



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
 - <http://www.accessdata.fda.gov/scripts/drugshortages/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

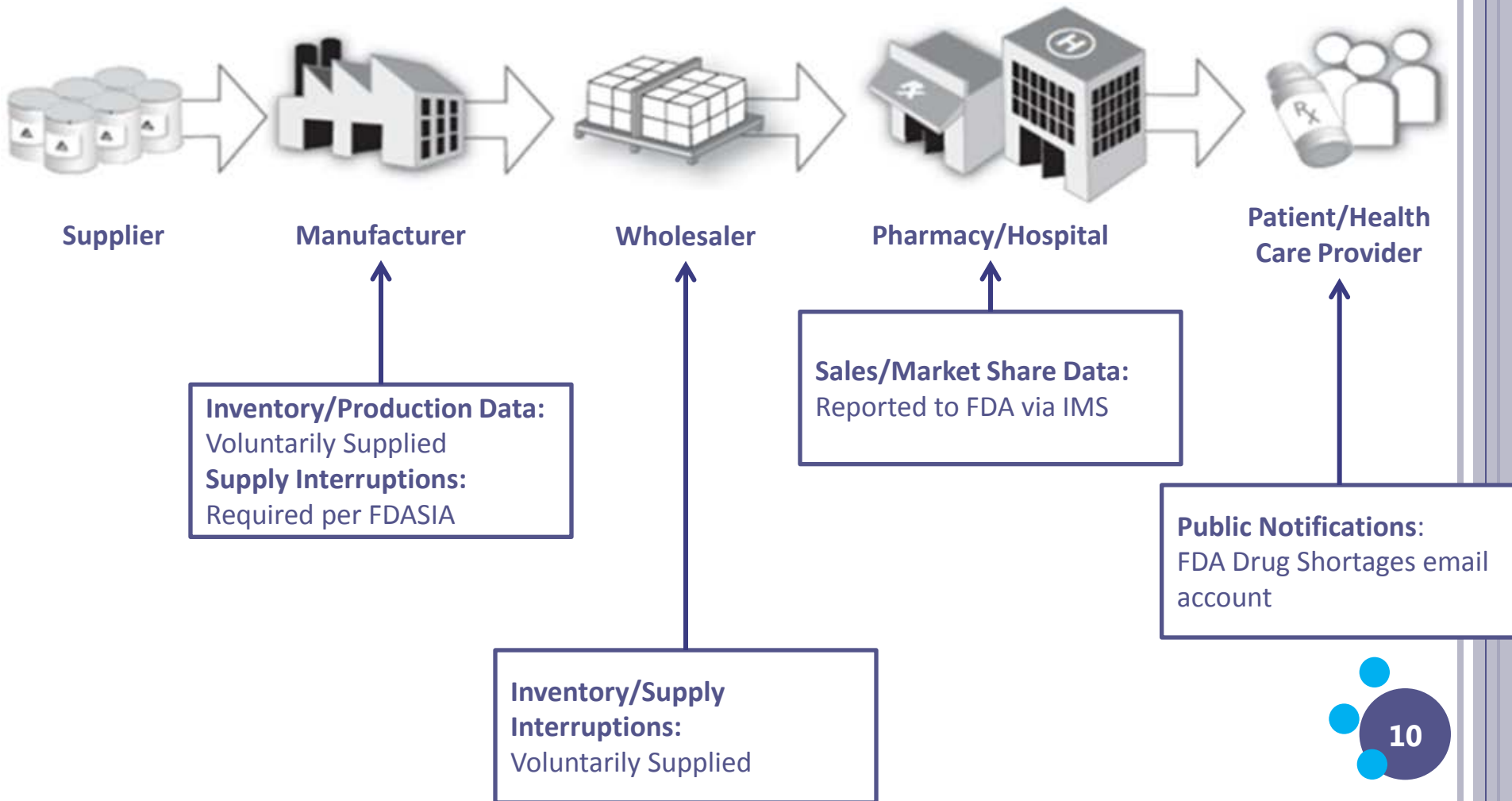
SHORTAGES, LEGISLATION, AND THE FDA RESPONSE

- 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)

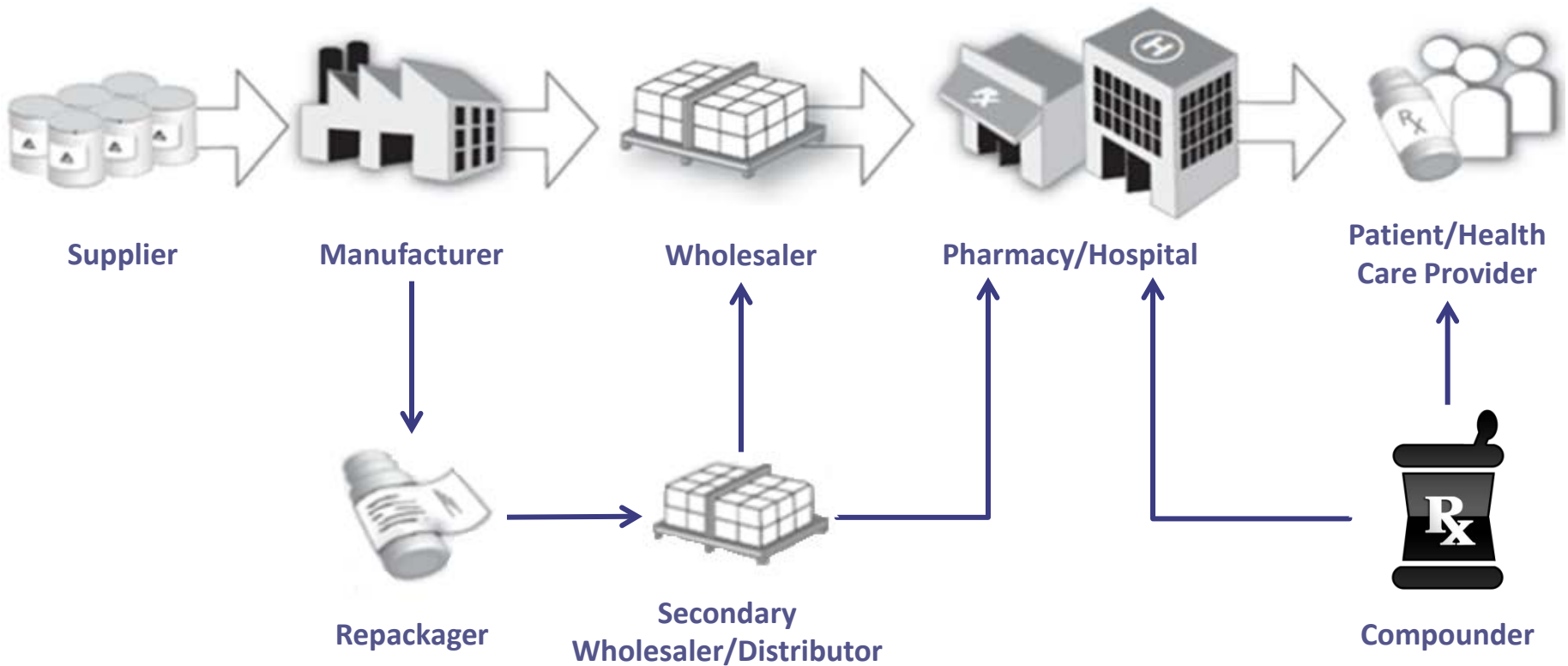
DRUG SHORTAGE DATA SOURCES

- 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/distributors
 - Compounders

DRUG SUPPLY CHAIN – 1ST TIER



DRUG SUPPLY CHAIN – 2ND TIER



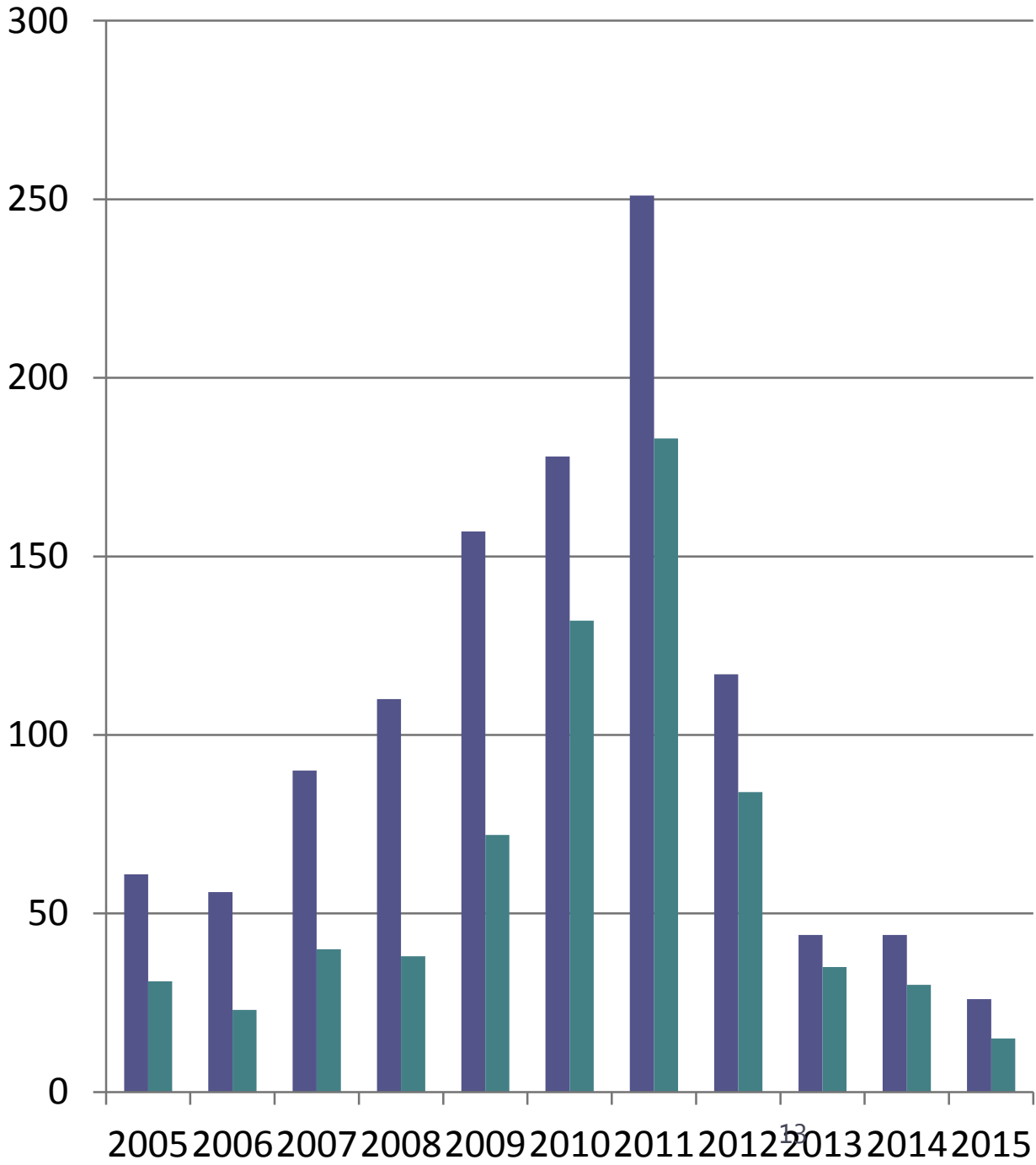
Very limited to no data available to FDA regarding these 2nd tier supply sources.

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**

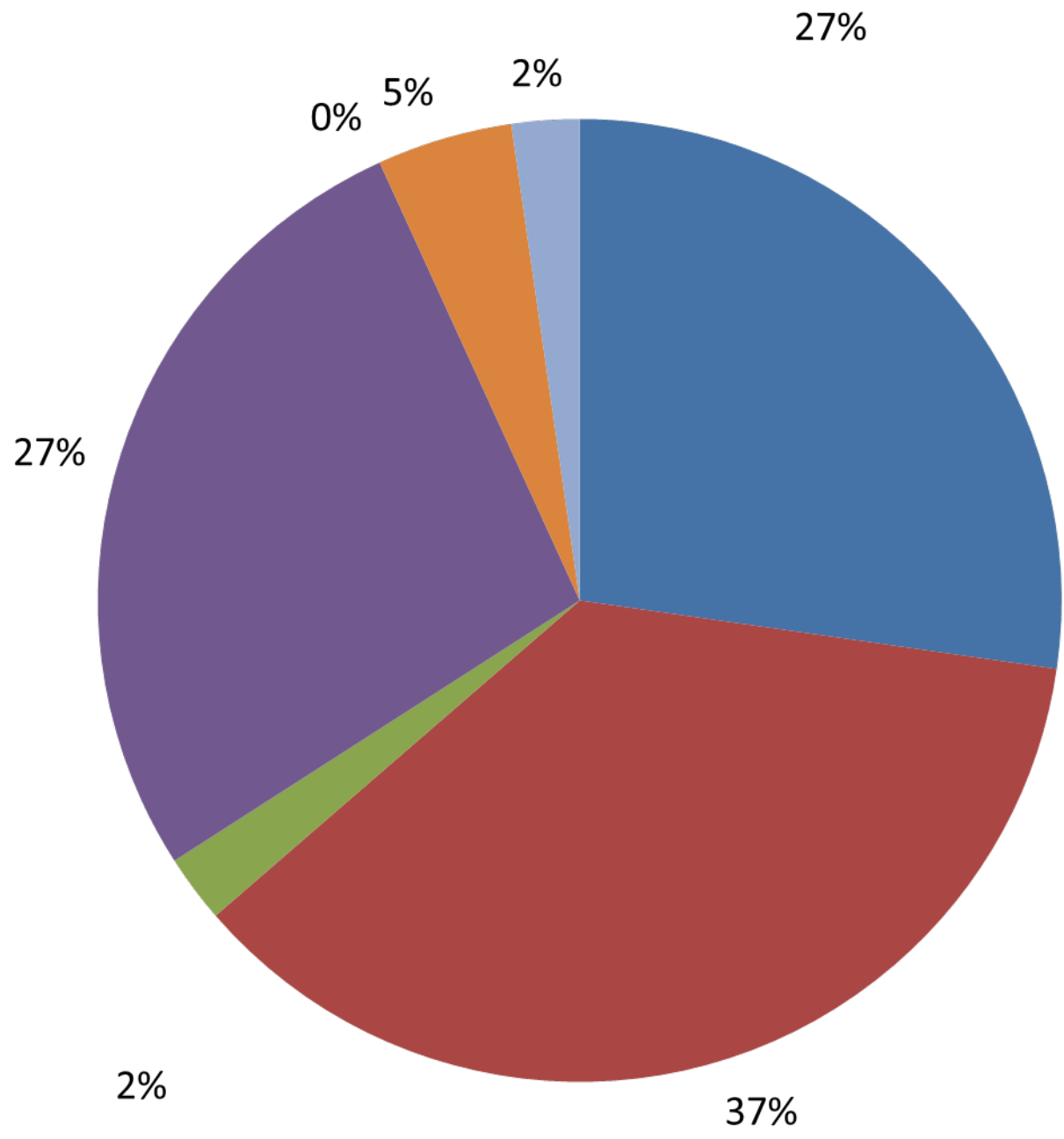
TOTAL US DRUG SHORTAGES PER YEAR

- All Forms
- Sterile Injectables



REASONS FOR DRUG SHORTAGES: 2013

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



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

<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm079936.pdf>



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

<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm079936.pdf>



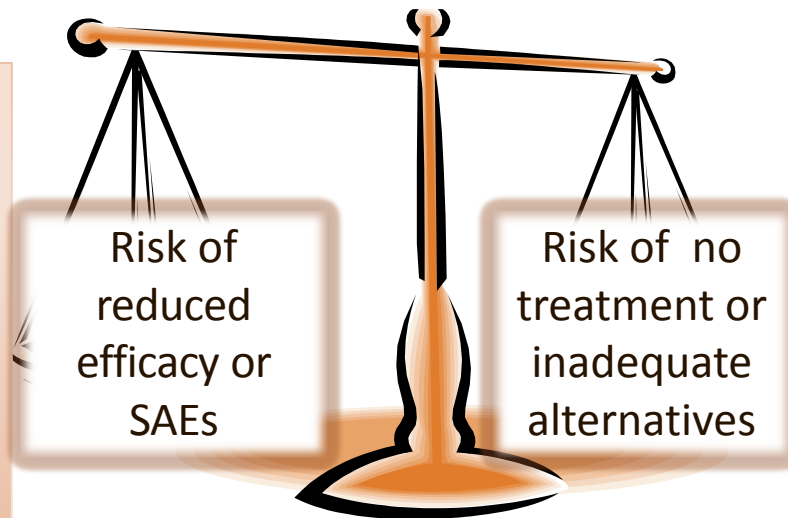
HOW DOES THE FDA FIT?

- 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

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

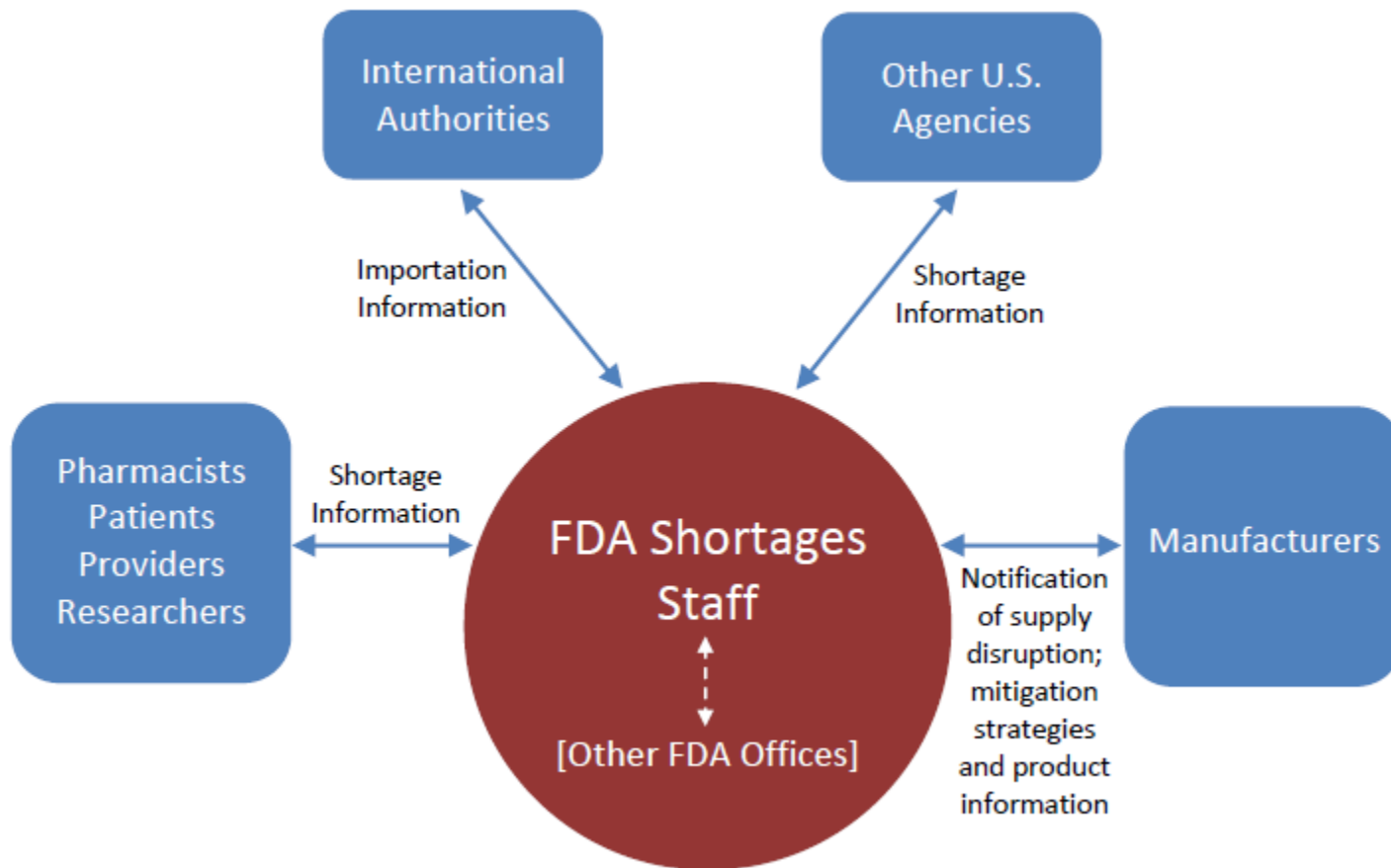
THE FDA'S APPROACH TO PREVENTION AND MITIGATION

- 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

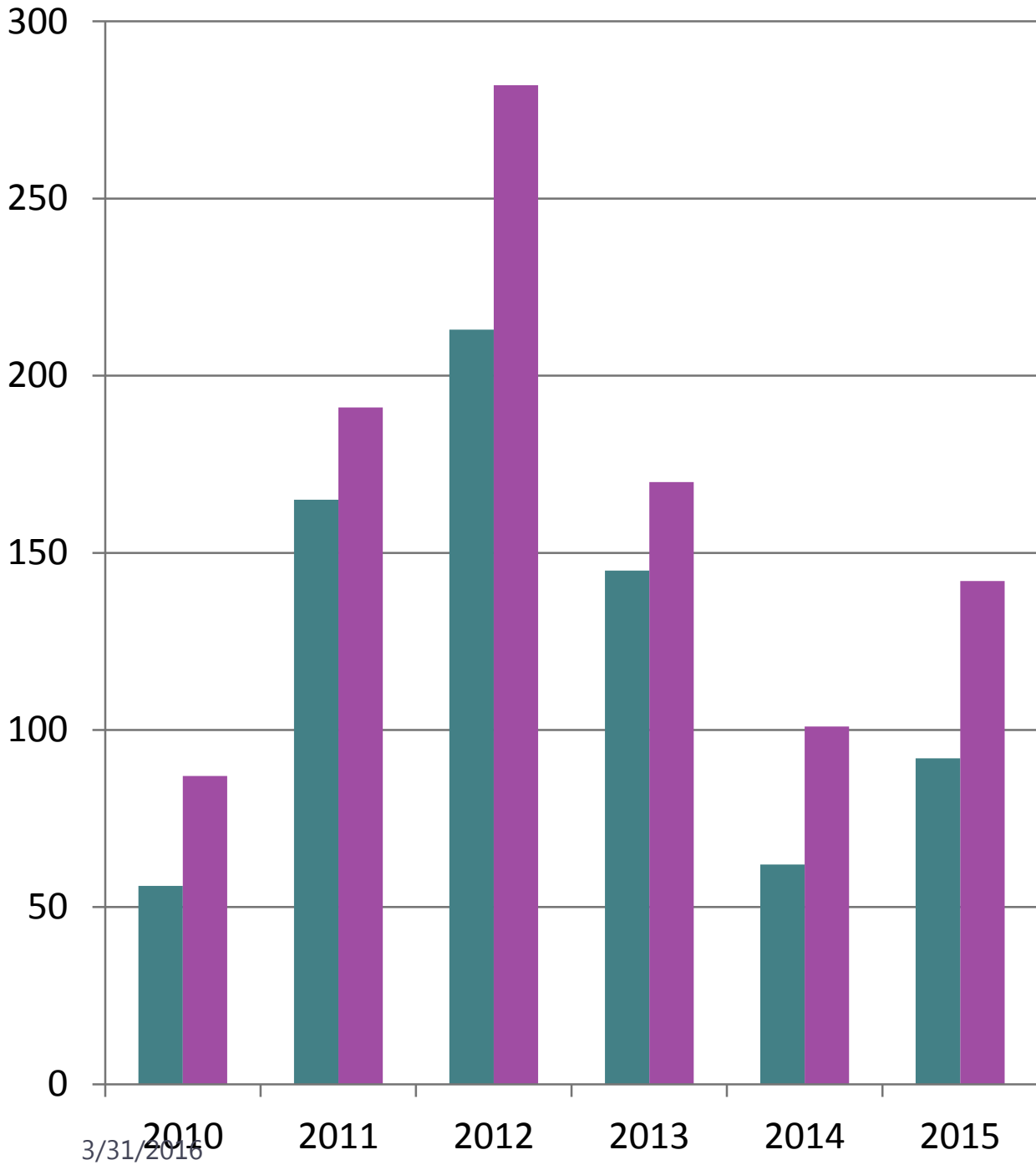
THE FDA'S APPROACH TO PREVENTION AND MITIGATION

- 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



AVERTED DRUG SHORTAGES: 2010-2013



- Injectables
- All Forms

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

○ Center for Biologics Evaluation and Research (CBER)

- Email: CBERshortage@fda.hhs.gov
- Phone: (240) 402-8380
- <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/ucm351921.htm>

HOW TO REPORT SHORTAGE/SUPPLY ISSUE TO FDA

○ Center for Veterinary Medicine (CVM)

- Email: ASKCVM@fda.hhs.gov
- Phone: (240) 276-9300

○ Center for Devices and Radiological Health (CDRH)

- Email: dsmica@fda.hhs.gov
- Phone: 1-800-638-2041 or (301) 796-7100

○ Center for Food Safety and Nutrition (CFSAN)

- Website:
<http://www.fda.gov/Food/RecallsOutbreaksEmergencies/default.htm>
- Phone: 1-888-SAFEFOOD or 1-888-723-3366

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:**

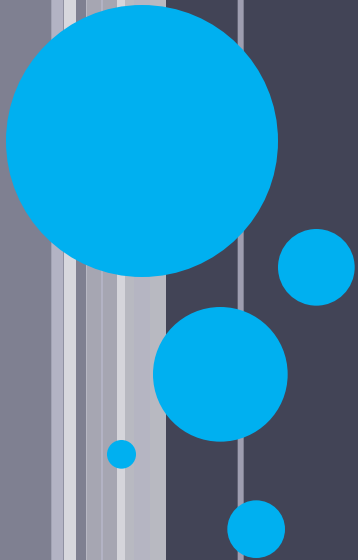
<http://www.fda.gov/AboutFDA/Transparency/Basics/ucm272223.htm>

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

**Office of the Center Director: Drug Shortage
Management:**

<http://www.fda.gov/downloads/aboutfda/centersoffice/s/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm079936.pdf>

**THANK YOU FOR YOUR
TIME!**



APPENDIX

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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Current and Resolved Drug Shortages and Discontinuations Reported to FDA

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Search by Generic Name or Active Ingredient:

Current/Resolved Shortages | Discontinuations | Therapeutic Categories | New and Updated

Current and Resolved Shortages Listed by Generic Name or Active Ingredient

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

A drug receives Resolved status when the Drug Shortages Staff (DSS) determines that the market is covered, based on information from all manufacturers. The market is considered covered when supply is available from at least one manufacturer to cover total market demand. However, some manufacturers may not have all presentations available. DSS monitors the supply of products with Resolved status. For the most current supply information, contact the manufacturers.

Generic Name or Active Ingredient	Status
Acetohydroxamic Acid (Lithostat) Tablets	Currently in Shortage
Ammonium Chloride Injection	Currently in Shortage
Anagrelide Hydrochloride Capsules	Currently in Shortage
Aprepitant (Emend) Capsules	Currently in Shortage
Atropine Sulfate Injection	Currently in Shortage
Azathioprine Tablet	Currently in Shortage
Barium Sulfate for Suspension	Resolved
Bupivacaine Hydrochloride (Marcaine, Sensorcaine) Injection	Resolved
Caffeine Anhydrous (125mg/mL), Sodium Benzoate (125mg/mL) Injection	Currently in Shortage
Calcium Chloride Injection, USP	Currently in Shortage

APPENDIX

