



Navigating Drug Shortages

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Disclosure Information

- Ali McBride has no financial relationships to disclose and will not discuss off-label use and/or investigational use in this presentation.



Objectives

- List reasons for medication shortages
- Outline management strategies for medication shortages
- Describe potential safety issues resulting from medication shortages

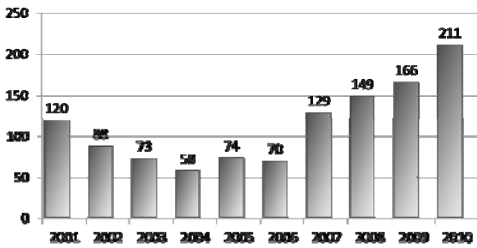


Headlines

- “Genzyme Drug Shortage Leaves Users Feeling Betrayed”-NY Times 3/15/2010- Production Plant Contamination
- “States Face Shortage of Key Lethal Injection Drug” NY Times - Hospira decided to “exit the market.”
- “Teva Propofol Recall Leads to FDA Warning, Drug Shortage”- Failed to have proper quality control measures in place to prevent bacterial contamination from entering batches of their generic version of the anesthetic propofol.
- “Pharmacies run out of Potassium Iodide”
- The list goes on, without much end in sight...



National Medication Shortages



Data from University of Utah Drug Information Service



Medication Shortages in 2010

- Total of 211 drug shortages
 - 157 reported in 2009
- Over 77% were parenteral products
 - Greatest number in past years
- Critical drugs involved succinylcholine, naloxone, furosemide, emergency syringes, etc...
- The largest increase in antimicrobial and chemotherapy agent shortages since being reported



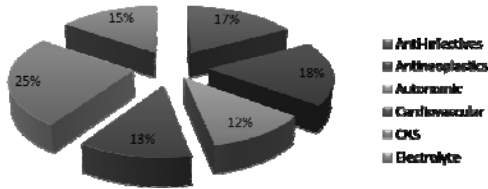
Reasons for Shortages in 2010

- Regulatory 1%
- Raw Materials 3%
- Discontinuation 7%
- Supply Chain 14%
- Manufacturing 28%
- **Unknown 47%**



Medication Shortages

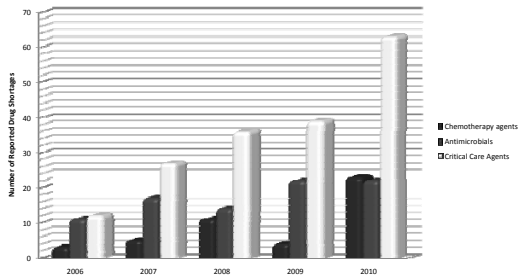
Listed Drug Shortage in 2010



Data from University of Utah Drug Information Service



Medication Shortages



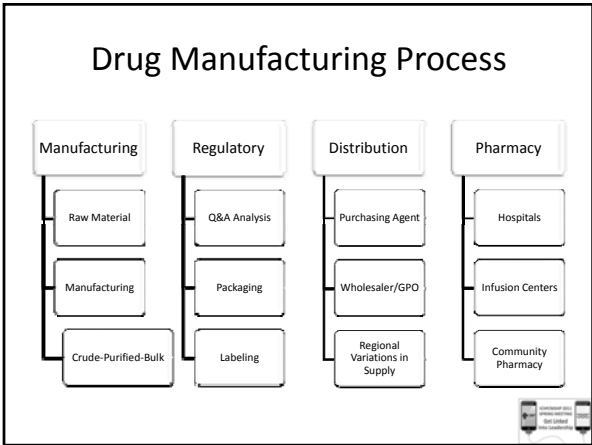
Data from University of Utah Drug Information Service



Reasons for Shortages

- Manufacturing
- Regulation and enforcement
- Distribution and use
- Changes in clinical practice
- Emergency situations
- Global market demand
- Economics
- Unknown

AJHP.2002;59:2173-82



Causes of Shortages

- Raw Materials
 - Sole source
 - Required time to develop or purchase raw materials
 - Often not disclosed to the public
 - Noted as the “greatest vulnerability to our supply”
 - Over 70% of raw materials obtained overseas
 - Few manufacturers for parenteral injections
 - One production line for multiple items
 - Batch failures

AJHP.2002;59:2173-82

Causes of Shortages

- **Manufacturer**
 - Consolidation of the market
 - Developing business decisions
 - Economic profitability
 - Production quota
 - Source allotments
 - Shutdowns
 - Lead to 45 individual products impacted
 - Amikacin, Bactrim drug shortages are still unresolved

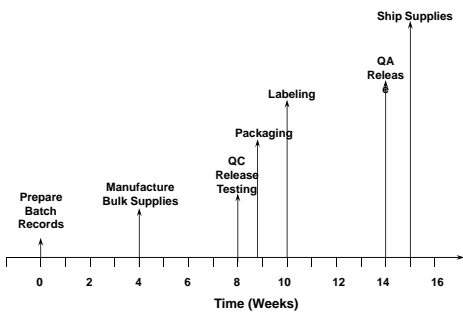


Causes of Shortages

- **Regulatory Issues**
 - Develop into immediate shortages
 - Ex phosphenytoin, propofol, TMP/SMX, cytarabine
 - Q& A measures demanding tighter regulations
 - Unapproved Drugs
 - DESI drugs
 - Develops uncertainty in the market
 - Examples: phenylephrine, thiopental




Manufacture & Release Timeline



Causes of Shortages

- Regional Variances
 - Wholesaler
 - GPO
 - Patient population/patient characteristics
- Clinical Use
 - Vary depending on practice setting
- Grey Market
- Stockpiling
 - “Feeling Safe”





Causes of Shortages

- Supply Chain
 - Global market economy
 - Consolidation of companies (Brand & Generic)
 - Tighter inventories
 - Failure to recapture market share
 - Lack of ability by companies to produce drug at the market demand



Medication Shortages



FDA's Role in Drug Shortages

- FDA can expedite issues related to addressing drug shortages(e.g., new manufacturers, increased expiration, increased capacity, changes in specifications)

AIHP 2002;59:1423-5



FDA's Roles in Drug Shortages

- Develop contracts for temporary importation(e.g., propofol, foscarnet, ethiodol, cytarabine)
- Manufacturing /Quality
 - Work with the company to address the issues
- Encourage firms to ramp up production



FDA Role in Drugs Shortages

What They Cannot Do


- *FDA cannot force the manufacturing of a drug*
- Manufacturers are not required to report plans to discontinue producing a product unless they are the *sole manufacture of a drug that is life-sustaining; or intended for the use of a debilitating disease or condition* (Medical Necessity)
- No Penalty for not notifying FDA of a discontinuation

21 CFR 314.81 FR published 10/2007




FDA Identification of Issues

- Notification from firms is important for all shortage issues
- Early notification leads to better chance of timely resolution
 - 24 product shortages prevented to date due to firms notifying FDA in advance




Drug Shortages and Patient Safety

- Clinical Affect of Drug Shortages
 - Prevent appropriate care for patients
 - Withholding or delay in medical treatments
 - Reduced dose for efficacy with unknown results
 - Potential to lead to increase in medication errors and patients outcomes




Drug Shortages and Patient Safety

- Medication Errors
 - Stability issues in compounding
 - Using expired medication
 - Delay in IT updates(i.e., bar code scanning, dispensing issues, override and administration)



ASHP/ISMP Survey

- In 2010 ASHP/ISMP developed a survey to evaluate the current state of drug shortages
- Focus on issues related to drug shortages and patient safety
- Over 1, 800 healthcare practitioners
 - 68% Pharmacists




ISMP. ISMP survey on drug shortages. ISMP Medication Safety Alert! 2010;15(15):4.

ASHP/ISMP Survey

(% of respondents who frequently or always encountered these problems in past year past year)


Questionnaire	Percent Response
No information about duration of shortage	85
No advanced warning and suggested alternatives	84
No information about cause of shortage	83
Substantial resources developing plan of action	82
Difficulty obtaining suitable alternative	80
Experience significant financial impact	78
Lack of suitable alternative product	70
Substantial resources preparing alternative	69
Risk of adverse patient outcome	64
Internal hoarding of product	58
Physician anger towards staff/hospital	55



ISMP. ISMP survey on drug shortages. ISMP Medication Safety Alert! 2010;15(15):4.

ASHP/ISMP Survey


- Near Misses
 - 35% reported a near miss at their facility due to a drug shortage
 - 20% reported errors associated with the drug shortage
 - 19.2% reported an adverse patient outcome
 - 33% reported by physicians
 - 21% reported by pharmacists
 - 16% reported by nurses



ISMP. ISMP survey on drug shortages. ISMP Medication Safety Alert! 2010;15(15):4.

Examples of Dosing Errors


- Medication Misadventures
 - IV HYDRomorphone prescribed at the intended dose of morphine, resulted in death of two patients
 - Switched from 6 mg morphine to HYDRomorphone without changing the dose; patient received two doses; over-sedation reversed with naloxone



Dosing Errors on the Front Lines

Medication Mix-Ups

- Medication switch between pharmacy prepared syringes of morphine and HYDRomorphone
- Morphine 10 mg vial (dispensed to unit after 2 mg vials no longer available) mixed up with vial of heparin 5,000 units; morphine administered IV instead of heparin



Dosing Errors on the Front Lines

Dosing errors


- Miscalculated rate of infusion for Precedex or entered wrong concentration in smart pump
- Infused alternative drug (Ativan) at typical rate for propofol

Therapy omissions

- Cancellation of procedures/anesthesia/ unnecessary use of general

Suboptimal outcomes

- Inadequate sedation and self-extubations
- Difficulty weaning patients from ventilators



Dosing Errors on the Front Lines

- Chemotherapy
 - Delays in transplants
 - Errors in dosing conversion in patients with IV to oral chemotherapy
 - Changes in chemotherapy among antineoplastic classes
 - Maximum efficacy with minimally dosing
- Neuromuscular blockers
 - Switching between doses
- Antibiotics
 - Lower doses of Bactrim for patients
- 50% dextrose injection
- Fosphenytoin
 - Phenytoin, which was reintroduced into the OR because of the fosphenytoin shortage, was administered IV too rapidly during surgery, which resulted in an arrhythmia and cardiac arrest



Management of Drug Shortages



Health-System Action Plan


- Point Person for contact on drug shortages issues
 - Monitor & establish a process
 - P&T committee member
- Assessment Plan
- Preparation Phase
- Contingency Phase

ASHP Guideline on Managing Drug Shortages
http://www.ashp.org/s_ashp/docs/files/BP07/Procure_Gdl_Shortages.pdf




Health System Action Plan

- Assessment phase
 - Duration of shortage
 - Threat to patient care
 - Evaluation of cost
 - Inventory on hand




Health System Action Plan

- Preparation Phase
 - Therapeutic alternatives
 - Communication and patient safety
 - External Relations with Other Health Systems
 - Patient Prioritization
 - Evaluate Other Supply Services




Health-System Action Plan

- Contingency Phase
 - Risk management & liability
 - Budget considerations
 - Information and communication
 - Government intervention




Caveats

- Drugs with no viable alternatives
 - Foscarnet
 - Amikacin
 - A patient with a pseudomonas infection sensitive only to amikacin died when the drug could not be provided
 - Inability to treat with amikacin in a patient with established resistance caused readmission due to treatment failure with ineffective alternatives
 - Acyclovir
 - Pancreatic Enzymes
- Clinical Studies
 - Studies are being put on hold due to issues with obtaining concomitant medication and continued maintenance therapy.



Caveats

- Alternatives to drugs with superior efficacy and/or lower risk profile
 - Propofol
- Alternative medications vulnerable to shortage when supply and demand picks up suddenly
 - HYDROmorphine
 - Bumetanide
- Enhanced risk of errors and/or adverse outcomes
 - Cannot remember all drugs and alternatives, how to safely prescribe, dispense, administer




Drug Shortage Ethics

Ethical dilemma with rationing

- Who gets the drug?
- Who gets the appropriate dose of the drug?
- Who gets the lesser or reduced dose?

“You had a curable disease but not anymore.”



Fiduciary Costs of Drug Shortages

- Financial effects of shortages
 - Expends tremendous resources
- Costly alternative medications for provider and patient
- Significant time spent on addressing shortages
- Additional costs associated with treatment of adverse outcomes



Legislation

Preserving Access to Life Saving Medications Act (S. 296)

- Senators Amy Klobuchar (D-Minn.) and Robert Casey (D-Pa.) have introduced S. 296, the Preserving Access to Life Saving Medications Act.
- Requires
 - Drug manufacturers to notify FDA about manufacturing problems or when a drug product will be discontinued
 - The agency to maintain an online list of drugs in shortage situations
 - Revises FDA’s definition of medically necessary.




Legislation (Cont’d)

- Manufacturer Reporting
 - Must notify FDA of any discontinuance, interruption or adjustment in the manufacture of a drug that may result in a shortage.
 - If the manufacturer plans on discontinuing the drug, notification must be made to FDA at least 6 months in advance.
 - FDA would then be required to promulgate regulations establishing penalties for non-compliance with the reporting requirement.




Legislation (Cont'd)

- Develop Criteria for Drugs Vulnerable to Shortage
 - The bill would require FDA to implement evidence-based criteria for identifying drugs vulnerable to a shortage.
 - Number of manufacturers, sources of raw material or active pharmaceutical ingredients, supply chain characteristics, and the availability of therapeutic alternatives.
 - If FDA can determine based upon the above criteria that a drug is vulnerable to a shortage, FDA would have to publish that information on its web site.
 - Further, for those drugs deemed vulnerable to a shortage and medically necessary, FDA would collaborate with manufacturers to establish continuity of operations plans to address drug shortages.




Legislation (Cont'd)

- Public Notification by FDA
 - The bill would additionally require FDA to publish information relating to manufacturing problems and drugs experiencing an actual shortage on its web site
- Revise Medically Necessary Definition
 - The bill would require FDA to revise the definition of medically necessary to include the prevalence of use of a drug as a factor in determining whether the drug is medically necessary.



Addressing the Issue

- Legislative Acts to Increase Awareness
- Fiduciary Incentives to Increase Generic Supply
- Prevent Stockpiling within Health-Systems
- Disincentive Grey Market Purchasing



Resources for Managing Drug Shortages

- FDA Drug Shortage Website
 - <http://www.fda.gov/drugs/drugsafety/default.htm>
 - Report Drug Shortages - drugshortages@fda.hhs.gov
- ASHP Drug Product Shortages Management Resource Center
 - <http://www.ashp.org/DrugShortages/Current/>



Questions



ICHP/MSHP 2011 Spring Meeting
Navigating Through Medication Shortages
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121-000-11-010-L04-P
121-000-11-010-L04-T

Post Test Questions:

1. How many drug shortages were reported in 2010?
 - a. 211
 - b. 70
 - c. 74
 - d. 166

2. What are reported reasons for drug shortages?
 - a. Manufacturing
 - b. Communication
 - c. Distribution and use
 - d. Regulation and enforcement
 - e. All of the above

3. The ASHP / ISMP survey evaluated physicians, pharmacists and nurses regarding drug shortages. Which of the following were issues noted to NOT lead to dosing errors?
 - a. Dosing errors during the transition between morphine to hydromorphone
 - b. Overdosing of norepinephrine due to a change in concentration
 - c. Continued procedures without cancellation due to appropriate availability of anesthesia
 - d. Underdosing of oral etoposide due to IV etoposide drug shortage

4. What defines a medically necessary drug according to the Food and Drug Administration (FDA)?
 - a. Increase volume of drug utilization in a one year period
 - b. Treat or prevent a serious disease or medical condition without other available sources of that product or an equally suitable alternative drug
 - c. Drug utilized to treat chronic disease states
 - d. A parenteral drug product

5. The preserving access to life saving medications act (S. 296) requires drug manufacturers to manufacture drugs that are in short supply.
True or False