Clinical Implications of Drug Shortages: FDA Perspective

Douglas C. Throckmorton, MD
Deputy Director for Regulatory Programs,

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Disclosure Statement

I have no financial relationships with proprietary entities that produce health care goods and services.

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA.
Outline

• Shortages as significant public health threat
  – Sources of drug shortages
• FDA role in drug shortages
  – Role and impact of early notification by manufacturers
• Recent Activities
  – Expanded International Work
  – Recognition of manufacturer contributions to shortage issues
• Future Directions
  – Continued Cooperation
  – Support for Quality Manufacturing
Public Health Importance of Drug Shortages

- Tretinoin capsules for acute promyelocytic leukemia (APL)
- Erwinaze for children with acute lymphoblastic leukemia (ALL)
- Sucraid for genetic sucrase-isomaltase
- IV Normal Saline for hydration
- Zinc for parenteral nutrition in neonates/premature infants
- Doxorubicin for ovarian cancer and other cancers
Sources of Drug Shortages: Quality Manufacturing Issues

- Quality: Facility Remediation Efforts (35%)
- Quality: Product Manufacturing Issues (14%)
- Discontinuation of Product (8%)
- Raw Materials (API) Shortage (6%)
- Other Component Shortage (4%)
- Increased Demand (2%)
- Loss of Manufacturing Site (14%)
Examples of Quality Manufacturing Issues

- Sterility: Bacterial and fungal contamination
- Particulates: Glass, metal or fiber in vials
- Crystallization: Drug may form crystals
- Precipitation: Reaction between drug and container or diluent
- Impurities: Can be toxic (heavy metals)
- Degradants: Lead to less effective drug product
- Equipment breakdown, need for remediation
- Natural Disasters
Sources of Shortages: Sterile Injectables

• State of the Industry
  – Small number of manufacturers make up most of the market
  – Contract manufacturers acting as both firms contracting out manufacturing as well as acting as contract manufacturers

• Lack of redundant manufacturing
  – Multiple products made on existing manufacturing lines
  – 24/7 production with no time cushion
Sources of Drug Shortages: Sterile Injectables (cont)

• Complex manufacturing processes
  – Problems typically affect multiple products at once

• Investment economics question
  – One vial of propofol 20 mL sells for $0.48
  – Is there profit to be made in producing propofol?
FDA and USG Response to Drug Shortages: Early Notification
Early Notification

• October 31, 2011
  – Executive Order from President Obama directing FDA to use its authorities to encourage early notification of potential shortages

• December 19, 2011
  – Interim Final Rule published to improve advance notification of potential shortages

• July 9, 2012
  – FDASIA broadens scope of early notification requirements
  – Requires Strategic Plan and Annual Report on Drug Shortage Efforts
Early Notification

• Early notification is key
• The sooner FDA knows about a potential disruption in supply the better chance of resolution
• Failure to notify will result in a non-compliance letter to the manufacturer
• Four non-compliance letters issued to date for failure to notify
Manufacturer Notifications of Potential Supply Disruptions

- **Number of Notifications**
- **Number of Manufactures**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Notifications</th>
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<tr>
<td>2011</td>
<td>220</td>
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<tr>
<td>2012</td>
<td>400</td>
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<td>2014</td>
<td>150</td>
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<td>2015</td>
<td>200</td>
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Notification Source: Sterile Injectable Drug Shortages: 2013

- Manufacturer: 40%
- FDA - Inspection: 43%
- FDA - Other: 14%
- Public: 3%
- ASHP: 0%
Averted Drug Shortages: 2010-2015
FDA Response to Drug Shortages: Strategic Plan

- Created by Taskforce of FDA personnel
  - Drug Shortage Staff, Office of Compliance, Office of Generic Drugs, Office of Regulatory Programs, Center for Biologics Evaluation and Research, ORA
- Strategic Plan released October 31, 2013
- Two Overarching Goals:
  - Strengthening FDA’s ability to respond to notices of a disruption in supply, including improving our mitigation tools and communications
  - Developing long-term prevention strategies to address the underlying causes of supply disruptions and prevent drug shortages
Strengthening FDA’s Response to Potential Shortage: FDA Actions

• Respond promptly and efficiently to notification of a shortage

• Perform risk-based analysis to determine ways to address shortage
  – Determine if other manufacturers can increase production
  – Expedite inspections and reviews of submissions
  – Exercise temporary enforcement discretion for new sources of medically necessary drugs
  – Work with the manufacturer to ensure adequate investigation into the root cause of the shortage
  – Review possible risk mitigation measures for remaining inventory

• Communicate effectively to stakeholders
Strengthening FDA’s Response to Potential Shortage: FDA Actions

• Current shortage information updated daily at fda.gov
  – http://www.accessdata.fda.gov/scripts/drugs/hortages/default.cfm
  – 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
Strengthening FDA’s Response to Potential Shortage: FDA Actions

• 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
    - Repackers
    - Secondary wholesalers/distributers
    - Compounders
Current State: Drug Shortages

All Forms

Sterile Injectables

Current State: Ongoing Shortages at End of Calendar Year
The Future of Drug Shortages

• FDA
  – Drug Shortages are a continued priority for FDA resources and attention
  – Ongoing FDA focus on internal agency processes
  – Ongoing FDA focus on cooperation with manufacturers, patients, patient groups, international regulators, other stakeholders
  – Ongoing FDA focus on improved communications
  – Ongoing FDA focus on data quality and transparency
The Future of Drug Shortages

• Focus on Cooperation: no one party can solve drug shortages
  – FDA can only prevent shortages we know about
  – Role for international regulatory cooperation

• Focus on Industry commitment to a culture of quality manufacturing
  – Work to support improved manufacturing practices, methods and quality testing
  – Role for acknowledging critical contributions
  – Promptly report and correct even small production and quality problems
  – Continued discussions with FDA about ways to support quality manufacturing
Focus on International Collaboration

• Expanded international interactions
• Quarterly meetings held between FDA and other regulatory authorities (EMA, TGA, HC, and others). Six meetings held to date
• Information sharing about shortages experienced in the various countries and any other activities related to shortages
• Has been beneficial for all parties in shortage situations to explore potential alternate sources
Recognizing Manufacturing Excellence: Drug Shortage Assistance Award

- Recognizes companies for their efforts in preventing or alleviating a drug shortage
- Brings attention to companies that assist in addressing a drug shortage and prioritizing quality manufacturing
- Serves as an incentive for companies to assist in addressing drug shortages
Drug Shortage Assistance Award

• To date, three companies have been recognized and given this award
  – Guerbet for its efforts related to the shortage of Ethiodol (ethiodized oil) injection
  – Clinigen for its efforts related to the shortage of Foscavir (foscarnet sodium) injection
  – Eurohealh, a subsidiary of Hikma Pharmaceuticals, for its efforts related to the shortages of thiotepa for injection and phentolamine mesylate for injection
Long-term Goal: Prevention of Drug Shortages

• Focus on the underlying causes of production disruptions to prevent drug shortages.
  – Develop Methods to Incentivize and Prioritize Manufacturing Quality
  – Use Regulatory Science to Identify Early Warning Signals of Shortages
    • Proposed Office of Pharmaceutical Quality
  – Increase Knowledge to Develop New Strategies to Address Shortages
    • Important data limitations exist
    • ISPE survey an important tool to aide in this work!
Summary: FDA Role In Drug Shortages

• Working 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
THANKS

• CDER staff who work on drug shortage issues
  – Drug Shortage Staff (Captain Valerie Jensen and her staff)
  – Office of Compliance
  – Office of New Drugs
  – Office of Pharmaceutical Quality
  – Office of Generic Drugs
  – Office of Regulatory Programs
  – Office of Communications