PREVENTING AND MITIGATING DRUG SHORTAGES – FDA’S AND MANUFACTURERS’ ROLES

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DISCLAIMER

- Nothing to disclose
OBJECTIVES

- Drug Shortage Staff (DSS) Mission
- Drug Shortage and legislation
- FDA response to prevent and mitigate
- FDA and manufacturer’s 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)
  - Drug Shortages Staff (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!
SHORTAGES, LEGISLATION, AND THE FDA RESPONSE

- Executive order to require early notification (2011)
- Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted in July 2012, requiring increased notifications
- 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:
  - American Society of Health-System Pharmacists (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

- **Sales/Market Share Data:** Reported to FDA via IMS

- **Public Notifications:** FDA Drug Shortages email account
**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.

- 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.**
REASONS FOR DRUG SHORTAGES: 2013

- Quality: Delays/Capacity
- Quality: Manufacturing issues
- Discontinuation
- Raw Materials (API)
- Shortage of Component
- Increased Demand
- Loss of Mfg Site

R E A S O N S 
F O R 
D R U G 
S H O R T A G E S :
2013

27%
37%
2%
27%
5%
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
**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

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

→ Risk to Patients

- Risk of reduced efficacy or SAEs
- Risk of no treatment or inadequate alternatives
THE FDA’S APPROACH TO PREVENTION AND MITIGATION

What we CAN require:
- Notification by manufacturers (FDASIA)
  - Supply disruptions
  - Delays
  - Discontinuations
- Notification of manufacturing changes

What we CANNOT require:
- A company to make a drug
- A company to make more of a drug
- How much and to whom the drug is distributed
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 firms 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
THE FDA’S APPROACH TO PREVENTION AND MITIGATION

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
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

- **Drug Shortages Mobile App**
  
  The FDA Drug Shortages app is available for free download via iTunes (for Apple devices) and the Google Play store (for Android devices) by searching "FDA Drug Shortages."
HOW TO REPORT SHORTAGE/SUPPLY ISSUE TO FDA

- **Center for Biologics Evaluation and Research (CBER)**
  - Email: [CBERshortage@fda.hhs.gov](mailto:CBERshortage@fda.hhs.gov)
  - Phone: (240) 402-8380

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

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

FDA Drug Shortages Homepage:
http://www.fda.gov/drugs/drugsafety/default.htm

To report drug shortages, email:
drugshortages@fda.hhs.gov

FDA Webinar on Prescription Drug Shortages of September 30, 2011:
http://www.fda.gov/AboutFDA/Transparency/Basics/um272223.htm

Manual of Policies and Procedure (MAPP 4190.1 Rev.2)

Office of the Center Director: Drug Shortage Management:
THANK YOU FOR YOUR TIME!
## Appendix

### FDA Drug Shortages

**Current and Resolved Drug Shortages and Discontinuations Reported to FDA**

Report a Drug Shortage | Contact Us | FAQ | Background Info | Get Email Alerts | RSS Feed

**Search by Generic Name or Active Ingredient:** Enter at least three characters [Submit]

#### Current and Resolved Shortages Listed by Generic Name or Active Ingredient

<table>
<thead>
<tr>
<th>Generic Name or Active Ingredient</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetohydroxamic Acid (Ibogaine) Tablets</td>
<td>Currently in Shortage</td>
</tr>
<tr>
<td>Ammonium Chloride Injection</td>
<td>Currently in Shortage</td>
</tr>
<tr>
<td>Anagrelide Hydrochloride Capsules</td>
<td>Currently in Shortage</td>
</tr>
<tr>
<td>Aprajitant (Emera) Capsules</td>
<td>Currently in Shortage</td>
</tr>
<tr>
<td>Atropine Sulfate Injection</td>
<td>Currently in Shortage</td>
</tr>
<tr>
<td>Azathioprine Tablet</td>
<td>Currently in Shortage</td>
</tr>
<tr>
<td>Barium Sulfate for Suspension</td>
<td>Resolved</td>
</tr>
<tr>
<td>Bupivacaine Hidrochloride (Marcaine, Enozonaine) Injection</td>
<td>Resolved</td>
</tr>
<tr>
<td>Caffeine Anhydrous (125mg/mL), Sodium Benzoate (125mg/mL) Injection</td>
<td>Currently in Shortage</td>
</tr>
<tr>
<td>Calcium Chloride Injection, USP</td>
<td>Currently in Shortage</td>
</tr>
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APPENDIX