Understanding and Minimizing the Impact of Current Drug Shortages

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DISCLOSURE

• This presentation represents my own opinions.
• University of Utah Drug Information Service receives some funding from Vizient™ to provide drug shortage content.
LEARNING OBJECTIVES

• Explain current trends in drug shortages and the most recent data on causes of drug shortages.
• Describe how recent manufacturing and drug quality trends relate to drug shortages.
• Evaluate progress towards drug shortage solutions.
• Identify best practices for minimizing the impact of drug shortages.
NATIONAL SHORTAGES AND UNIVERSITY OF UTAH DRUG INFORMATION SERVICE

• UUDIS provides drug shortage content to ASHP and Vizient™

• Public website at www.ashp.org/shortages
  – Partners since 2001
  – Receive voluntary reports submitted via web
  – Collaboration is key to success
  – Frequent communication with FDA drug shortage team
DIFFERENCES BETWEEN WEBSITES

**ASHP**
- [www.ashp.org/shortage](https://www.ashp.org/shortage)
- Drugs impacting clinical practice (biologics, devices, dosage forms)
- How to access
- Frequent updates
- Alternatives, safety

**FDA**
- [www.fda.gov/cder](https://www.fda.gov/cder)
- Fewer products
- No biologics or devices
- Information from manufacturer

NATIONAL DRUG SHORTAGES BY YEAR
JAN 1, 2001 TO JUNE 30, 2017

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ACTIVE AND ONGOING SHORTAGES – 5 YEAR TREND

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ACTIVE SHORTAGES
TOP 5 DRUG CLASSES

Antimicrobials: 26
Chemotherapy: 15
Cardiovascular: 12
CNS: 19
E-Lytes, Nutrition: 20

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REASONS FOR SHORTAGES AS DETERMINED BY UUDIS DURING INVESTIGATION

2016

- Unknown 52%
- Manufacturing 29%
- Supply/demand 15%
- Regulatory 1%
- Discontinued 6%

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WHAT DO THESE NUMBERS MEAN?

• The rate of new shortages has decreased
• Long-term active and ongoing shortages are not resolving
• Shortages of basics like sodium bicarbonate, emergency syringes, antibiotics, electrolytes, and cardiovascular agents still impact large numbers of clinicians and patients

WHY IS THIS HAPPENING?
WHAT ARE KEY CAUSES OF DRUG SHORTAGES?

a. Raw material issues  
b. Counterfeit products  
c. US manufacturing moving overseas  
d. None of the above
SHORTAGE REASONS – MYTHS VS. REALITY CHECK

- US problem only
- Raw materials
- Foreign manufacturing
- Imports are the fix
- Counterfeits cause shortages in US
- One single reason for shortages

- Europe, Canada, US
- Rare cause
- Issues at US facilities
- No product to import
- Rare cause, global problem
- Complex problem
JUNE 2016 GAO ANALYSIS

- GAO reviewed UUDIS, FDA data
- Factors associated with shortages – 2012 to 2015
  - Fewer suppliers with at least 1 with a warning letter for not following CGMP
  - Generic products – lower profit margins
ARE SHORTAGES FDA’S FAULT?

a. True
b. False
ARE SHORTAGES FDA’S FAULT?

NO
- FDA shortage team is extremely collaborative
- Violations must be extreme for a shut-down (safety first!)
- Work diligently to prevent shortages

YES
- Enforcement actions can cause shortages
- Manufacturers may have trouble complying with regulations
- Regulatory discretion = unintended consequences?
FDA’S STRATEGY

• Prioritize medically necessary agents (determined on a case by case basis)
• Evaluate risks and benefits for patients
• Offer assistance and advise, but up to the manufacturer to fix
• Success hinges on early notification

HOW DOES FDA PREVENT SHORTAGES?

• Regulatory discretion
  – Require filters, double checks
• Ask others to increase production
• Expedite reviews (new product, longer expiration, new raw material, new manufacturing sites)
• Imports

IMPORTS

• Multiple examples since 2010
  – propofol, foscamet, ethiodol, thiotepa, norepinephrine, capecitabine, leucovorin, levoleucovorin, methotrexate, doxorubicin liposomal, phentolamine, sodium bicarbonate, nitroglycerin, saline, bleomycin

• Limited by quantity available to share with US market
  – May be difficult to access or use
  – May not be an option for some clinical trials
FDA STRATEGIC PLAN

• Mandated as part of FDASIA law
• 2 key goals
  – Enhance mitigation efforts
  – Develop long-term prevention
• Suggestions for external stakeholders
  – Manufacturing incentives
  – Use quality data when purchasing
  – Capacity, redundancy

HOW DID WE GET HERE?
Early 2000’s “Find production efficiencies”

Dr. Hamburg FDA increases scrutiny

Irvine plant closes

New York plant closes

30% manufacturing capacity is closed

2008

Heparin

Warning letters, 483’s document serious quality problems

2009

Ohio plant closes

2010+

FORM 483 AND WARNING LETTERS

• 483 - documents inspection findings
• Warning letters – significant issues
• Worth reading – even with redactions
  – Metal particles, mold, contamination
  – Insects, animals
  – Urine
  – Manipulating data, mixing good with failed API
FRAGILE SUPPLY CHAIN
GENERIC INJECTABLES

- Few suppliers
  - 3 manufacturers supply 71% of market
  - Only 1 or 2 manufacturers for > 1/3 products
- Capacity is limited
  - Concentrated, “just in time” production
  - Multiple products made on single line
  - No backup manufacturing lines

Mayo Clinic Proc. 2014.89(3):361-373
Drug manufacturing is a business

- Profitability
- Manufacturing fixes
- Capacity – most factories running 24/7
- Prioritization (new opportunities)
- Forecasting (contracts)
- Aging facilities
NO QUICK AND EASY FIX

- Complex manufacturing process
  - Quality problems are difficult to fix
  - Investigation of root cause takes time
  - Changes take time
  - Capacity or redundancy not available
ECONOMIC DRIVERS OF DRUG SHORTAGES

Quality

No Incentive  Not Transparent

Mayo Clinic Proc. 2014. 89(3):361-373
WHAT DOES QUALITY MEAN?

- Difficult to observe
- Microbial contamination difficult to detect (non-uniform, patients already sick)
- Purchasers rely on FDA to ensure quality
- FDA inspects, but relies on manufacturer to self-report between inspections
- Does quality = availability?
NO REQUIREMENT TO REPORT MANUFACTURER OF PRODUCT

• Contract manufacturing means we don’t always know who makes the product
• No requirement to disclose manufacturer (or location) in product label (or 483)
• Your brand product may be manufactured by a generic company
ISN’T THIS A FREE MARKET ISSUE?

• Supply and demand doesn’t work - choice, market entry not easy
• How to purchase for quality?
• Shortages generally don’t impact profits
• Patients and clinicians impacted, not suppliers
FIXING THE SHORTAGE PROBLEM
INDUSTRY BASED EFFORTS

• Accelerated Recovery Initiative (2011)
  – GPhA developed plan
  – Partnership between IMS and generic manufacturers
  – No case studies yet – capacity

INTERNATIONAL SOCIETY FOR PHARMACEUTICAL ENGINEERING

• Survey -2013
  – Key deficits in quality systems, aseptic processing equipment

• Shortage initiative
  – Root causes of manufacturing problems

• Prevention Plan (October 2014)
  – 6 dimension plan

• Quality Metrics

Office of Pharmaceutical Quality

CDER’s Office of Pharmaceutical Quality’s (OPQ) mission is to assure that quality medicines are available for the American public.

What OPQ Does

OPQ is a new office within CDER that creates a single unit dedicated to product quality. The new structure, which stood-up in January 2015, provides better alignment among all drug quality functions at CDER, including review, inspection, and research.

OPQ combines non-enforcement-related drug quality work into one super-office, creating one quality voice and improving our oversight of quality throughout the lifecycle of a drug product. OPQ creates a uniform drug quality program across all sites of manufacture, whether domestic or foreign, and across all drug product areas – new drugs, generic drugs, and over-the-counter drugs.
QUALITY METRICS GOALS

• Modernize drug quality oversight
• Risk based inspection scheduling, predictive of drug shortages
• Objective criteria including:
  – Lot acceptance rate
  – Product quality complaint rate
NEW IDEAS FOR MANUFACTURING

• Janet Woodcock advocates continuous manufacturing for:
  – Faster, improved quality, lower prices, fewer shortages
  – Domestic plants - fully integrated from API to finished product

CONTINUOUS MANUFACTURING

• Traditional manufacturing = batch process
  – At every step, product is assessed and collected
  – Off-line labs test finished product
  – Days to weeks processing time

• Continuous manufacturing = monitoring throughout
  – Minutes to hours processing time
BEST PRACTICES TO MINIMIZE IMPACT
Rationing Salt Water — Disaster Planning and Daily Care Delivery

John L. Hick, M.D., Dan Hanfling, M.D., Brooke Courtney, J.D., M.P.H., and Nicole Lurie, M.D., M.S.P.H.

NEJM, March 19, 2014

• Mitigation
• Preparedness
• Response
• Recovery
MANAGING MEDICATION SHORTAGES

- No single emergency – daily emergencies
- Pharmacists and other clinicians successfully manage shortages every day
- Best practice = **Have a Plan**
- Best practice = **Make a Team**
TEAM CHECKLIST – WHO WILL...

✓ Gather data, monitor the shortage?
✓ Make purchasing decisions?
✓ Make storage, preparation, and dispensing change decisions?
✓ Make rationing decisions?
✓ Change technology?
✓ Communicate information?
SHORTAGE MANAGEMENT TEAM COMMUNICATIONS

• Make sure each member understands their role and shares back information
• Situations can change quickly
• Efficient management relies on good team communication
• Timeliness is essential
COMPLEX PROBLEM SOLVING

Clinical Impact

Operations Impact

Patient Impact
MANAGEMENT STRATEGY

- Customize – what type of shortage?
  - Some drug available
    - Ration vs. use until gone
  - No drug available, use alternatives
  - No drug available, no alternatives
    - Postpone therapy vs. no therapy
  - Must customize for acuity / impact
    - (IV fluids vs. chemotherapy vs. vaccine)
MOST COMMON SITUATION
WE CAN GET SOME BUT...

- It’s a different strength
- It’s in different packaging
- It’s a different size
- It’s from a different manufacturer
- It’s imported
- It’s not enough!
WHICH SITUATION COULD LEAD TO THE GREATEST HARM?

a. Same drug – different strength
b. Same drug – different packaging
c. Imported drug
d. No drug available
• It depends….
• Different strength most concerning according to failure modes and effects analysis
  – SALA errors possible with different packaging, manufacturers
  – Imported product (lack of barcode, NDC, packaging differences)
  – Range of patient impact

Hospital Pharmacy. 2011;46(12):943-951
RATIONING AND ETHICS

• Don’t ration alone
• Example tools available by drug class
• Chemotherapy
• Antimicrobials
MESSAGING

- Balance timeliness and completeness.
- Initial plan and ongoing status updates:
  - Will product look different - pictures!
  - Alternative agents - include dose, drug interactions, safety issues.
  - Conservation strategy - which patients are eligible?
  - Decision making process transparency.
THE TREND IN DRUG SHORTAGES FOR 2016 IS ONE OF:

a. Decreasing new shortages and increasing active shortages
b. Increasing new shortages but decreasing active shortages
c. Slight increase in new shortages and decreasing active shortages
d. Decreasing new shortages and a gradual decrease in active shortages
THE REASON FOR MOST SHORTAGES IS:

a. Raw material shortages
b. Natural disasters
c. Manufacturing or quality problems
d. Corporate decisions
PACKAGE INSERTS MUST INCLUDE:

a. Name of the company that manufactured the drug
b. Location of the factory
c. Country of origin for the active pharmaceutical ingredient (API)
d. None of the above
FDA CAN PREVENT SOME SHORTAGES BY:

a. Prioritizing approvals of new products
b. Forcing companies to increase production
c. Forcing companies to continue to produce a drug
d. Decreasing drug prices
DETERMINING POTENTIAL CLINICAL IMPACT OF A SHORTAGE INCLUDES:

a. Whether an alternative is available
b. Identifying which patients will be most impacted
c. Determining if the product is life-saving or curative
d. All of the above
FINAL THOUGHTS
IT MAY GET WORSE BEFORE IT GETS BETTER.

• FDA increasing inspectors in India, China
• Factories with past problems sold – will $$ be spent to truly fix?
• Focus on biosimilars
• Who will make the basics that we need?
BUT THERE IS SOME HOPE

• Trend of decreasing new shortages is real
• Action is moving towards prevention, early identification of manufacturing issues
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