Understanding Drug Shortages
June 6, 2016
Poll

Please take a moment to answer the open poll question.

What is your affiliation?

• Federal Government
• State Government
• Local (City or County) Government
• Other
Introduction of moderators

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Introduction of speakers

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Agenda

• Welcome
• Introduction and Overview
• Understanding Drug Shortages
• Preventing and Mitigating Drug Shortages – FDA’s and Manufacturers’ Roles
• Discussion
• Recap and Closing
Objectives of this session

• Understand the basic challenges surrounding drug shortages.

• Understand how drug shortages occur.

• Understand what steps are currently being undertaken to resolve them.

• Understand the role of the FDA in drug shortages.
Understanding Drug Shortages
This presentation represents my own opinions.

University of Utah Drug Information Service (UU DIS) receives some funding from Vizient to provide drug shortage content.
UU DIS provides drug shortage content to American Society of Health-System Pharmacists (ASHP) and Novation

Public website at www.ashp.org/shortage

- Partners since 2001
- Receive voluntary reports submitted via web
- Collaboration is key to success
- Frequent communication with FDA drug shortage team
Please take a moment to answer the open poll question.

Are drug shortages an immediate concern for your preparedness plans?

• Yes
• No
• Not sure
# Shortage Website Differences

<table>
<thead>
<tr>
<th>ASHP</th>
<th>FDA</th>
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</thead>
<tbody>
<tr>
<td><a href="http://www.ashp.org/shortage">www.ashp.org/shortage</a></td>
<td><a href="http://www.fda.gov/cder">www.fda.gov/cder</a></td>
</tr>
<tr>
<td>• Shortages impacting clinical practice (biologics, devices, dosage forms)</td>
<td>• No biologics or devices</td>
</tr>
<tr>
<td>• How to access</td>
<td>• Information from manufacturer</td>
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<tr>
<td>• Alternatives, safety</td>
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Current Trends in Drug Shortages
National Drug Shortages (Source: UU DIS)
New Shortages by Year (Jan 2001 to Mar 2016)

Note: Each column represents the number of new shortages identified during that year.
National Drug Shortages Active Shortages by Quarter (Source: UU DIS)

Note: Each column represents the number of active shortages at the end of each quarter.
Active Shortages: Top 5 Drug Classes (Source: UU DIS)

Active Shortages March 31, 2016

- Antimicrobials: 34
- Chemotherapy: 16
- Cardiovascular: 20
- CNS: 25
- E-Lytes, Nutrition: 28
What Do These Numbers Mean?

• The rate of new shortages has decreased

• Long-term active and on-going shortages are beginning to resolve

• Shortages of basics like antibiotics, electrolytes, and diagnostic dyes impact large numbers of clinicians and patients

http://www.gao.gov/products/GAO-14-194
Why are shortages happening?
Poll

Please take a moment to answer the open poll question.

What do you think is the most common cause of drug shortages?

• Increase in demand
• Production issues (manufacturing)
• Availability of generic products
• Government regulation
• I don’t know
### Shortage Reasons: Myths vs. Reality Check

<table>
<thead>
<tr>
<th>Myths</th>
<th>Reality</th>
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<tbody>
<tr>
<td>U.S. problem only</td>
<td>Europe, Canada, U.S.</td>
</tr>
<tr>
<td>Foreign manufacturing</td>
<td>Rare cause</td>
</tr>
<tr>
<td>Raw materials</td>
<td>Issues at U.S. facilities</td>
</tr>
<tr>
<td>Imports are the fix</td>
<td>No product to import</td>
</tr>
<tr>
<td>Counterfeits cause shortages in U.S.</td>
<td>Rare cause, global problem</td>
</tr>
<tr>
<td>One single reason for shortages</td>
<td>Complex problem</td>
</tr>
<tr>
<td>Shortages are FDA’s fault</td>
<td>FDA works to prevent shortages</td>
</tr>
</tbody>
</table>
Example: Cascade of Events

Early 2000’s “Find production efficiencies”

Dr. Hamburg FDA increases scrutiny

2008

Heparin

Warning letters, 483’s document serious quality problems

2009

Irvine plant closes

New York plant closes

2010+

Ohio plant closes

2012 - 30% manufacturing capacity is closed

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 back up manufacturing lines

IV Fluids Shortage

• 3 suppliers
• Real reason why shortage happened unclear
  – Low capacity, increased demand, recalls
• Major impact
  – Treatment and supply
  – Impact to all treatment settings
• Additional manufacturing approved
Unique Safety Issues

• Hospitals, infusion centers rely on specific volumes, solutions, and concentrations

• Changes to product concentrations are high risk
  – Stability issues
  – Administration errors
  – IV pump issues
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
Poll

Please take a moment to answer the open poll question.

What strategies do you have in place to deal with a shortage?

- Sharing plans
- Partnerships
- No plan
- Not sure
Isn’t This A Free Market Issue?

• Supply and demand doesn’t work - consumers don’t choose products

• How to purchase for quality?

• No suppliers to step in when others can’t produce

• Shortages generally don’t impact profits

• Patients and clinicians impacted, not suppliers
Economic Drivers of Drug Shortages

Quality

No Incentive

Not Transparent
Label Transparency Needed

• 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

*Form 483 (Inspectional Observations) is a form used to document findings from inspections (More information here: http://www.fda.gov/ICECI/Inspections/ucm256377.htm)
High Costs

• Many reasons for increases
  – Shortages
  – Unapproved products approved
  – Sole source product
  – Opportunity / Free Market

• Require shortage management strategies
Action on High Cost Meds?

• Senate hearings to continue

• FDA will now prioritize abbreviated new drug applications (ANDAs) for drugs without competition
  – Will suppliers step up?
  – Any suppliers with good quality?

• Executive order to allow Medicare to negotiate?
Managing Medication Shortages is Similar to Disaster Management

- No single emergency – daily emergencies
- Pharmacists and other clinicians successfully manage shortages every day, minimizing patient impact
- Increasing rates of shortages means many hospitals operating in crisis mode for their medication supply chain.
- Best practice = **Have a Plan!**
PREVENTING AND MITIGATING DRUG SHORTAGES – FDA’S AND MANUFACTURERS’ ROLES

CAPT Valerie Jensen R.Ph.
Associate Director, Drug Shortage Staff
Center for Drug Evaluation and Research
US Food & Drug Administration
DISCLAIMER

- Nothing to disclose
OBJECTIVES

- Drug shortage staff (DSS) mission
- Drug shortage and legislation
- FDA response to prevent and mitigate
- FDA and manufacturer roles/responsibilities/communication
- Report a shortage/supply issue
DRUG SHORTAGE STAFF

- Our mission is to prevent, mitigate and help resolve shortages
- DSS also does outreach to professional organizations, patient groups, the public and other stakeholders
- Part of the Center for Drug Evaluation & Research (CDER)
  - DSS began in 1999
  - Today: 13 full-time staff (from 4 in 2011)
Drug Shortage Staff

- DSS facilitates prevention and resolution of shortages by working with key stakeholders from the FDA, other government agencies, industry, and the public
  - Within the FDA, DSS works closely with:
    - Office of New Drugs (OND)
    - Office of Pharmaceutical Quality (OPQ)
    - Office of Generic Drugs (OGD)
    - Office of Compliance
    - Office of Regulatory Affairs Field Inspectors
    - And many more!
Please take a moment to answer the open poll question.

How aware of legislation and rules that impact drug shortages are you?

• I am aware of the legislation/rules
• I am aware of some of the legislation/rules
• I am not aware of the legislation/rules
• Unsure
SHORTAGES, LEGISLATION, AND THE FDA RESPONSE

- Executive order (EO #13588) to require early notification (2011)
- Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted in July 2012, requiring increased notifications
- FDA Strategic Plan issued October 31, 2013- FDA’s response to drug shortages
SHORTAGES, LEGISLATION, AND THE FDA RESPONSE

- Current shortage information updated daily at fda.gov
  - Mobile App: The app is available for free download via iTunes (for Apple devices) and the Google Play store (for Android devices) by searching “FDA Drug Shortages.”

- Resources were increased and staff expanded
SHORTAGES, LEGISLATION, AND THE FDA RESPONSE

- Reporting shortages is encouraged
  - Email: drugshortages@fda.hhs.gov
    - Contact from the public about existing shortages
    - Contact from industry about potential shortages

- Collaboration on system fixes and root problem resolution by working with various stakeholders
  - ASHP
  - Professional associations and patient groups
  - Industry groups:
    - Generic Pharmaceutical Association (GPhA)
    - Pharmaceutical Research and Manufacturers of America (PhRMA)
Drug Shortage Data Sources

Data about drug shortages comes from points all across the supply chain:

- FDASIA required reporting – enacted July 2012
  - Industry required to supply information
  - Wholesalers voluntarily supply inventory and interruptions
  - Pharmacy hospital sales provided via IMS sales/marketing data
  - Public notification via email from patients/practitioners
- Not all points in the supply chain are required to report supply data per FDASIA
  - Repackagers
  - Secondary wholesalers/distributers
  - Compounders
Drug Supply Chain – 1st Tier

Supplier → Manufacturer → Wholesaler → Pharmacy/Hospital → Patient/Health Care Provider

Inventory/Production Data:
Voluntarily Supplied
Supply Interruptions:
Required per FDASIA

Inventory/Supply Interruptions:
Voluntarily Supplied

Sales/Market Share Data:
Reported to FDA via IMS

Public Notifications:
FDA Drug Shortages email account
**Drug Supply Chain – 2\textsuperscript{nd} Tier**

Very limited to no data available to FDA regarding these 2\textsuperscript{nd} tier supply sources.
DRUG SHORTAGE DATA

- There were 251 shortages reported in 2011; 117 shortages were reported in 2012; 44 shortages were reported for both 2013 and 2014, and 26 in 2015 (Source: FDA)

- A high percentage are sterile injectables
  - Chemotherapy, anesthesia, injectable nutritional medications, and other acute meds
  - Highly specialized manufacturing processes
  - High risk to patient if process is not meticulous

- When there are quality or production problems for sterile injectables, the result is almost always a shortage
Number of Shortages from FDA Database (2005 – 2015)

- **All Forms**
- **Sterile Injectables**
Reasons for Drug Shortages: 2013

- Quality: Delays/Capacity (37%)
- Quality: Manufacturing issues (27%)
- Discontinuation (2%
- Raw Materials (API) (27%)
- Shortage of Component (27%)
- Increased Demand (5%)
- Loss of Mfg Site (0%)
CAUSES OF SHORTAGES: STERILE INJECTABLES

- Quality and manufacturing issues
  - Sterility: Bacterial and fungal contamination
  - Particulates: Glass, metal or fiber in vials
  - Crystallization: Drug may form crystals
  - Precipitate: Reaction between drug and container or diluent
  - Impurities: Can be toxic (heavy metals)
  - Degradants: Lead to less effective drug product
  - Equipment breakdown
  - Natural disasters
HOW DOES THE FDA FIT?

- Patient care is our #1 concern
- We get involved when we are informed
  - Early notification is critical
  - FDASIA: requires pharmaceutical companies to notify FDA, when manufacturing interruptions or production changes could lead to a supply disruption or discontinuation at least six months in advance or as soon as practicable
  - Not limited to sole source manufacturers or medically necessary product
**Drug Shortage: Definition**

“A period of time when the demand or projected demand for the drug within the United States exceed the supply of the drug. In general, the DSS focuses on shortages of medically necessary product that have a significant effect on public health.”

CDER Manual of Policies and Procedures on Drug Shortage Management 4190.1 Rev 2

MEDICAL NECESSITY: DEFINITION

“Any drug product used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other drug that is judged by CDER medical staff to be an appropriate substitute or there is an inadequate supply of an acceptable alternative as determined by the DSS. Off-label uses of approved drugs, marketed unapproved drugs, and IND drugs may be considered medically necessary. Patient inconvenience alone is an insufficient reason to classify a drug product as medically necessary.”

CDER Manual of Policies and Procedures on Drug Shortage Management 4190.1 Rev 2
Please take a moment to answer the open poll question.

Are you clear on the authorities that the FDA has to avoid and address shortages?

• Yes – I am aware of their authorities
• Yes – they have no authorities
• No
**How Does the FDA Fit?**

- Some can be addressed quickly while others require more time
  - Risks to the patient are always considered

- Quality issues
- CGMP issues

Approved products that are considered adulterated or misbranded

→ Risk to Patients

- Risk of reduced efficacy or SAEs
- Risk of no treatment or inadequate alternatives

→ Risk to Patients

- Lack of sufficient supply or treatment alternatives
- Unapproved supply
- Grey market

→ Risk to Patients
# The FDA’s Approach To Prevention and Mitigation

<table>
<thead>
<tr>
<th>What we CAN require</th>
<th>What we CANNOT require</th>
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<tbody>
<tr>
<td>Notification by manufacturers (FDASIA)</td>
<td>A company to make a drug</td>
</tr>
<tr>
<td>- Supply disruptions</td>
<td></td>
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<tr>
<td>- Delays</td>
<td></td>
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<tr>
<td>- Discontinuations</td>
<td></td>
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<td>Notification of manufacturing changes</td>
<td>A company to make more of a drug</td>
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<td></td>
<td>How much and to whom the drug is distributed</td>
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THE FDA’S APPROACH TO PREVENTION AND MITIGATION

- DSS first verifies any risk of shortage
  - Immediacy, shortfall, and duration relative to market data
  - Timing or capacity constraints across other manufacturers
  - Availability of adequate alternative drug treatments
- Prioritize products that are medically necessary
- Coordinate across agency from timely and comprehensive, risk/benefit decisions
THE FDA’S APPROACH TO PREVENTION AND MITIGATION

- Maintain availability while minimizing risk to patients
- Work with manufacturing companies to address problems
  - We can advise, assist and expedite but the manufacturer must fix the problem
  - Early notification is key!!
INTERNAL AND EXTERNAL COMMUNICATION DURING SHORTAGE MANAGEMENT
Averted Drug Shortages: 2010-2013

Injectables
All Forms

2010 2011 2012 2013 2014 2015

10/25/2016
Drug shortages can not always be prevented

- Unanticipated events occur
  - Manufacturing line breakdown or natural disaster (tsunami)
- Sometimes manufacturer may not make up production shortfall
- If systemic issues present, the plant may have to close to repair
- The FDA and the manufacturer can work together to encourage smart distribution
  - No easy way to do this well
FDA TOOLBOX

- **Regulatory Discretion:**
  - Allows for manufacture of medically necessary products to continue
    - Minor, low risk issues are best suited for this tool
  - May require additional safety controls
    - Filters with product; extra testing; 3rd party oversight of production; special instructions for safe use

- **Request** other firms to increase production
FDA TOOLBOX

- Expedite any review of company proposals
  - New manufacturing sites, increased expiry date, new raw material source, changes in specifications, etc.

- In rare cases, temporary importation from unapproved sources
  - 2010: propofol
  - 2011: foscarnet, ethiodol, thiotepa, norepinephrine, Xeloda, levoleucovorin, leucovorin injection
  - 2012: methotrexate injection, doxorubicin liposomal, propofol, phentolamine
  - 2013: sodium bicarbonate injection, phosphate injection, trace elements (pediatric and adult), IV Lipids, calcium chloride injection, zinc injection, lomustine
  - 2014: IV saline, nitroglycerin injection, peritoneal dialysis (PD) solution
  - 2015: ethiodol injection
  - 2016: tretinoin capsules
Please take a moment to answer the open poll question.

What role do you think importing (from a country like Canada) plays on drug shortage management?

- Importing plays a large role
- Importing plays some role, but not significant
- Importing plays no role
- Unsure
ROLE OF INDUSTRY

- Communicate early about potential shortages
- Provide shortage information for posting on FDA website when shortage is unavoidable
- Provide short term and long term plans for preventing and addressing shortages while maintaining and improving quality
- Work with FDA to minimize shutdowns or slowdowns that will lead to shortages
STRENGTHENING RESPONSE TO POTENTIAL SHORTAGE: FDA AND MANUFACTURERS

- FDA responds promptly and efficiently to notification of a shortage
- Perform risk-based analysis to determine ways to address shortage
  - Work with the manufacturer to address the problem and utilize regulatory discretion for release if possible
  - Determine if other manufacturers can increase production
  - Expedite inspections and review of submissions
  - Exercise regulatory discretion for new sources of medically necessary drugs
- Communicate effectively to stakeholders
THE FUTURE

FDA drug shortages work will continue

- Multidisciplinary: clinicians, pharmacists, chemists, biotechnology, regulatory and manufacturing
- We can only prevent shortages if problems are reported
- Public communication of existing shortages

Focus on industry commitment to a culture of quality manufacturing

- Need focus on manufacturing infrastructure, quality systems
- Need production redundancy
- Need appropriate facility maintenance
- Promptly report and correct even small production and quality problems
- Continued discussions with FDA about ways to support quality manufacturing
IN SUMMARY

FDA and Manufacturer Roles in Drug Shortages

- Work with manufacturers, progress is being made to prevent and mitigate critical shortages
- Challenges remain: a single shortage of a critical drug is unacceptable
- FDA has strategic vision, but cannot solve drug shortages alone
- Industry commitment to a culture of quality manufacturing needed
HOW TO REPORT SHORTAGE/SUPPLY ISSUE TO FDA

- **Center for Drug Evaluation and Research (CDER)**
  - Email: drugshortages@fda.hhs.gov
  - Phone: 1-888-INFOFDA or 1-888-463-6332, or (301) 796-3400

- **Center for Biologics Evaluation and Research (CBER)**
  - Email: CBERshortage@fda.hhs.gov
  - Phone: (240) 402-8380
HOW TO REPORT SHORTAGE/SUPPLY ISSUE TO FDA

- **Center for Veterinary Medicine (CVM)**
  - Email: ASKCVM@fda.hhsgov
  - Phone: (240) 276-9300

- **Center for Devices and Radiological Health (CDRH)**
  - Email: dsmica@fda.hhs.gov
  - Phone: 1-800-638-2041 or (301) 796-7100

- **Center for Food Safety and Nutrition (CFSAN)**
  - Website:
    [http://www.fda.gov/Food/RecallsOutbreaksEmergencies/default.htm](http://www.fda.gov/Food/RecallsOutbreaksEmergencies/default.htm)
  - Phone: 1-888-SAFEFOOD or 1-888-723-3366
Discussion
Questions for all speakers
Poll

Please take a moment to answer the open poll question.

How valuable did you find this webinar?

• Very valuable
• Moderately valuable
• Minimally valuable
Poll

Please take a moment to answer the open poll question.

What other topics would you like to see covered in this webinar series?

• Open answer question (Please type your answer in the text box on the screen)
Upcoming webinars

Previous Webinars:
• Navigating the Pharmaceutical Supply Chain
• Partnering with the Pharmaceutical Supply Chain

Slides and recordings for both webinars are available at: https://www.healthcareready.org/programs/healthcare-supply-chain

Upcoming Webinar:
• Principles of Pharmaceutical Regulation
  June 23, 2016 1:30 EDT

Questions? Email – ContactUs@HealthcareReady.org