U.S. Drug Shortages

Overview

- Background on CDER Drug Shortage Program
- U.S. Drug Shortage Trends
- Reasons for Drug Shortages
- Industry's Role
- CDER's Approach to Prevention/Mitigation of Drug Shortages (includes, drugs, therapeutic proteins, monoclonal antibodies)

Drug Shortage Program History

- Drug Shortage Program (DSP) began in 1999
- Mission: to address potential and actual drug shortages
- Currently 4 full time staff and Coordinator
  - Facilitate prevention and resolution of shortages by collaborating with FDA experts, industry, and external stakeholders
  - Provide drug shortage information to the public
  - Outreach to healthcare professional organizations, patient groups and other stakeholders

Current Relevant Authorities

- Very limited authorities directly related to drug shortages
- Limited notification requirement
  - Only requirement is notification of sole source discontinuation
  - No consequence for failure to notify
- Manufacturing capacity - FDA cannot dictate the production quantity
- Program operates largely based on voluntary participation of industry

DISCONTINUANCE OF A LIFE SAVING PRODUCT

SEC. 506C. [21 U.S.C. 356c] DISCONTINUANCE OF A LIFE SAVING PRODUCT.

(a) IN GENERAL.—A manufacturer that is the sole manufacturer of a drug—

(1) that is—

(A) life-supporting;

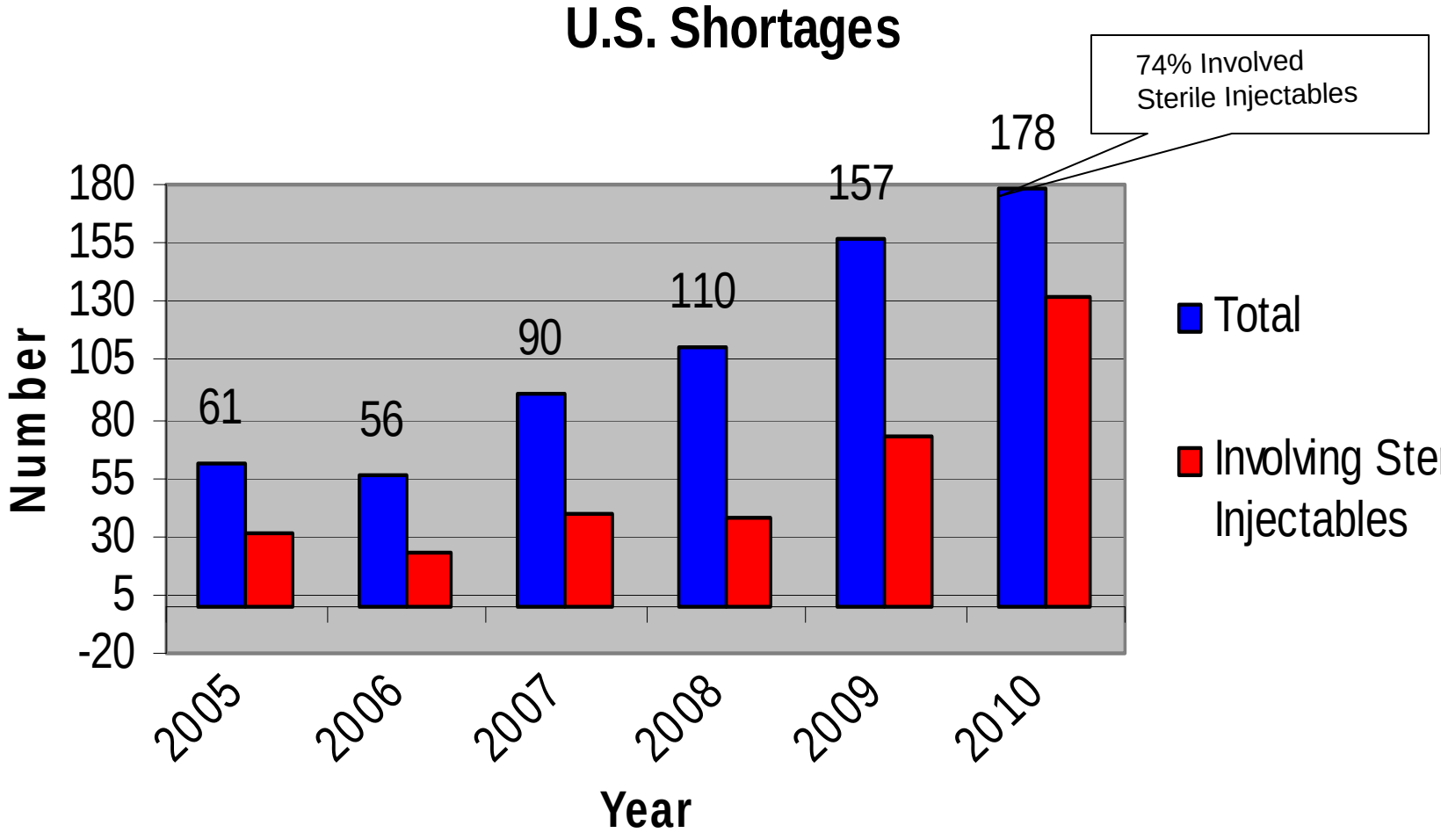
(B) life-sustaining; or

(C) intended for use in the prevention of a debilitating disease or condition;

(2) for which an application has been approved under section 505(b) or 505(j); and

(3) that is not a product that was originally derived from human tissue and was replaced by a recombinant product, shall notify the Secretary of a discontinuance of the manufacture of the drug at least 6 months prior to the date of the discontinuance.

- See also 21CFR 314.81(b)(3)(iii)


U.S. Shortages
74% Involved Sterile Injectables
178
157
110
90
61
56
180
155
130
105
80
55
30
5
-20
Number
2005
2006
2007
2008
2009
2010
Year
Total
Involving Sterile Injectables

Shortage Trends Injectables-- 2010

- 54% - Due to Product Quality/significant CGMP issues (e.g., particulate, contamination, impurities)
- 21% - Due to Delays/Capacity issues
- 11% - Due to Discontinuations
- 5% - Due to raw material (API) issues
- 4 % - Increase in demand due to another shortage
- 3% - Due to loss of manufacturing site
- 2% - Due to component problems/shortage

Reasons for Shortages – Older Sterile Injectables

When a firm has manufacturing/quality problem with older injectables or discontinues a product, a shortage usually occurs

- Not enough manufacturing capacity
- Industry consolidation
  - Fewer firms making these products
  - Seven (7) manufacturers make up large percentage of this market
  - Contract manufacturers – firms contract out manufacturing as well as acting as contract manufacturers
- Lack of redundancy
  - Multiple products made on existing manufacturing lines
- Complex manufacturing process
- Generally not economically attractive
  - e.g., propofol 20ml sells for $0.48/vial

FDA's Approach to Shortage Prevention/Mitigation - 1

- Consider medical necessity
- Risk/Benefit of the drug always considered
- FDA does everything possible within our authority to continue availability while minimizing risk to patients.
- For manufacturing/quality problems – work with the firm to address the issues.
- Flexibility may be employed to address shortages to mitigate any significant risk to patients (e.g., Cytarabine injection)

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

http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM079936.pdf

FDA's Approach to Shortage Prevention/Mitigation - 2

- Encourage remaining firms to ramp up if others manufacturing.
- FDA can and does expedite issues related to addressing shortages (e.g. new manufacturers, increased expiry, increased capacity, new raw material source, changes in specifications).
- In rare cases, temporary importation from unapproved sources
  - 2010 temporary importation of propofol
  - 2011 temporary importation of foscarnet, ethiodol, thiotepa, norepinephrine, Xeloda, levoleucovorin, leucovorin

Prevented Shortages - 2010

- In 2010, 38 shortages were prevented due to early notification from firms
  - 16 prevented through regulatory discretion (risk of quality/manufacturing issue able to be mitigated and was outweighed by benefit of the drug)
  - 13 prevented through expedited review (new manufacturing sites, suppliers, changes in specification or other changes)
  - 8 prevented through encouraging other firms to ramp up
  - 1 prevented through communication with DEA regarding firm's report to FDA regarding need for quota increase

Prevented Shortages – 2011 (to date)

- In 2011, have seen increased reporting by manufacturers of potential shortages.
- 99 shortages have been prevented so far due to early notification from firms
  - 84 prevented through expedited review (new manufacturing sites, suppliers, changes in specification or other changes)
  - 12 prevented through regulatory discretion (risk of quality/manufacturing issue outweighed by benefit of the drug)
  - 1 prevented through encouraging others to ramp up
  - 1 prevented through communication with DEA regarding firm's report to FDA regarding need for quota increase
  - 1 prevented through assisting a firm with an import delay

Within FDA/CDER

- DSP works with
  - Review division(s) in OND that regulates the therapeutic areas for the drug
  - Office of Generic Drug Products
  - Office of New Drug Quality Assessment
  - Office of Biotechnology Products
  - Office of Compliance
    - Office of Regulatory Affairs
  - Others

Important to Note:

- FDA plays a key role working with manufacturers to facilitate responses to prevent or mitigate a drug shortage
  - This is a secondary response to mitigate a problem that has already happened
- Manufacturers play a key role in responding to shortages as they make the products that doctors and patients use
- It is important to consider the root cause of a shortage
- If the root cause that leads to a shortage can be prevented, one can get to primary prevention
- Some shortages can be prevented – others cannot be prevented
  - Some shortages involve unforeseen (unanticipated) problems such as a manufacturing line breakdown or other event that causes an unavoidable shortage
  - Manufacturer(s) may not be able to make up production shortfall
  - In some cases risks are significant and would cause patient harm (e.g. sterility problems)

Examples of Recent Quality and Manufacturing Issues Involving Sterile Injectables - 1

- Significant quality issues that have occurred
  - Sterility problems – including bacterial and mold contamination
  - Particles of foreign matter (glass, metal and fibers) in vials
  - Crystallization of the active ingredient
  - Precipitate formation (due to reaction with raw materials or container/stopper with the drug)
  - Newly identified impurities or degradants

Examples of Recent Quality and Manufacturing Issues Involving Sterile Injectables - 2

- Issues that are more easily able to be addressed
  - Errors in labeling or packaging
  - Slightly out of specification results that do not unfavorably alter benefit / risk
- Unforeseen/ Unanticipated issues
  - Manufacturing equipment breakdown
  - Natural disasters or other events causing loss of manufacturing time and in some cases loss of inventory
    - Fire at raw material or finished product manufacturing site
    - Japan earthquake caused several potential shortages
    - Icelandic volcano caused transportation delays

Flexibility - examples

- Allow release of medically necessary products with extra testing and third party oversight
- Build in exemptions for medically necessary products into enforcement actions (e.g., consent decrees)
- Allow distribution of product with filters and alerts to health care providers

Industry's Role - Potential solutions

- Plan ahead by adding redundancy to manufacturing & raw material supply to prevent shortages of medically necessary drugs (flexible regulatory approaches possible)
- Commitment to quality: proactively identify & promptly correct issues
- Prevent sudden lack of lifesaving medications for consumer
- Notify FDA as soon as aware of an issue that could impact supply. Contact Drug Shortage Program at drugshortages@fda.hhs.gov
  - 38 shortages prevented in 2010 due to early notification by firms
  - 99 shortages prevented in 2011 so far due to early notification

Continuing Role for CDER's DSP

- Continue working with firms
- Encourage voluntary reporting
- Continue tracking number of shortages and reasons for shortages
- Outreach
  - Health care professionals
  - Consumers
  - Manufacturers

Thank You

- FDA drug shortage website is: http://www.fda.gov/Drugs/DrugSafety/default.htm
- To report shortages our e-mail account is Drugshortages@fda.hhs.gov
- FDA Webinar on Prescription Drug Shortages
  Sept. 30, 2011, 11:00 a.m.
  http://www.fda.gov/AboutFDA/Transparency/Basics/ucm272223.htm