



Overview of U.S. Drug Shortages

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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 Program

Our mission is to prevent, mitigate and help resolve shortages

- Center for Drug Evaluation & Research
 - Drug Shortage Program (DSP) began in 1999
 - Today have 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!

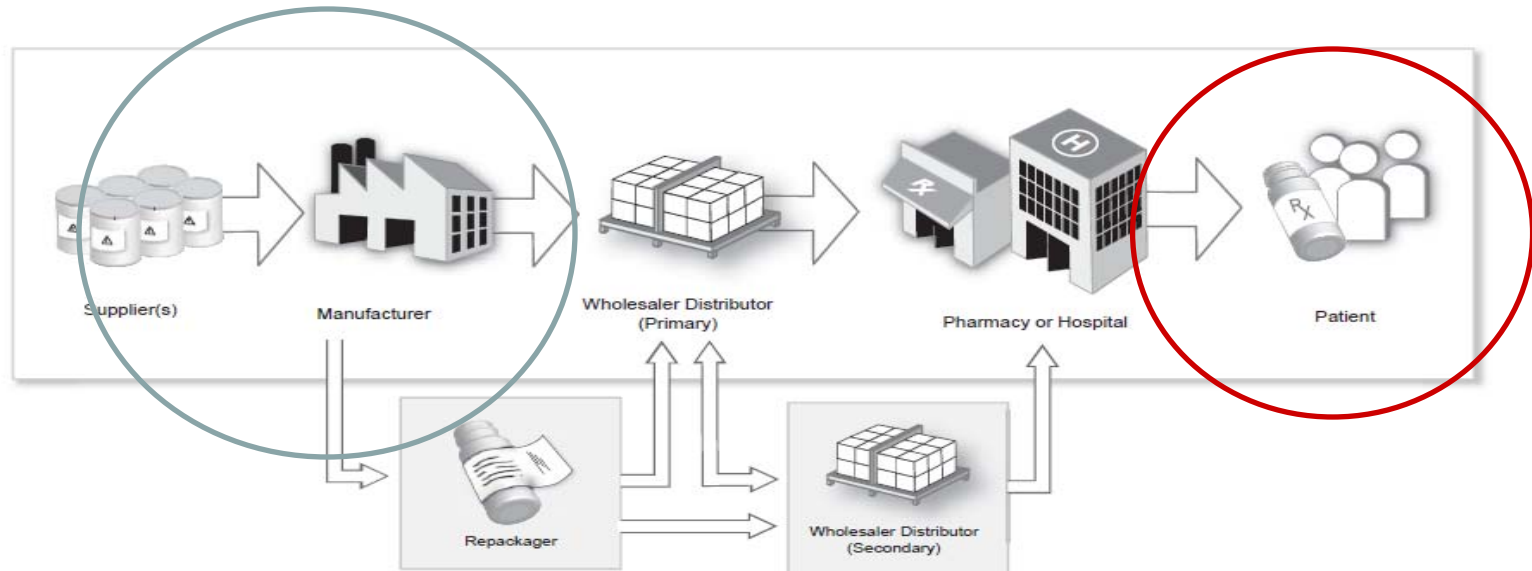
Growing problem – and FDA response

- 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
 - Expand application of authority to require early notifications ([Interim Final Rule, Dec. 19, 2011](#)).
 - New FDASIA legislation
- Public workshop September, 2011
- Collaboration on system fixes and root problem resolution
 - American Society of Health-System Pharmacists (ASHP)
 - Industry (GPhA, PhRMA, BIO)



A Drug Supply Chain Example

From Supplier to Patient



FDA Authorities are very limited

What we can require

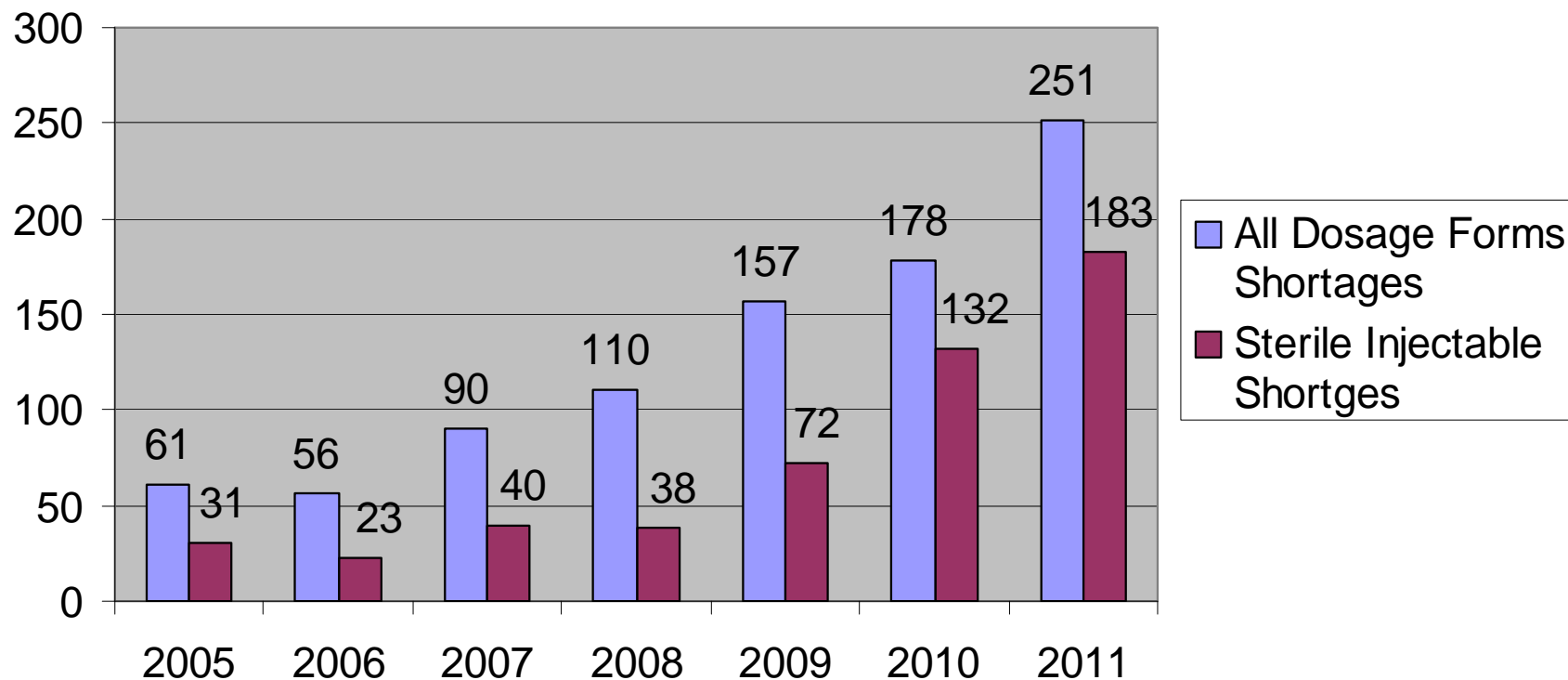
- Notification by manufacturers (new FDASIA requirement)
 - Supply disruptions, delays, discontinuations
 - No penalty for not reporting
- Notification of manufacturing changes

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 Program largely depends on notification by manufacturers and the public.

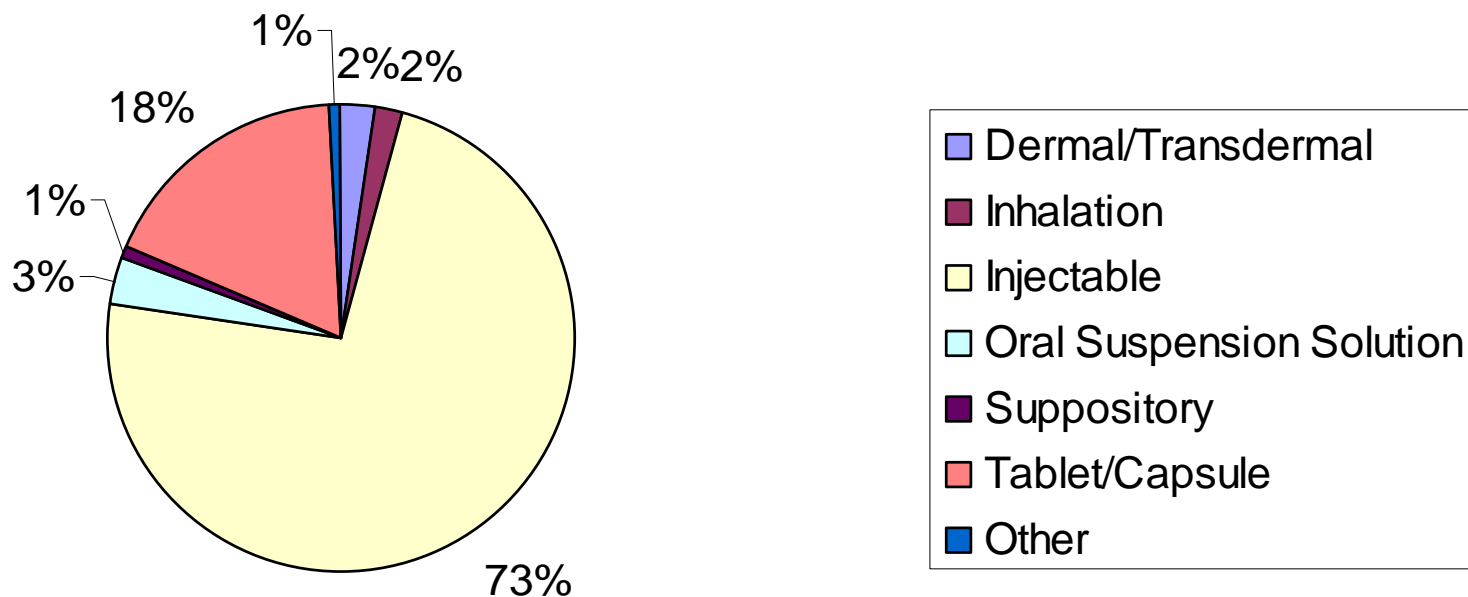
U.S. Drug Shortages



Most shortages do get resolved.

Drug shortages 2011: Dosage Forms

Drug Dosage Form of 2011 Shortages

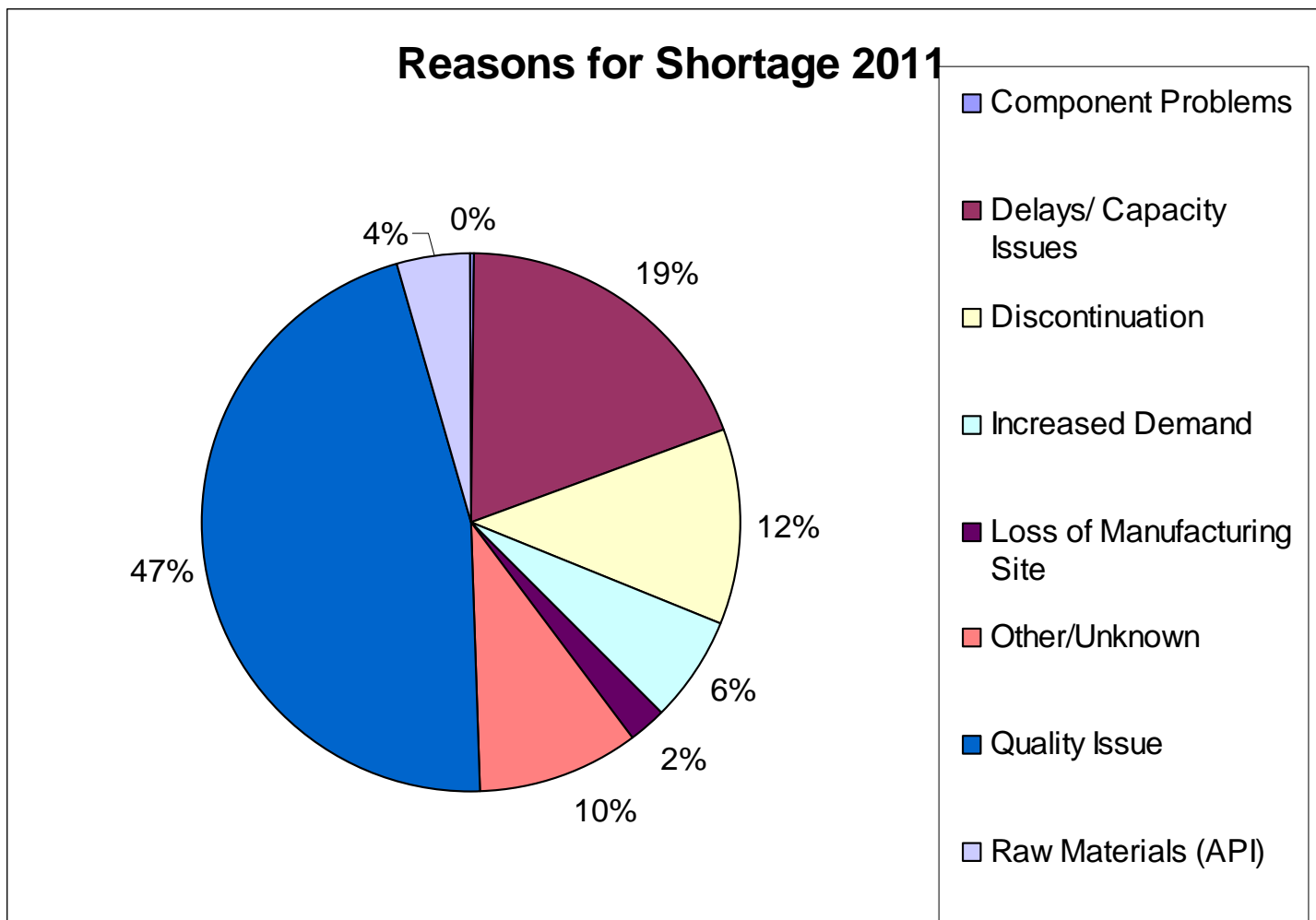


2011 Shortage Data

- There were 251 shortages reported in 2011
- High percentage are sterile injectable products
 - Treatments for cancer, anesthesia, serious illness
 - Highly specialized manufacturing
 - High risk to patient if not meticulous

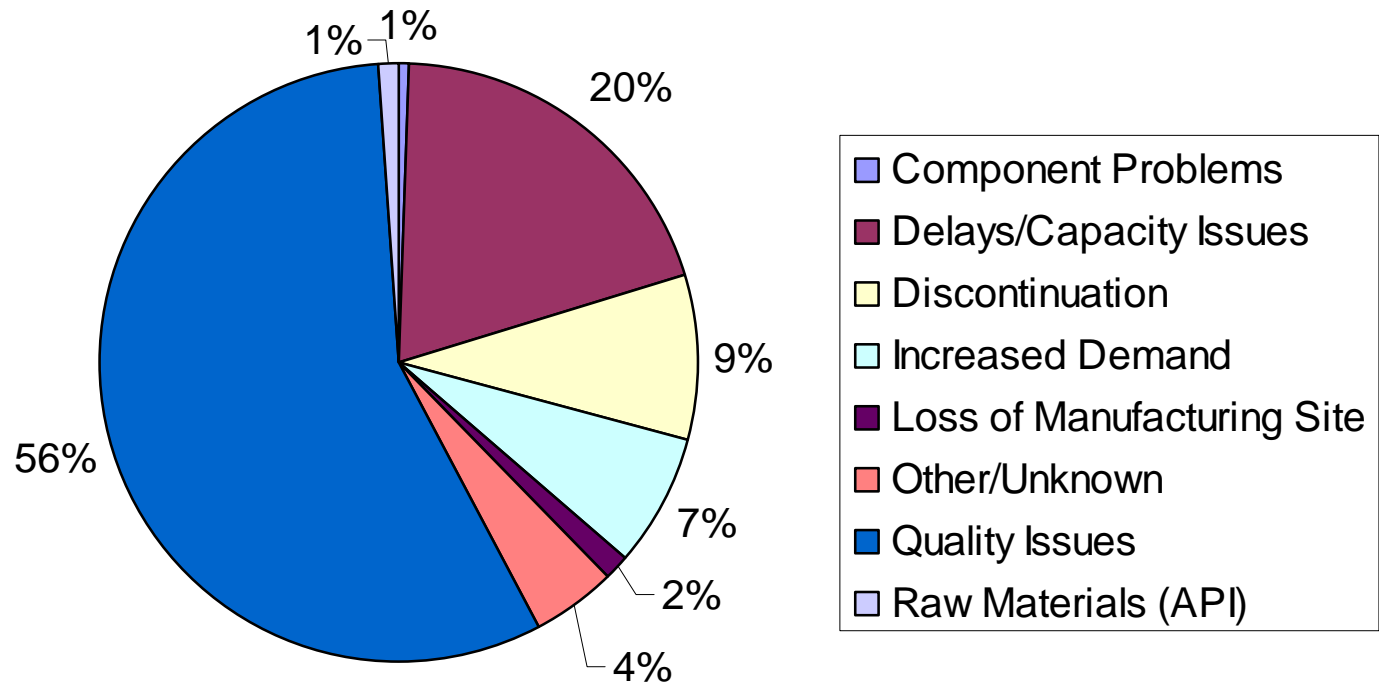
**When there are quality or production problems
for a sterile injectable drug,
a shortage almost always results**

Reasons for Drug Shortages in 2011: All Dosage Forms



Reasons for Sterile Injectable Shortages in 2011

Sterile Injectables Reasons for Shortages 2011



Reasons for Shortages: Sterile Injectables

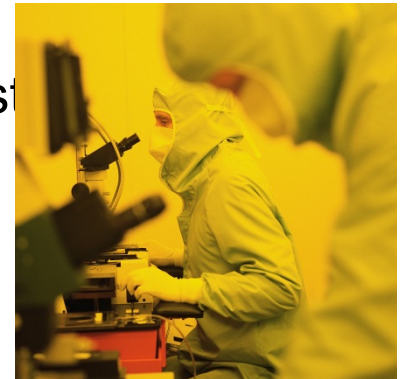
Report by Assistant Secretary for Planning & Evaluation 2011

- State of the industry
 - Seven (7) 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 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/solvent drug
- New impurities or degradants
- Equipment breakdown
 - Plant maintenance
- 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
- Do everything possible to continue availability while minimizing risk to patients.
- Work with firm to address
 - We can advise, assist and expedite, but only the manufacturer can fix the problem
 - Why 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

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



FDA Tool Box

- Regulatory discretion: allow 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, 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
 - 2012 methotrexate, doxorubicin liposomal, propofol, phentolamine

38 Shortages Prevented in 2010

- All due to firms notifying FDA of problems early
- 16 through regulatory discretion
 - Risk of quality/manufacturing issue able to be mitigated and was outweighed by benefit of the drug
- 13 through expedited review
 - New manufacturing sites, suppliers, etc.
- 8 through encouraging other firms to ramp up
- 1 through communication with DEA regarding firm's need for controlled substance quota increase

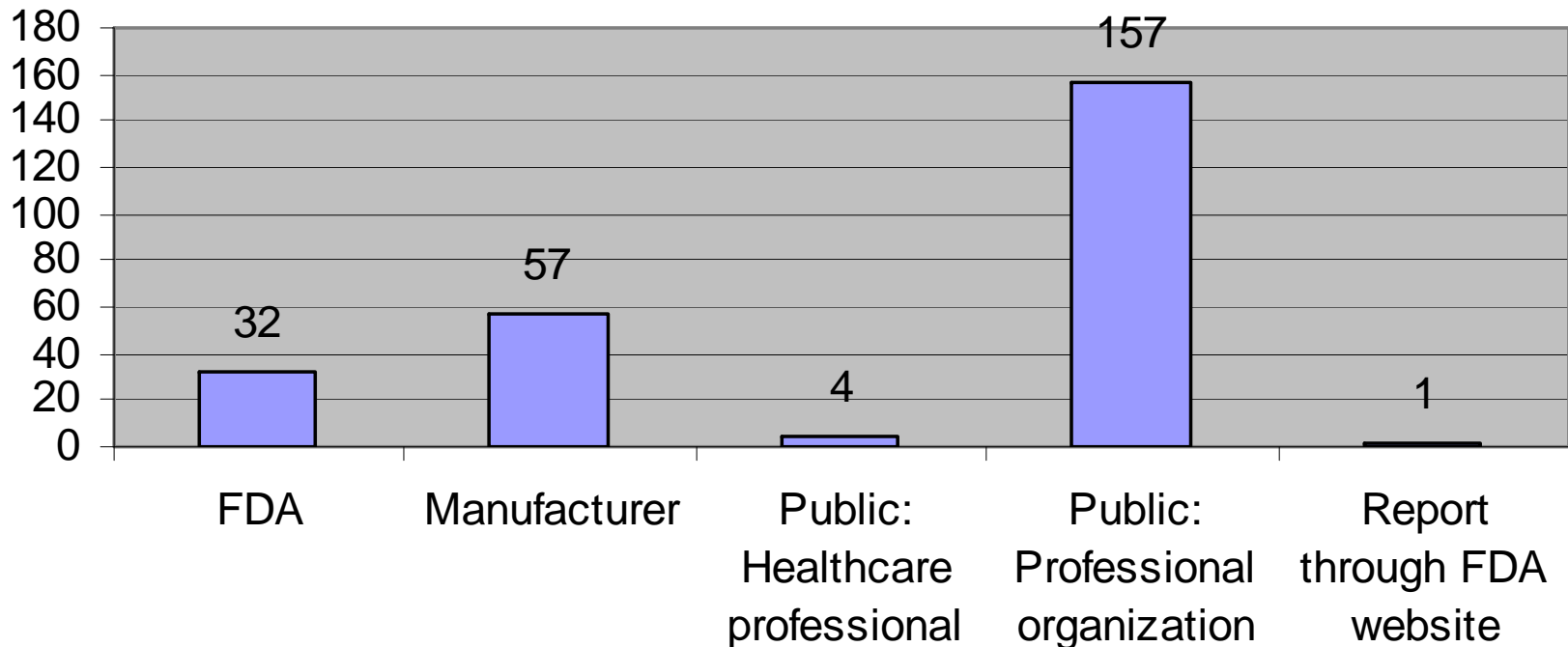
195 Shortages Prevented in 2011

- Most due to firms notifying the FDA of early problems
- 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



Reporting

Drug Shortage Notification Source 2011



2011 Data Higher – Executive Order

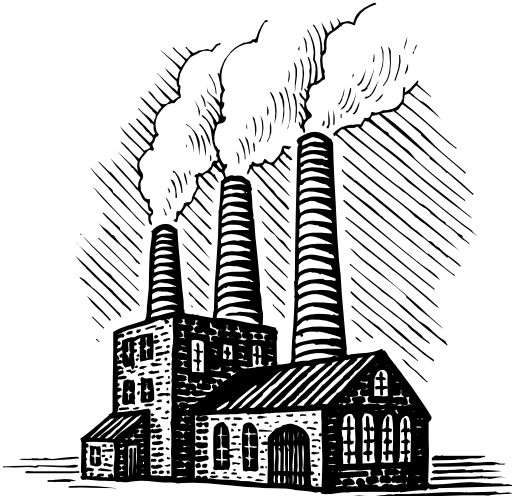
*President's Executive Order issued 10/31/11
encouraged more voluntary reporting by
manufacturers*

- 6 fold increase in notifications of potential shortages
 - Usual 10 per month (2010) rose to 60 per month!
- Total of 195 shortages prevented in 2011
- 98 shortages prevented as of August, 2012

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, plant may have to close to repair
- FDA works with company to encourage smart distribution
 - No easy answers on how to do this well

Anatomy of Propofol



APP – continuing
to produce

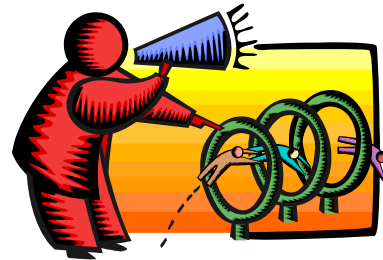


Importation

Fresenius Kabi

Teva discontinued Fall 2009

40%



Hospira –
Recalled Fall 2009
Restarted Fall 2010
Recalled Spring 2012

Anatomy of Methotrexate



Mylan
2 ml & 40 ml vials

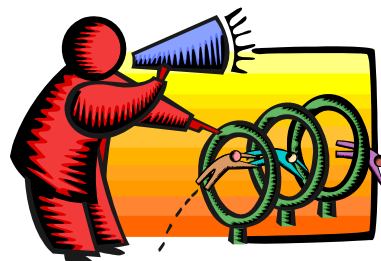
Pediatric leukemia



APP
10 ml vials

Bedford Labs/ Ben Venue

2ml, 4 ml, 8 ml
& 10 ml vials



Sandoz
2ml vials RECALL
10 ml vials DELAY
40 ml vials DELAY



Hospira
2ml & 40 ml vials

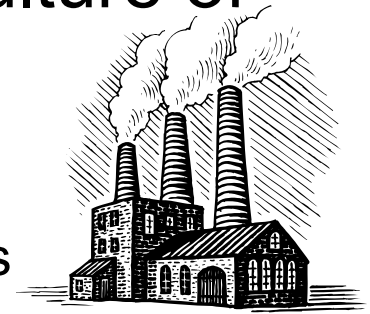
50%

“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

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
- New FDASIA legislation
 - REQUIRES broader reporting by industry to FDA
- Must have industry commitment to culture of quality manufacturing
 - Many firms are building new plants today
 - Need better methods and redundancy
 - Promptly report and correct even small problems



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,
<http://www.fda.gov/AboutFDA/Transparency/Basics/ucm272223.htm>



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Questions?