

Where Did All Our Drugs Go? Drug Shortages: What is the Current Situation?

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Disclosure Statement – no financial relationships to disclose

- Clark Lyda, PharmD
- Statement of Disclosure
 - I have no relevant financial relationships with commercial interests pertaining to the content presented in this program.

Objectives

- Identify common medications affected by current drug shortages
- Delineate impact of drug shortages on anesthesia services
- List resources to identify up to date drug shortage information and resolution dates
- Discuss recent governmental actions to address the drug shortage crisis
- Discuss alternative therapies being used in clinical practice as a result of drug shortages

What is a Drug Shortage?

- Food and Drug Administration
 - 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

A review of FDA's approach to medical product shortages. Available at: www.fda.gov/DrugShortageReport

What is a Drug Shortage?

- American Society of Health-System Pharmacist
 - A supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent

Fox ER, Birt A, James KB et al. ASHP guidelines on managing drug product shortages in hospitals and health systems. Am J Health-Syst Pharm. 2009;66:1399-406

Examples of shortages

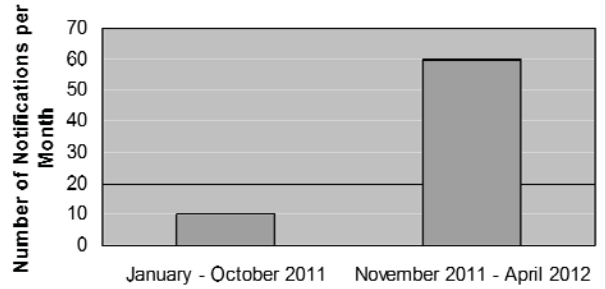
FDA	ASHP	FDA	ASHP	FDA	ASHP
• Asmanex	• Acetazolamide	• Copper Injection	• Ganaxovir	• Meperidine	• Retyrape
• Becanabaclofen	• Aeydovir PO/IV	• Cysocobalamin	• Gemtacin	• Mirazoline	• Relatropin
• Digoxin	• Alprostadil	• Cyclospamine	• Glyceropuridate	• Marfanon	• Rocuronium
• Helicid	• Amisophillone	• Decarbazine	• Granisetron	• Methazolamide	• Ropivacaine
• Insulin glargine	• Anisidarone	• Dantrolene	• Haloperidol	• Methoxsalen	• Rotigone
• Isomaxid	• Ampotericin B	• Deferoxamine	• Heptasis A vira	• Methylphenovine	• Securin
• Levocabronit	• Ampicillin	• Denclacolin Delirium	• Hyaluronicase	• Mefenidol	• Sodium Thiosulfate
• NeoProfen	• Ascorbic Acid	• Desamethasone	• Dextrose	• Mefenidol	• Terbutaline
• Neopro	• Azathioprine	• Dextrose	• Dopexidine	• Mifentone	• Testosterone
• Norethindrone/ Ethinyl Estradiol	• Anthromycin	• Dipyrindazole	• Droperidol	• Mifentone	• Thioapp
• Oxid	• Arrovosum	• Droprazine	• Drospirenone	• Naloxone	• Thyroglobin
• Oxoiden	• BCG Live Vaccine	• Doxycycline	• Eranipine	• Nicotinic	• Tiochloral
• Oxoiden	• Black Widow Antivenin	• Doxycycline	• Eranipine	• Nitazoxanide	• Toradol
• Pagays	• Bismycin	• Doxycycline	• Kanamycin	• Norepinephrine	• Trazodone
• Thyogen	• Buicetamide	• Ecodrophate	• Kanamycin	• Nystatin	• Trimetoprim/HCTZ
• Thyral	• Calcium Acetate	• Enalapril	• Ketamine	• Oxcarbazepine	• Valproate
• Tromethamine	• Carboplatin	• Estazolam	• Lansoprazole	• Oxycodone	• Valbaron
• Xenon Xe 133	• Cefaclor	• Ethinyl Estradiol	• Lethlamide	• Papaverine	• Vancomycin
	• Cefepime	• Famotidine	• Levofloxyline	• Phenytoin	• Vitamin A
	• Cefuroxime	• Fentanyl	• Lisin	• Polysorb Chloride	• Warfarin
	• Ciprofloxacin	• Fluoridate	• MMR vaccine	• Potassium	• WGA tube/vials
	• Clarithromycin	• Fluorouracil	• Mechlorethamine	• Rabies vaccine	• Surgical lubricant
				• Raxitidine	• Sterile Empty vials

ASHP Shortage list: <http://www.ashp.org/DrugShortages/Current/>
 FDA Shortage list: <http://www.fda.gov/drugs/drugsafety/DrugShortages/ucm050792.htm>

How are Drug Shortages Reported?

- drugshortages@fda.hhs.gov
- “Report a Drug Shortage to ASHP” link
- University of Utah Drug Information Services

Average Monthly Number of Notifications of Potential Drug Shortages



Why Drug Shortages?

- Government- FDA, DEA
- Materials
- Manufacturing
- Distributors
- Business Decisions
- Inventory
- Recalls

Fox ER, Biri A, James KB et al. ASHP guidelines on managing drug product shortages in hospitals and health systems. Am J Health-Syst Pharm. 2009;66:1393-406

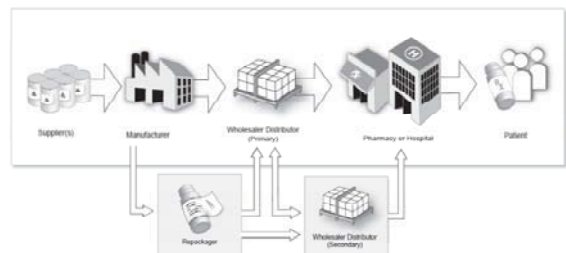
Role of DEA

- Limits of yearly production of controlled medications, C-II – C-V
- Fill their allocated quantity of controlled drugs.
- Not able to make any more until the next January
- Recent shortages of fentanyl, morphine, hydromorphone

Supply Chain

Supply Chain

FDA A Drug Supply Chain Example
From Supplier to Patient



A review of FDA's approach to medical product shortages. Available at www.fda.gov/DrugShortageReport

New FDA Commissioner, 2009

- Margaret Hamburg, MD
- Aggressive campaign to increase the FDA inspections
- Contaminated Heparin 2008
- 1st year, FDA warning letters to MFR companies increased 42%
- Second year (2010), the letters increased 158%
- Spring 2012, generic production had **decreased 30%**

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FDA Inspections

- From the US House of Representatives, Committee on Oversight and Government Reform report on the FDA's contribution to the drug shortage crisis, June 2012,
- “the FDA field force does not believe that it is within the scope of their authority to worry about the implications of their actions, even if it means a manufacturer closing a manufacturing line or facility.”

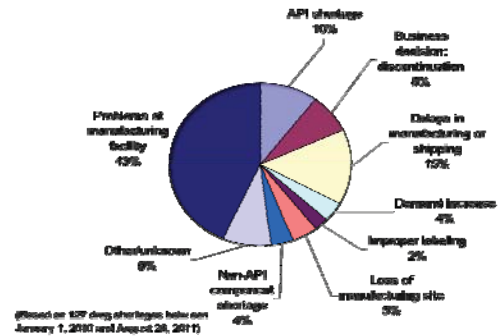
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FDA Findings

- Teva- Endotoxin in propofol (2009)
- Bedford Labs- lack of sterility, glass and stainless steel particles (2011)
- Hospira- stainless steel particle contamination propofol, morphine vials overfilled up to 2x volume (2009, 2010 and 2011)
- Sandoz – crystal formation in solutions, contaminated opioids (2011 and 2012)

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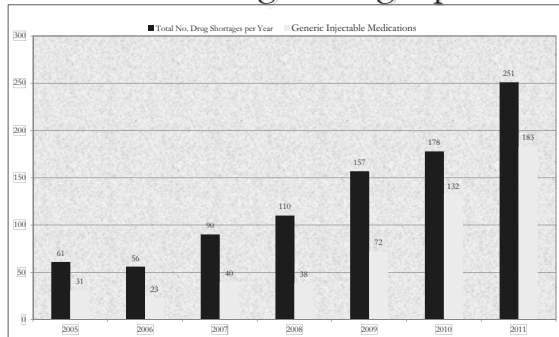
Drug Shortages by Primary Reason



A review of FDA's approach to medical product shortages. Available at: www.fda.gov/DrugShortageReport

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Number of Drug shortages per Year



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Medicare Modernization Act 2003

- Prescription benefit for seniors
- Government price cap for generic medications
- Changed the reimbursement rate for injectable drugs delivered in outpatient settings
- Limits price increases to 6% per year
- Low profit margins of generic injectables (6%) – change production lines to a more lucrative drug

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Group Purchasing Organizations

- Increased purchasing power
- 98% of US hospitals use GPO contracts
- Six GPO's have 90% of market, 2 have 60%
- Intense competition, prices driven down
 - Intended goal
- Ultimately limits production to 1 or 2 companies
 - Contract losers, quit making the generic drug

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Hospital Inventory Control

- “Just In Time Ordering”
- Order enough product for 2 or 3 days
- Delivery 1 to 2 times every day
- Limit inventory costs
- Maximize turnover and profits
- Limits ability to respond to any drug shortage

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National Survey

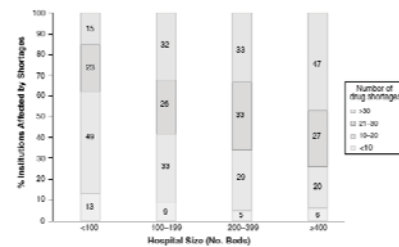
- University of Michigan Health System (UMHS) distributed an online survey to directors of pharmacy
- Collected data from four domains
 - Demographics
 - Impact of drug shortages
 - Resource utilization to manage shortages
 - Adequacy of current resources

Kaaleh R, Sweet BV, Reilly C, et al. Impact of drug shortages on U.S. health systems. Am J Health-System Pharm. 2011; 68: 1811-19

Is Everyone Affected?

- 99% of hospitals were affected by at least one drug shortage

Figure 1. Number of shortages affecting health systems by hospital size in calendar year 2010.



Kaaleh R, Sweet BV, Reilly C, et al. Impact of drug shortages on U.S. health systems. Am J Health-System Pharm. 2011; 68: 1811-19

Less Drugs, More Frustrations

- Drug shortages have lead to increased:
 - Time spent managing shortages
 - Labor costs
 - Frustration
- Estimated annual labor cost of \$216 million for all health systems nationwide

Kaaleh R, Sweet BV, Reilly C, et al. Impact of drug shortages on U.S. health systems. Am J Health-System Pharm. 2011; 68: 1811-19

A Change in Practice

- Alternatives
 - Using different or unfamiliar agents
 - Temporary guidelines/policies
- Assessment of inventory
 - Changing dispense location of medications
 - Changing strengths or concentrations stocked in Pyxis

Kaaleh R, Sweet BV, Reilly C, et al. Impact of drug shortages on U.S. health systems. Am J Health-System Pharm. 2011; 68: 1811-19

Impact on Medication Safety

- ISMP released a special issue addressing the effects of drug shortages
- Drug shortages have lead to an increase in medication errors
 - One in three reported having a near miss
 - One in four reported having an actual error
 - One in five reported adverse patient outcomes

ISMP. Drug Shortages (National Survey reveals high level of frustration, low level of safety. ISMP Medication Safety Alert 2010;15(10):1.

Alternative Therapy

- Problems with alternatives
 - Less effective
 - Increase side effects
 - Unfamiliar with alternative agent
- Hydromorphone 2 mg IV ordered by MD, verified by pharmacy and given by RN.
 - Patient to ICU after Naloxone

ISMP. Drug Shortages (National Survey reveals high level of frustration, low level of safety. ISMP Medication Safety Alert 2010;15(10):1.

Unfamiliar Agents: A Patient Case

- A 47 year old female is admitted for an elective procedure
- Propofol shortage
- Unfamiliarity with Brevital[®] Sodium
- Serious dilution error, massive overdose
- Patient died despite resuscitation efforts

ISMP. Drug Shortages (National Survey reveals high level of frustration, low level of safety. ISMP Medication Safety Alert 2010;15(10):1.

Compounding Error

- Shortage of Bupivacaine 0.5% w/epinephrine 1:200,000
- Pharmacy mixed small amount for anesthesia
- Added too much epinephrine
- Two patients: HTN, V-Fib, Pulmonary edema, extended stay in SICU

ISMP Med safety Alert 7/7/2012. A shortage of everything except errors: Harm associated with drug shortages.

Changes in Supply

- Drug shortages have lead to changes in current supply
 - Different strengths
 - Different concentrations
 - Different packaging

Obama Becomes Involved

- On October 31, 2011 Obama issued an executive order



Chalster B. Drug Shortages: A Critical Challenge for the Generic-Drug Market. N Engl J Med 2011; 365 (23): 2147-49

Executive Order

- Executive Order 13588
 - Required drug companies to report to the FDA when critical supplies were threatened
 - Required FDA to expedite regulatory reviews and increase staffing in its Drug Shortage Program

Wilson D. Deepening Drug Shortages. Health Aff. 2012;31(2):263-4.
 Devi S. US Drug Shortages could continue for years. Lancet. 2012; 379: 990-91.
 Gehret B. A prescription for drug shortages. JAMA 2012; 307 (2):153-54.

Obama Administration Acts

- Continued efforts by the Obama administration included
 - A letter to drug manufacturers reminding them of their legal responsibilities to report the discontinuation of certain drugs to the FDA
 - Encouraged manufacturers to voluntarily report potential shortages when not required by law

Rochelle B. Obama takes action on drug shortages. BMJ 2011;343:d7158. doi:10.1136/bmj.d7158

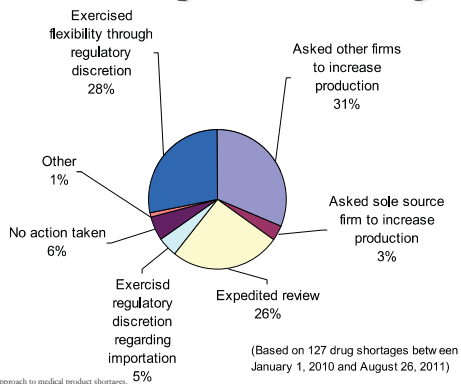
FDA's Role

- Has taken multiple steps to help prevent drug shortages
 - Asking other firms to increase production
 - Working with manufacturers to identify steps to prevent the dangers of manufacturing products with quality issues
 - Expediting review of regulatory submissions
 - Approved Import of propofol from Europe

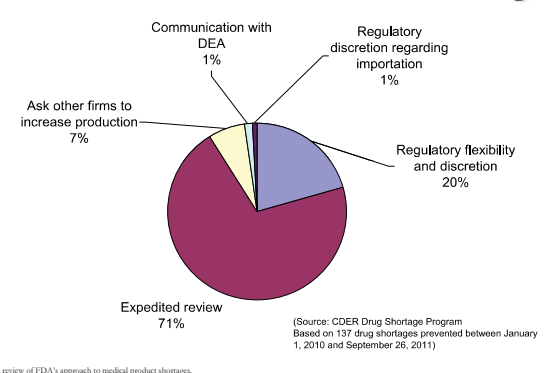
FDA's Role

- FDA has helped prevent several drug shortages
 - In 2010, prevented 38 drug shortages
 - In 2011, prevented 99 drug shortages
 - In 2012, prevented 128 drug shortages

FDA's Response to Shortages



FDA's Actions to Prevent Shortages



FDA Provides Resources

- Increased resources provided on their website regarding drug shortages
 - List of drugs on shortage
 - Report of the FDA's actions in decreasing the number of shortages
 - Links to actions by the Obama administration on drug shortages
- <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>

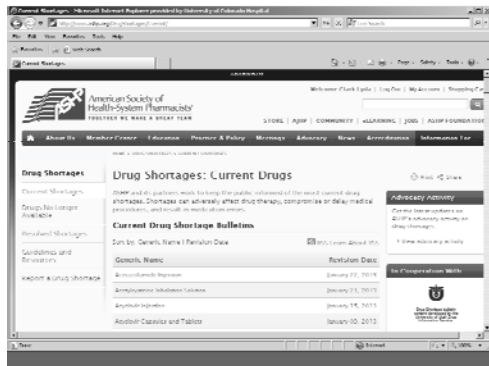


ASHP Provides Resources

- Increased resources provided on their website regarding drug shortages
 - List of drugs on shortage and the reason behind the shortages
 - ASHP's actions involving drug shortages
 - Guidelines to managing drug shortages
 - Links to articles and news on drug shortages
- <http://www.ashp.org/shortages>



ASHP's Website



ASHP's Website



ASHP's Website

- Nalbuphine Injection
- [21 January 2013]
- **Products Affected - Description**
- Nalbuphine injection, Hospira
- 10 mg/mL, 1 mL ampules (NDC 00409-1463-01)
- 10 mg/mL, 10 mL vials (NDC 00409-1464-01)
- 20 mg/mL, 1 mL ampules (NDC 00409-1465-01)
- 20 mg/mL, 1mL Novaplus ampule (NDC 00409-1465-49) - *discontinued*
- **Reason for the Shortage**
- Endo discontinued Nubain in 2008.
- Teva discontinued all nalbuphine injections in July, 2010.
- Hospira has nalbuphine on shortage due to manufacturing delays. Hospira discontinued the 20 mg/mL 1 mL Novaplus ampules in December 2012.

43 <http://www.ashp.org/DrugShortages/Current/Bulletin.aspx?id=166>

Actions to Implement

- Partner with other institutions
 - Different wholesale distributor
- Social media
- Collegial networks with professional organizations
- Professional list-serves and discussion groups
- Group Purchasing Organizations

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Hospital Action

- Hospital developed Policy
- 1. Transparent and open for review.
- 2. Relevant to population of patients affected
- 3. System by which patient can appeal a decision
- 4. Institution implement policy so that everyone follows the rules

Erich, J EMS World 2012, Clark, C HealthLeaders Media 2012, Golembiewski, J J Perianes Nursing 2012

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Hospital Action

- 5. Allocation must be fair, similar patients always treated similarly, no special people, physicians or patients
- 6. No gray market drugs
- 7. Prohibit use of drugs in short supply to be used in research studies.
- 8. Close inventory management and control

Erich, J EMS World 2012, Clark, C HealthLeaders Media 2012, Golembiewski, J J Perianes Nursing 2012

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Hospital Action

- 9. Schedule patients to avoid waste of partial vials
- 10. Coin toss to decide between two equal patients
- 11. Protocol to update information systems, electronic POE systems

Erich, J EMS World 2012, Clark, C HealthLeaders Media 2012, Golembiewski, J J Perianes Nursing 2012

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Resources

- ASHP <http://www.ashp.org/DrugShortages/Current/>
- FDA <http://www.FDA.gov/Drugs/DrugsSafety/DrugShortages/ucm050792.htm>
- ASA- Link to Drug shortages
 - <http://www.asahq.org/>
- AANA – Link to FDA
 - <http://www.aana.com/resources2/professionalpractice/Pages/U.S.-Food-and-Drug-Administration.aspx>

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Propofol Shortage: Teva to Restart Production

- Continue Importation of Propoven
 - Fresenius/APP increased production & shipment
- Domestic production improved
- Teva expected to release product February 2013
 - Discontinued in 2010, now reentering market
- Etomidate production increasing

<http://www.aaha.org/For-Members/Advocacy/Federal-Regulatory-and-Bioscience/Drug-Shortages.aspx>
23, 2013

Trends in Drug Shortages

- Significantly increasing
- Generic, sterile injectables
- Critical drugs
- Older drugs
- Generic Pharmaceutical Association
- May Improve in 2014?

Conclusion

- Drug shortages caused by multiple factors
- FDA implemented some actions that may help
- Resources for information presented
- Future of drug shortages....
 - Politics, Medicare Modernization Act, Obama Care, etc.

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Thank You

- Questions?

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