Overview of U.S. Drug Shortages

Susie Dill RN, B.S.N.
Misu Ahn Pharm.D.
Program Management Officer
CDER Drug Shortage Staff
Center for Drug Evaluation & Research
U.S. Food & Drug Administration

DISCLOSURE
I have no financial relationships with industry to disclose.
At the conclusion of this activity, participants should be able to:

- Describe U.S. drug shortage trends
- Describe reasons for drug shortages
- Gain an understanding of FDA’s role and view of the future
- Identify how healthcare professionals can assist the FDA with shortages
Drug Shortage Staff

Our mission is to prevent, mitigate and help resolve shortages

• Center for Drug Evaluation & Research
  – Drug Shortage Staff (DSS) began in 1999
  – Today there are 11 full time staff
• Facilitate prevention and resolution of shortages
• Bring together FDA experts, industry, and external stakeholders
• Inform the public
• Outreach to healthcare professional organizations, patient groups and other stakeholders

Who works on this?
Office of New Drugs
Office of New Drug Quality Assessment
Office of Generic Drugs
Office of Compliance
Field Inspectors
MANY OTHERS!
Shortages – and FDA response

- Current shortage information - website updated daily
- Resources – staff expanded and high level oversight
- Encourage reporting
  - From general public about existing shortages
  - From industry about potential shortages
  - Executive order to promote early notification
  - New FDASIA legislation
- Collaborating on system fixes and root problem resolution by working with various stakeholders
  - American Society of Health-System Pharmacists (ASHP)
  - Industry (GPhA, PhRMA, BIO)
Progress to Date

- Public workshop September, 2011
- President’s Executive Order 13588, October 2011
- FDASIA regulations were signed July 2012
  - Title X of FDASIA, lists the mandatory reporting requirements for manufacturers
- Strategic Plan- submitted to Congress October 2013
Shortages and the FDA Response

**What we can require**

- Notification by manufacturers (FDASIA)
  - Interruptions that could lead to a meaningful supply disruption, discontinuations
  - No penalty for not reporting
  - Notification of manufacturing Changes

**What we can’t require**

- A company to make a drug or make more
- How much and to whom drug is sold or distributed

FDA Drug Shortages Staff largely depends on notification by manufacturers and the public.
Drug Shortage Data

• 251 shortages reported in 2011
• 117 shortages reported in 2012
• 44 shortages reported in 2013
• A high percentage are sterile injectables
  – Chemotherapy, anesthesia 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
Total New US Drug Shortages Per Year

- **All Forms**
- **Sterile Injectables**
Drug Shortages 2012: By Dosage Form

- 73% Injectable
- 15% Oral Solid
- 3% Oral Suspension
- 2% Contrast Agent
- 2% Topical
- 2% Inhalation
- 2% Other
- 1% Ophthalmic
Drug Shortages 2013: By Dosage Form

- Injectable: 80%
- Oral Solid: 18%
- Oral Suspension: 2%
- Contrast Agent: Other
- Topical: Other
- Inhalation: Other
- Ophthalmic: Other
Reasons for Drug Shortages: 2013

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

- **Quality: Manufacturing issues**
- **Delays/Capacity**
- **Discontinuation**
- **Increased Demand**
- **Raw Materials (API)**
- **Loss of Mfg Site**
Reasons for Sterile Injectable Drug Shortages: 2013

- Quality: Manufacturing issues: 37%
- Quality: Delays/Capacity: 23%
- Discontinuation: 6%
- Increased Demand: 3%
- Raw Materials (API): 3%
- Loss of Mfg Site: 28%
Reasons for Shortages: Sterile Injectables

Report by Assistant Secretary for Planning & Evaluation 2011

• State of the industry
  – Six (6) manufacturers make up most of market
  – Contract manufacturers – firms contract out manufacturing as well as acting as contract manufacturers

• Lack of redundancy
  – Multiple products made on existing manufacturing lines
  – 24/7 production with no “cushion”

• Complex manufacturing process
  – No simple fixes
  – Problems typically affect multiple products

• Investment economics question
  – e.g., propofol 20ml sells for $0.48/vial
Quality and Manufacturing Examples

- **Sterility**: Bacterial and fungal contamination
- **Particles**: Glass, metal or fibers in vials
- **Crystallization**: Drug may form crystals
- **Precipitate formation**: Due to reaction with raw materials or container/stopper with the drug
- **Impurities**: Can be toxic (heavy metals)
- **Degradants**: Lead to less effective drug product
- **Equipment breakdown
- **Natural disasters**
How does FDA fit?

• Patient care is our #1 concern
• We get involved when we are informed
  – Early notification is critical
• Seek ways to prevent & mitigate shortages
  – Secondary response to industry problem
  – Find root cause and get manufacturer on track
• Some shortages can be prevented, but not all
  – Unforeseen breakdown in manufacturing system
  – Longstanding quality manufacturing problems
• Some can be addressed quickly, others not
  – Risks to the patient always considered
FDA’s Approach to Prevention/Mitigation

• Prioritize products that are medically necessary
• Risk/Benefit of the drug always considered
• Maintain availability while minimizing risk to patients.
• Work with firm to address issues
  – We can advise, assist and expedite, but the manufacturer must fix the problem
  – We encourage early notification so we are aware of problems quickly
• Be flexible and creative – and fast
Medical Necessity

“A medically necessary drug product is a product that is used to treat or prevent a serious disease or medical condition for which there is no other alternative drug, available in adequate supply, that is judged by medical staff to be an adequate substitute.”

CDER Manual of Policies and Procedures on Drug Shortage Management 6003.1
FDA Tool Box

• Regulatory discretion: allows for manufacture of medically necessary product(s) to continue
  – Minor, low risk issues usually best suited for this tool
  – In some cases, require additional safety controls
    • Filters packaged with product; extra testing at plant; 3rd party oversight of production; special instructions for safe use

• Request other firms to ramp up manufacturing.

• Expedite any review of company proposals
  – New manufacture site, increased expiry date, new raw material source, changes in specifications, etc.

• Alternative ex-U.S. supply from unapproved sources
  – 2014: IV fluids
  – 2013: sodium bicarbonate, phosphate injection, trace elements (pediatric and adult), IV lipids, calcium chloride injection, zinc injection
  – 2012: methotrexate, doxorubicin liposomal, propofol, phentolamine
  – 2011: foscarnet, ethiodol, thiotepa, norepinephrine, Xeloda, levoleucovorin, leucovorin
Averted Drug Shortages: 2010-2013

- **Injectables**
- **All Forms**

<table>
<thead>
<tr>
<th>Year</th>
<th>Injectables</th>
<th>All Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>2011</td>
<td>150</td>
<td>180</td>
</tr>
<tr>
<td>2012</td>
<td>220</td>
<td>270</td>
</tr>
<tr>
<td>2013</td>
<td>140</td>
<td>160</td>
</tr>
</tbody>
</table>
Notification Source: Sterile Injectable Drug Shortages: 2013
Drug Supply Chain- 1st Tier

Supplier -> Manufacturer -> Wholesaler -> Pharmacy/Hospital -> Patient/Health Care Provider

**Inventory/Production Data:** Voluntarily Supplied

**Manufacturing Interruptions that could affect supply:** 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 – 2nd Tier

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

- Repackager
- Secondary Wholesaler/Distributor
- Compounder

Very limited to no data available to FDA regarding these 2nd tier supply sources.
“Gray Market”

• Sources that have extra product (may collect it) and sell at higher than market prices
  – Close link to “local stockpiling” with blurred margins
• Not clear what, if any laws are being broken
• Extent unknown, but many complaints
• FDA reports these to the Department of Justice for investigation
• Raises FDA concern about potential for counterfeit drugs filling gaps
170 Shortages Prevented in 2013

- Most due to early notification from firms
- The main FDA action taken to prevent drug shortage was Expedited Review
- Other actions taken include:
  - Regulatory discretion
  - Ramping up production
  - Assistance with release
  - Extension of expiry of available products
  - Additional testing
The Future

• FDA Drug Shortage 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
  – Strengthen mitigation responses
  – Develop long term prevention strategies

• Must have industry commitment to culture of quality manufacturing
  – Many firms are building or upgrading facilities
  – Need better manufacturing practices, methods and quality testing
  – Need more production redundancy
  – Promptly report and correct even smallest problems
Shortages can Not Always be Prevented

• Unanticipated events occur
  – manufacturing line breakdown or natural disaster

• Sometimes manufacturers can’t 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
  – May not be an easy way to do this well
Thank You!

• FDA drug shortage website is:

• To report shortages our e-mail account is
  Drugshortages@fda.hhs.gov

• FDA Webinar on Prescription Drug Shortages
  Sept. 30, 2011,
  http://www.fda.gov/AboutFDA/Transparency/Basics/ucm272223.htm
Questions?