available to respond in the event of production problems. Overall, it does appear that inventories are smaller due to a shift to “just in time” production, and that leaves little leeway for even small changes in supply.

Even if long-term manufacturing capacity is sufficient to meet demand, the difficulty of producing some types of drugs and drug manufacturing problems may lead to sporadic shortages in the short-term. As previously noted, there has been an increasing number of serious manufacturing and quality problems with sterile injectable drugs. These drugs are complex to manufacture because special techniques and processes are used to maintain sterility so the product is not contaminated. When quality or manufacturing problems are discovered by the company or healthcare providers and reported to FDA or are found by FDA upon inspection, FDA works closely with the company to address any risks involved to help prevent harm to patients. FDA also considers the impact a shortage would have on patient care and access before taking any enforcement action.

**FDA ACTIONS TO PREVENT OR ALLEVIATE 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. Shortages of these drugs not only have an impact upon clinical decision-making, but they could also significantly affect patient outcomes. For example, a shortage of generic propofol led clinicians to substitute etomidate, resulting in eight suspected cases of phlebitis (inflammation in a vein) in a single hospital system. Other drugs that have experienced shortages, such as the cancer drug cytarabine, are important drugs not only because they treat a critical disease, but also because they lack an effective alternative. FDA’s awareness of these consequences drives efforts to prevent and resolve shortages as soon as possible.

In 1999, FDA formed the Drug Shortage Program (DSP) within CDER in an effort to begin monitoring and mitigating the impact of potential and actual drug shortages. DSP facilitates the prevention and resolution of shortage issues by collaborating with FDA experts, industry and other external stakeholders. In addition, DSP provides information about drug shortages to the public, healthcare professional organizations, patient groups and other stakeholders.

When FDA becomes aware of a potential drug shortage, the Agency works collaboratively with the affected firm(s) to return the product to its usual market availability as quickly and as safely as possible while helping prevent any harm to patients. Although FDA cannot require firms to continue production of a product or increase production in response to a shortage, it does encourage other firms that make the drug to ramp up production if they are willing to do so. FDA also expedites the review of submissions from manufacturers which may include requests to extend the expiration date of products, increase capacity, use a new raw material source, license new manufacturers, and permit changes in product specifications. For manufacturing and quality problems, FDA works with the firm to address the issues. Problems that require intervention may pose very low risk (e.g. wrong expiration date on package) or high risk (particulate in product or sterility issues) to patients. In addition, FDA may also use flexibility and discretion to alleviate shortages while mitigating any significant risk to patients.

Through the actions of the FDA working with the manufacturer, shortages are often mitigated. One notable example involves the treatment for leukemia. In this recent case there was a shortage of the drug cytarabine (used to treat certain types of leukemia) which resulted from
crystal formation in the vials, FDA worked with the manufacturer and found that if the vials were warmed the crystals would dissolve and the danger to patients was mitigated. The manufacturer was then able to ship the vials with a letter to healthcare professionals notifying them to inspect for crystal formation and if present, to warm the vials to dissolve crystals to ensure patient safety.

In another case, FDA was able to mitigate a shortage by allowing the use of a filter to safely remove foreign particles contained within vials of injectable drugs, averting the obvious risk to patients of having metal shavings or other particulate matter injected into their veins. If the firm can provide data to FDA showing that the particles can be safely filtered out of the drug without impacting the drug's effectiveness, FDA can prevent a shortage using enforcement discretion to allow the drug to be shipped with the necessary filter until the firm is able to correct the problem for future production. A recent example was sodium phosphate, which is a medically necessary electrolyte needed for IV nutrition in critically ill patients. The firm found particles in the drug product, which is a significant safety concern. The manufacturer was able to generate data showing the particles could successfully be removed with a filter and the drug was shipped with a letter to notify healthcare professionals that the filter needed to be used with the drug. This allowed the drug to be available for patients while the firm addressed the particulate issue for future production and it represents a success story in the collaboration between FDA and companies in addressing drug shortages.

FDA can also use its regulatory enforcement discretion with regard to the temporary import of non-FDA approved versions of critical drugs when a shortage cannot be resolved immediately. However, there are several factors that limit the applicability of this option. The product may already be in shortage abroad, and importation to the United States could exacerbate the shortage. In addition, while there may be foreign suppliers that possess or have access to a particular drug, these suppliers are not necessarily FDA-approved and may need to be inspected and their drug labels evaluated before a product can be imported into the United States. Once a foreign firm is identified as willing and able to supply the drug, FDA exercises enforcement discretion for the temporary import of a foreign drug after ensuring there are no significant safety or efficacy risks for U.S. patients. For example, FDA must ensure that drugs imported from
abroad are manufactured in a facility that meets FDA quality standards. FDA will then post
information about the imported drug on the drug shortage website. FDA has done this for the
import of a number of critical drugs during a shortage, including: propofol, Foscarnet, ethiodol,
thiotepa, norepinephrine, Xeloda, leucovorin and levoleucovorin. All of this is necessary to
ensure that the non-FDA approved version is safe for U.S. patients.

Currently, companies voluntarily provide much of the drug shortage information posted on
FDA’s website. FDA staff work very closely with firms to address the issues that led to the
shortages and work with manufacturers to fill the market void. The Agency also works to
communicate information about shortages to the public and stakeholders based on information
provided by manufacturers.

As noted above, FDA does not have the statutory authority to require a firm to continue
production if they decide to stop, nor are firms required to increase production in response to a
shortage. Firms are not required to provide notice of discontinuations (except for some sole-
source medically necessary products), nor does FDA have explicit authority to impose a penalty
on firms that do not submit required reports of discontinuations to FDA. Notification is
important for all discontinuations or disruptions that could lead to shortage issues and not just for
sole source drug products. It is helpful when manufactures report to FDA any disruption or
discontinuation that could lead to potential shortages as soon as it is known. Early notification
leads to a better chance of timely resolution. Although FDA does not have explicit authority to
require a firm to notify the Agency of shortages, such authority may enable FDA to help prevent
or mitigate more potential drug shortages.

In 2010 FDA was able to prevent 38 drug shortages i due to early voluntary notification from
firms and thus far in 2011, FDA has already prevented 99 drug shortages.

THE IMPACT OF DRUG SHORTAGES ON MEDICAL RESEARCH

The Department is concerned about the market impact of drug shortages on patients and their
health care providers. Drug shortages can result in operational difficulty and strain for medical
studies and clinical trials sponsored by the National Institutes of Health (NIH) within HHS. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. NIH conducts approximately 630 intramural clinical trials on its Bethesda, Maryland campus and extramurally funds about 5,100 clinical trials at research institutions across the country. As I outline below, drug shortages create significant difficulty and disruptions for medical researchers and the patients they treat.

**National Cancer Institute (NCI)**

Shortages of cancer drugs are having an impact on studies sponsored by the NIH National Cancer Institute (NCI). While there have been periodic shortages of different cancer drugs over the past several years, nothing to date has approached the scale of the current shortages of chemotherapy drugs. We are now facing shortages of several generic cancer drugs that are widely used in treatment and are essential for clinical research. These drugs include standard therapies for the treatment of lung, breast, ovarian, testicular, and colorectal cancers, as well as several types of lymphomas and leukemias.

Many of the cancer drugs in short supply – including doxorubicin, daunorubicin, 5-FU, paclitaxel, bleomycin, and cytarabine – are mainstays of the anti-cancer arsenal, and were largely developed through federally-funded research begun 20, 30, even 40 years ago. They are still essential to treatment and research: the NCI currently is sponsoring 96 clinical trials that include combination or control arm drug regimens that require a supply of doxorubicin; 13 trials that require daunorubicin; 69 trials that require 5-FU; 108 that require paclitaxel; 8 that require bleomycin, and 55 that require cytarabine.\(^1\) Taken together, these studies represent thousands of patients, as well as a significant federal investment in clinical trials research. The inability to obtain adequate supplies of these cancer drugs for research has resulted in promising clinical trials being suspended indefinitely; patient enrollment being abruptly halted; and trials being delayed while alternative treatment regimens are developed. In some cases, patients are either foregoing treatment entirely, or receiving suboptimal therapies.
Drug shortages have also been a major issue for the NIAID-supported AIDS Clinical Trial for its randomized trial comparing three different regimens of chemotherapy, each used in combination with compatible antiretroviral therapy, for the treatment of advanced AIDS-related Kaposi Sarcoma. Due to shortages of liposomal doxorubicin (Doxil), and generic vincristine and bleomycin, the trial will likely be on hold for at least a year. There is also a shortage of intravenous trimethoprim-sulfamethoxazole, the first-line antibiotic therapy used to treat *Pneumocystis carinii* infection, a potentially life-threatening condition in individuals with HIV/AIDS, affecting the care of patients enrolled in NIAID intramural research protocols.

**HHS Actions and Activities**

As noted above, FDA has been actively engaged in tracking shortages and using existing authorities and mechanisms to work with the industry to prevent shortages from occurring, or to mitigate their impact when they do occur. In 2010, 38 drug shortages were prevented through the actions of FDA collaborating with drug sponsors, and in 2011 99 drug shortages have been prevented.

However, drug shortages continue to be a pressing public health problem. The Department has taken a number of steps to determine the extent of the problem, and to identify the best course of action for addressing the drug shortage problem.

In July of this year, I convened a series of meetings with representatives from across the Department to find out more about what is at the root of shortages, and what steps could be taken within existing authorities to decrease the frequency of shortages in the future. At these meetings were HHS representatives from FDA, NCI, CDC, the office of the Assistant Secretary for Preparedness and Response, Assistant Secretary for Planning and Evaluation and the Centers for Medicare and Medicaid Services, among others. The initial discussions were heavily focused on gaining a better understanding of the situation as it currently exists, as well as brainstorming about possible solutions. These have been productive meetings and are ongoing. We continue to
look for ways to collaborate within the Department to combine our collective experience and expertise to find workable solutions.

All parties involved in the supply of drugs to Americans have a responsibility to make sure patients have access to the drugs they need. To gain this perspective, the Secretary and the Department have engaged important external stakeholders to hear their individual views on the issue of drug shortages. Earlier this month, the Secretary, along with other senior leaders in the Department, hosted a meeting with over a dozen representatives from pharmaceutical manufacturers, professional medical organizations, hospitals, insurance companies, group purchasing entities and patient advocacy organizations. This meeting gave us firsthand insight to the challenges stakeholders face, as well as provided us with ideas about possible opportunities for collaboration and further discussions with these organizations as we work to address shortages.

In addition, FDA will be hosting a public meeting to discuss drug shortages on September 26. This meeting is being held to gain additional insight about the causes and impact of drug shortages, and possible strategies for preventing or mitigating drug shortages from all interested parties, including: professional societies, patient advocates, industry, researchers, pharmacists and other healthcare professionals.

Following this public meeting and consideration of the various comments, FDA will release a report which reflects the important analysis of the problem and recommendations with respect to its role. Potential solutions are also being rigorously examined. One suggestion is a mechanism for manufacturers to report impending supply disruptions and discontinuation of drugs, which could help to curb drug shortages and improve the continuity of the drug supply. The sooner FDA learns of a drug shortage, the more effective it can be in helping to notify providers and minimizing the impact on patients.

Meanwhile, the FDA will continue its efforts to work with manufacturers to mitigate shortages. For example, FDA already expedites requests to qualify new manufacturing sites, new production lines or new raw material suppliers to avert drug shortages. HHS remains committed
to working with manufacturers, providers, patient advocates, and other stakeholders to help minimize drug shortages, protect patients, and identify solutions to this serious problem.

**CONCLUSION**

The Department is committed to addressing the important issue of drug shortages. It is our goal to continue a healthy and substantive dialog with all interested stakeholders, both internally and externally, as we seek a solution to the problem of drug shortages. This is a challenge that we must work collaboratively to solve. We also recognize the important role that you and other members of Congress play, and we welcome the opportunity to discuss this important topic with you both today, and moving forward.
S 296 IS

112th CONGRESS
1st Session

S. 296

To amend the Federal Food, Drug, and Cosmetic Act to provide the Food and Drug Administration with improved capacity to prevent drug shortages.

IN THE SENATE OF THE UNITED STATES

February 7, 2011

Ms. KLOBUCHAR (for herself and Mr. CASEY) introduced the following bill; which was read twice and referred to the Committee on Health, Education, Labor, and Pensions

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to provide the Food and Drug Administration with improved capacity to prevent drug shortages.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the `Preserving Access to Life-Saving Medications Act'.

SEC. 2. DRUG SHORTAGES.


(1) in the section heading, by striking `discontinuance of a life saving product' and inserting `discontinuance or interruption of the manufacture of a prescription drug'; and

(2) by amending subsection (a) to read as follows:

` (a) In General-
(1) DEFINITION- In this section, the terms `drug shortage' and `shortage', when used with respect to a drug, mean a period of time when the total supply of all versions of a drug available at the user level will not meet the current demand for the drug at the user level.

(2) NOTIFICATION- A manufacturer of a drug described in paragraph (3) shall notify the Secretary of a discontinuance, interruption, or other adjustment of the manufacture of the drug that would likely result in a shortage of such drug--

(A) in the case of a discontinuance or planned interruption or adjustment, at least 6 months prior to the date of such discontinuance or planned interruption or adjustment; and

(B) in the case of any other interruption or adjustment, as soon as practicable after becoming aware of such interruption or adjustment.

(3) DRUGS DESCRIBED- A drug described in this paragraph is a drug--

(A) for which an application has been approved under section 505 (b) or 505(j);

(B) that is described in section 503(b)(1); and

(C) that is not a product that was originally derived from human tissue and was replaced by a recombinant product.

(4) TYPES OF ADJUSTMENTS- An adjustment for which a manufacturer shall submit a notification under paragraph (2) includes--

(A) adjustments related to the supply of raw materials, including active pharmaceutical ingredients;

(B) adjustments to production capabilities;

(C) business decisions that may affect the manufacture of the drug, such as mergers, discontinuations, and a change in production output; and

(D) other adjustments as determined appropriate by the Secretary.

(5) MODIFICATION OF TIME FRAMES- The Secretary may adjust the required time frame under paragraph (2) as determined appropriate by the Secretary based on--

(A) the type of interruption or adjustment at issue; and
(B) any other factor, as determined by the Secretary.

(6) ENFORCEMENT- Not later than 180 days after the date of enactment of this section, the Secretary shall promulgate regulations establishing a schedule of civil monetary penalties for failure to submit a notification as required under this subsection.

(b) Confidentiality of Information- Section 506C(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356c(c)) is amended to read as follows:

(c) Confidentiality of Information- The Secretary shall ensure the confidentiality of proprietary information submitted in a notification under subsection (a).

(c) Public Notification- Section 506C of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356c) is amended by adding at the end the following:

(d) Public Notification-

(1) NOTIFICATION OF SHORTAGES- The Secretary shall publish information on the types of adjustments for which a notification is required under subsection (a)(4) and on actual drug shortages on the Internet Web site of the Food and Drug Administration and, to the maximum extent practicable, distribute such information to appropriate health care provider and patient organizations.

(2) IDENTIFICATION AND NOTIFICATION OF DRUGS VULNERABLE TO DRUG SHORTAGE-

(A) IN GENERAL- The Secretary shall implement evidence-based criteria for identifying drugs that may be vulnerable to a drug shortage. Such criteria shall be based on--

(i) the number of manufacturers of the drug;

(ii) the sources of raw material or active pharmaceutical ingredients;

(iii) the supply chain characteristics, such as production complexities; and

(iv) the availability of therapeutic alternatives.

(B) NOTIFICATION- If the Secretary determines using the criteria under subparagraph (A) that a drug may be vulnerable to a drug shortage, the Secretary shall notify the manufacturer of the drug of such determination and of the collaboration described under paragraph (3).
CONTINUITY OF OPERATIONS PLANS- The Secretary shall collaborate with manufacturers of drugs identified pursuant to paragraph (2) to establish and improve continuity of operations plans with respect to medically necessary drugs, as defined by the Secretary, so that such plans include a process for addressing drug shortages.'.

SEC. 3. MANUFACTURER REVIEW.

Section 510(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360 (h)) is amended--

(1) by striking `(h)' and inserting `(h)(1)'; and

(2) by inserting at the end the following:

(2)(A) If an establishment registered with the Secretary pursuant to this section is subject to a reinspection due to failure to comply with a requirement of this Act, the Secretary shall conduct such reinspection not later than 90 days after the establishment certifies to the Secretary that the establishment has corrected the reason for such failure.

(B) The Secretary shall prioritize reinspections described in subparagraph (A) based on whether the establishment involved manufactures, propagates, compounds, or processes a drug involved in a drug shortage (as defined in section 506C).'.

SEC. 4. REPORTS TO CONGRESS.

Not later than 1 year after the date of enactment of this Act, and on an annual basis thereafter, the Secretary of Health and Human Services shall submit to Congress a report that describes the actions taken by such Secretary during the previous 1-year period to address drug shortages through all aspects of the prescription drug supply chain.

END
Preserving Access to Life-Saving Medications Act

Sponsor: Sen Klobuchar, Amy [MN] (introduced 2/7/2011)  
Cosponsors (14)

Latest Major Action: 2/7/2011 Referred to Senate committee. Status: Read twice and referred to the Committee on Health, Education, Labor, and Pensions.

SUMMARY AS OF:
2/7/2011--Introduced.

Preserving Access to Life-Saving Medications Act - Amends the Federal Food, Drug, and Cosmetic Act to require a prescription drug manufacturer to notify the Secretary of Health and Human Services (HHS) of a discontinuance, interruption, or other adjustment of the manufacture of the drug that would likely result in a shortage of such drug. Requires: (1) six months notice of any discontinuance or planned interruption or adjustment, and (2) notice as soon as practicable after becoming aware of such interruption or adjustment in the case of any other interruption or adjustment. Applies this Act to any approved prescription drug that is not a product that was originally derived from human tissue and was replaced by a recombinant product.

Sets forth the types of adjustment for which a manufacturer must submit notice, including: (1) adjustments related to the supply of raw materials, (2) adjustments to production capabilities, (3) business decisions that may affect the manufacture of the drug, and (4) other adjustments as determined appropriate by the Secretary.
HR 2245 IH

112th CONGRESS
1st Session

H. R. 2245

To amend the Federal Food, Drug, and Cosmetic Act to provide the Food and Drug Administration with improved capacity to prevent drug shortages.

IN THE HOUSE OF REPRESENTATIVES

June 21, 2011

Ms. DEGETTE (for herself and Mr. ROONEY) introduced the following bill; which was referred to the Committee on Energy and Commerce

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to provide the Food and Drug Administration with improved capacity to prevent drug shortages.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the `Preserving Access to Life-Saving Medications Act of 2011'.

SEC. 2. DISCONTINUANCE OR INTERRUPTION OF THE MANUFACTURE OF A PRESCRIPTION DRUG.

(a) In General- Section 506C of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356c) is amended to read as follows:

`SEC. 506C. DISCONTINUANCE OR INTERRUPTION OF THE MANUFACTURE OF A PRESCRIPTION DRUG.

(a) Definitions- In this section:

(1) The term `average historic demand' means the individual manufacturer's average monthly volume of sales of the drug during the last calendar year.
(2) The term 'discontinuance' means the permanent termination of the manufacture of a drug by an individual manufacturer.

(3) The term 'interruption' means a change that--

(A) may result in the total supply of a drug manufactured by the individual manufacturer not meeting average historic demand; and

(B) consists of--

(i) a change in the supply of one or more raw materials, including active pharmaceutical ingredients;

(ii) an unplanned interruption in ability to produce the drug;

(iii) a business decision affecting the manufacture of the drug, such as a merger or a change in production output; or

(iv) any other type change that could have the result described in subparagraph (A), as determined by the Secretary.

(b) Notifications by Manufacturers-

(1) IN GENERAL- A manufacturer of a drug that is subject to section 503(b)(1) and marketed in interstate commerce shall notify the Secretary of a discontinuance or interruption in the manufacture of such drug.

(2) NOTIFICATION PERIOD- A notification pursuant to paragraph (1) shall be submitted to the Secretary--

(A) in the case of a planned discontinuance, at least 6 months prior to the date of such discontinuance; and

(B) in the case of any other discontinuance or interruption--

(i) at least 6 months prior to the date of such discontinuance or interruption; or

(ii) if the manufacturer cannot provide 6 months advance notice, as soon as practicable after the manufacturer--

(I) becomes aware of such discontinuance; or

(II) becomes aware that such interruption may result in the total supply of the drug manufactured by the individual manufacturer not meeting average historic demand.
'(3) ADDITIONAL INFORMATION- A manufacturer may, but is not required to, include in a notification submitted pursuant to paragraph (1) information about an alternative source of the drug or the availability of a drug with the same active ingredient.

'(4) REDUCTION IN NOTIFICATION PERIOD- The notification period required under paragraph (2) for a manufacturer may be reduced if the manufacturer certifies to the Secretary that good cause exists for the reduction, such as a situation in which--

  '(A) a public health problem may result from continuation of the manufacturing for the 6-month period;
  
  '(B) a biomaterials shortage prevents the continuation of the manufacturing for the 6-month period;
  
  '(C) a liability problem may exist for the manufacturer if the manufacturing is continued for the 6-month period;
  
  '(D) continuation of the manufacturing for the 6-month period may cause substantial economic hardship for the manufacturer;
  
  '(E) the manufacturer has filed for bankruptcy under chapter 7 or 11 of title 11, United States Code; or
  
  '(F) the manufacturer can continue the distribution of the drug involved for 6 months.

'(5) OTHER REDUCTIONS IN NOTIFICATION PERIOD- The Secretary may reduce the notification period required under paragraph (2) based on--

  '(A) the type of discontinuance or interruption at issue; and
  
  '(B) any other factor, as determined by the Secretary.

'(6) CONFIDENTIALITY OF INFORMATION- Any information provided to the Secretary under paragraph (1) shall be treated as trade secret or confidential information subject to section 552(b)(4) of title 5 and section 1905 of title 18.

'(7) ENFORCEMENT-

  '(A) Any manufacturer that knowingly fails to submit a notification in violation of paragraph (1) shall be subject to a civil money penalty not to exceed $10,000 for each day on which the violation continues, and not to exceed $1,800,000 for all such violations adjudicated in a single proceeding.
(B) Not later than 180 days after the date of the enactment of the Preserving Access to Life-Saving Medications Act of 2011, the Secretary shall, subject to subparagraph (A), promulgate final regulations establishing a schedule of civil monetary penalties for violations of paragraph (1).

(C) The provisions of paragraphs (5), (6), and (7) of section 303 (f) shall apply with respect to a civil penalty under this paragraph to the same extent and in the same manner as such provisions apply with respect to a civil penalty under paragraph (1), (2), (3), (4), or (9) of section 303(f).

c) Notifications by Secretary-

(1) DRUG SHORTAGE DEFINED- In this section, the term `drug shortage' means, with respect to a drug, a period of time when the total supply of such drug available at the user level will not meet the demand for such drug at the user level as determined by the Secretary.

(2) PUBLIC NOTIFICATION-

(A) IN GENERAL- Subject to subsection (b)(6), the Secretary shall--

(i) publish on the public Internet Web site of the Food and Drug Administration information on--

(I) the types of discontinuances and interruptions for which a notification is required under subsection (b)(1); and

(II) actual drug shortages; and

(ii) to the maximum extent practicable, distribute such information to appropriate health care providers and patient organizations.

(B) DURATION- The Secretary shall include in any publication or distribution under subparagraph (A), when possible, an estimate of the expected duration of any discontinuance or interruption or actual drug shortage.

(3) IDENTIFICATION AND NOTIFICATION OF DRUGS VULNERABLE TO DRUG SHORTAGE-

(A) IN GENERAL- If the Secretary determines using the criteria under subparagraph (B) that a drug may be vulnerable to a drug shortage, the Secretary shall notify the manufacturer of the drug of--
(i) such determination; and

(ii) the Secretary's duty to collaborate to improve continuity of supply plans under paragraph (4).

(B) EVIDENCE-BASED CRITERIA- The Secretary shall implement evidence-based criteria for identifying drugs that may be vulnerable to a drug shortage. Such criteria shall be based on--

(i) the number of manufacturers of the drug;

(ii) the sources of raw material or active pharmaceutical ingredients;

(iii) the supply chain characteristics, such as production complexities; and

(iv) the availability of therapeutic alternatives.

(4) CONTINUITY OF SUPPLY PLANS-

(A) IN GENERAL- With respect to drugs that are vulnerable to a drug shortage (as determined under paragraph (3)), the Secretary shall collaborate with manufacturers and other stakeholders (such as distributors and health care providers) to establish and improve continuity of supply plans, so that such plans include a process for addressing drug shortages.

(B) LIMITATION ON SECRETARY'S AUTHORITY- The Secretary may not in any case require a manufacturer--

(i) to manufacture a drug in the event of a discontinuance or interruption; or

(ii) to delay or alter a discontinuance or interruption.

(C) ALLOCATION BY MANUFACTURER- No provision of Federal law shall be construed to prohibit a manufacturer from, or penalize a manufacturer for, allocating distribution of its products in order to manage an actual or potential drug shortage.

(d) Rulemaking- The Secretary shall carry out this section pursuant to regulations promulgated after providing notice and an opportunity for comment.'.

(b) Applicability; Transitional Period- Section 506C of the Federal Food, Drug, and Cosmetic Act, as amended by subsection (a), applies with respect to discontinuances, interruptions, and drug shortages (as such terms are used in such section 506C) that occur on or after the day that is 1 year after the
date of the enactment of this Act. Until such day, the provisions of section 506C of the Federal Food, Drug, and Cosmetic Act, as in effect on the day before the enactment of this Act, shall continue to apply.

SEC. 3. REPORTS TO CONGRESS.

The Secretary of Health and Human Services shall submit to the Congress--

(1) not later than the date that is 1 year after the date of the enactment of this Act, a report describing the actions taken by the Secretary during the previous 1-year period to address drug shortages (as defined in section 506C of the Federal Food, Drug, and Cosmetic Act, as amended by section 2) through all aspects of the prescription drug supply chain; and

(2) every 5 years thereafter, a report describing such actions taken by the Secretary during the previous 5-year period.

SEC. 4. GAO STUDY.

(a) Study- The Comptroller General of the United States shall conduct a study--

(1) to examine how the Food and Drug Administration identifies and responds to drug shortages (as defined in section 506C of the Federal Food, Drug, and Cosmetic Act, as amended by section 2);

(2) to examine the possible causes of such drug shortages, including manufacturing problems, breakdown in the supply chain delivery system, changes in the supply of raw materials, stockpiling at the wholesale or provider level, and restrictive regulatory requirements;

(3) to identify if there is adequate communication between industry, the Food and Drug Administration, distributors, and end users;

(4) to analyze the effects of the enactment of this Act on the ability of the Food and Drug Administration to identify and ameliorate such drug shortages; and

(5) to identify any additional measures that need to be taken to prevent or address such drug shortages.

(b) Report- Not later than 1 year after the date of the enactment of this Act, the Comptroller General shall submit a report to the Congress on the results of the study under subsection (a).

END
Preserving Access to Life-Saving Medications Act of 2011 - Amends the Federal Food, Drug, and Cosmetic Act to require the manufacturer of a prescription drug marketed in interstate commerce to notify the Secretary of Health and Human Services (HHS) of a discontinuance or interruption in the manufacture of such drug. Requires the notification to be submitted six months prior to the date of a discontinuance or interruption, if possible.

Allows the reduction of the notification period if the manufacturer certifies to the Secretary that good cause exists for the reduction. Authorizes the Secretary to reduce the notification period based on the type of discontinuance or interruption at issue or any other factor.

Treats any information provided to the Secretary under this Act as a trade secret or confidential information.

Establishes civil monetary penalties for violations.

Requires the Secretary to publish on the website of the Food and Drug Administration (FDA) and distribute to the appropriate health care providers and patient organizations information on discontinuances, interruptions, and drug shortages.

Requires the Secretary to notify a manufacturer of: (1) any determination by the Secretary that a drug may be vulnerable to a drug shortage, and (2) the Secretary's duty to collaborate to improve continuity of supply. Prohibits the Secretary from requiring a manufacturer to: (1) manufacture a drug in the event of a discontinuance or interruption, or (2) delay or alter a discontinuance or interruption.
Declares that no provision of federal law shall be construed to prohibit a manufacturer from, or penalize a manufacturer for, allocating distribution of its products in order to manage an actual or potential drug shortage.

Requires the Comptroller General to examine issues related to drug shortages.
Generic Drug Makers Want Distributor Communication Added To Shortage Bills

Posted: September 29, 2011

The generic medicine industry is seeking modifications to legislation that will create an early warning system for manufacturers to notify FDA of drug shortages, saying the measure should include distributors and others in the supply chain as part of the communications process alongside additional provisions to ensure the system won't contribute to growth of the gray market, the president of the Generic Pharmaceutical Association said on Monday (Sept. 26) at an FDA workshop on the issue. Doctors, pharmacists, hospitals and other stakeholders also proposed expanding the idea of the early warning system to include information about the cause of the shortage, the expected length of the shortage and possible substitutions for the drug that is unavailable.

FDA said it has prevented 99 drug dearths so far this year because of a record number of voluntary notifications by industry ahead of shortages, allowing the agency to perform expedited review, exercise regulatory discretion and allow temporary importation.

Legislation pending in both chambers would mandate drug firms notify FDA about any discontinuance or interruption in prescription drug manufacturing at least six months in advance or as soon as possible in the case of an unplanned supply shortage. The bipartisan House bill -- introduced by Rep. Diana DeGette (D-CO) -- subjects all drugs including all biologics to the requirements and includes specific monetary figures for civil penalties for manufacturers that fail to submit appropriate notification. The Senate bill -- introduced by Sen. Amy Klobuchar (D-MN) -- does not include biologics and leaves it up to FDA to determine penalties for not reporting shortages. The issue also spurred the House Energy and Commerce health subcommittee hearing last week on shortages (see related story).

GPhA does not oppose either bill, but legislation needs to be refined before the group is able to fully support it, said Ralph Neas, the trade lobby's new president. The group wants the bills to include similar requirements for all parts of the supply chain, including distributors. The generic industry also has concerns about how an early warning system could influence the gray market or contribute to supply disruptions by causing hoarding or price gouging.

"We need the refinements in the legislation in order to be able to support it," Neas said. "We don't oppose it. We have to be able to work with the FDA and with Congress to make sure those issues are addressed."

Anita Ducce, vice president of regulatory affairs at the Healthcare Distribution Management Association, said notification from distributors about shortages would depend on what manufacturers tell them, making the information they could provide FDA second hand. The group does not have a position on the early notification system legislation, saying it would not impact its members and that they see the shortages predominately as a manufacturing issue.
“It is really a too little too late kind of thing,” Ducca said of required reporting by distributors. “We really don't see that there is going to be a lot of utility in doing that kind of reporting.”

Stakeholders and lawmakers have acknowledged that the system would not fully address the root causes of the shortages, but would somewhat help to contain the problem in the short term.

Some stakeholders said along with early notification, FDA should communicate with hospitals and providers about the reasons for a shortage and its expected duration, which could help them create action plans to deal with the short supply. They also said the agency should coordinate a system that would allow providers to suggest alternatives for drugs that are subject to shortages and develop guidelines for oncology regimens when there is a shortage in a particular treatment area.

But Ilisa Bernstein, acting director at the FDA drug center’s office of compliance, said the agency is limited in how much it can communicate to providers. FDA officials said the agency and manufacturers often don't know about a shortage until it is occurring.

“We are limited in what we find out from the manufacturers and also in terms of what we can say,” Bernstein said. “In terms of people putting out that FDA needs to be more open and transparent, we need companies to be more open and transparent.”

Along with a better communication system, doctors, pharmacists, hospitals and patient advocates also suggested a slew of reforms to FDA to stem the shortages, including creating strong safeguards to prevent hoarding and price gouging, using emergency use authorization, mandating protection before market withdrawal, allowing importation, creating a fair and equitable distribution of drugs, restructuring price structures, creating incentives to manufacture older drugs, working with other agencies to expand manufacturing production quotas for controlled substances and creating a national stockpile.

In a letter to FDA drug center director Janet Woodcock, the American Society for Hematology said FDA also needs to examine if its evaluation of product quality is accurate, develop a national drug registry and expand orphan drug status to incentivize the continuous production of generics.

“We think it would be best addressed through a solutions oriented manner,” said Len Lichtenfeld, deputy chief medical officer for the American Cancer Society. “We need response and we need an effective response now.”

-- Nanci Bompey ( nbompey@iwnews.com )

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Drug Shortages Put Clinical Trial Data, Future Research In Jeopardy

Posted: September 29, 2011

Clinical trials -- especially for cancer medications -- are being suspended, altered or stopped because of drug shortages, with stakeholders telling Congress and FDA that these delays mean that data from trials might be less useful and could ultimately slow the pace of clinical research. The issue emerged as lawmakers, the agency and stakeholders analyze the problem through a series of recent hearings and meetings.

A cancer researcher told lawmakers last week that drug shortages are now affecting clinical trials because drugs in shortage are used on some level in the studies, whether in combination with novel treatments or as a placebo. Similarly, hospitals, research institutions, physicians and patient groups reinforced the message during a full day workshop on drug shortages hosted by FDA on Monday (Sept. 26).

Robert DiPaola, director of the Cancer Institute of New Jersey, told lawmakers that 50 percent of active clinical trials through the Coalition of Cancer Cooperative Groups, which facilitates patient involvement in trials nationwide, involve drugs in short supply. Further, he said shortages hinder progression through a critical stage of the drug development process, where a weeks-long shortage could translate into years of delay in bringing a product to market.

"If a clinical trial is compromised because it needed to substitute a particular drug for another drug -- or in in some cases clinical trials won't allow a substitution -- all of the work that went into the discovery, getting to the point of the clinical trial, is going to be compromised," he said.

Other stakeholders said the uncertain supply is leading patients to be more reluctant to enroll in studies. At Fred Hutchinson Cancer Research Center in Seattle, 5 to 10 percent of clinical trials have been impacted by the shortages, with the potential for 25 to 30 percent of trials potentially affected if the shortages continue, according to statistics presented to FDA.

In one case, a patient was enrolled in a trial and received his first dose of medication in Seattle, but when the drug went into short supply and the additional cycles couldn't be completed, the patient had to be transferred to another facility. Along with questioning why he had to change doctors and nurses, the patient also questioned why he would participate in another research study again.

Further, clinical trial activation has been suspended and patient accrual halted because of the shortages, according to the American Society of Hematology, saying that a recently opened large Eastern Cooperative Oncology Group randomized clinical trial for Acute Myeloid Leukemia had to be halted.

Pediatrics have been particularly hard hit by the clinical trial issues, where many advances have been made through these studies, with as many as 85 percent of children with certain types of cancer enrolled in the trials, said James Hoffman of St. Jude Children's Research Hospital.
Generic sterile injectable drugs, which are widely used in cancer treatments, have been pegged as a major source of the shortage problem. Shortages of these often used, older cancer drugs mean researchers have a difficult time comparing findings to the endorsed standard of care, said Karen Hagerty, director of reimbursement policy for the American Society of Clinical Oncology.

"It leads to later problems down the road with data analysis," she said. "It is a tremendous concern with us."

Drug shortages reached a record high in 2010 and are on pace to exceed that in 2011, with 210 shortages of different drugs being reported as of Sept. 15, including more than 20 oncology drugs, according to the University of Utah Drug Information Service, which tracks shortages. -- Alaina Busch (abusch@iwpnews.com) and Nanci Bompey (nbompey@iwpnews.com)

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