

# DRUG SHORTAGES AND THE ROLE OF FDA AND MANUFACTURERS

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Drug Shortage Staff

# DRUG SHORTAGES AND THE ROLE OF FDA AND MANUFACTURERS

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- Overview of Drug Shortage Staff
- Current State of Shortages
- FDA and Manufacturer Roles
- Future Goals



# DRUG SHORTAGE STAFF

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- **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 have 13 full-time staff



# DRUG SHORTAGE STAFF

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- 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 AND THE FDA RESPONSE

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- Current shortage information updated daily at [fda.gov](http://fda.gov)
- Resources were increased and staff expanded
- Reporting shortages is encouraged:
  - Contact from the public about existing shortages
  - Contact from industry about potential shortages
  - Executive order to require early notification (2011)
  - FDASIA legislation (2012)
  - Final Rule (2015)

# SHORTAGES AND THE FDA RESPONSE

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- FDASIA was enacted in July 2012, requiring increased notifications
- Strategic Plan issued October 31, 2013- FDA's response to drug Shortages
- Proposed Rule issued October 31, 2013- manufacture reporting requirements
- Final Rule July 2015 – includes Biologics



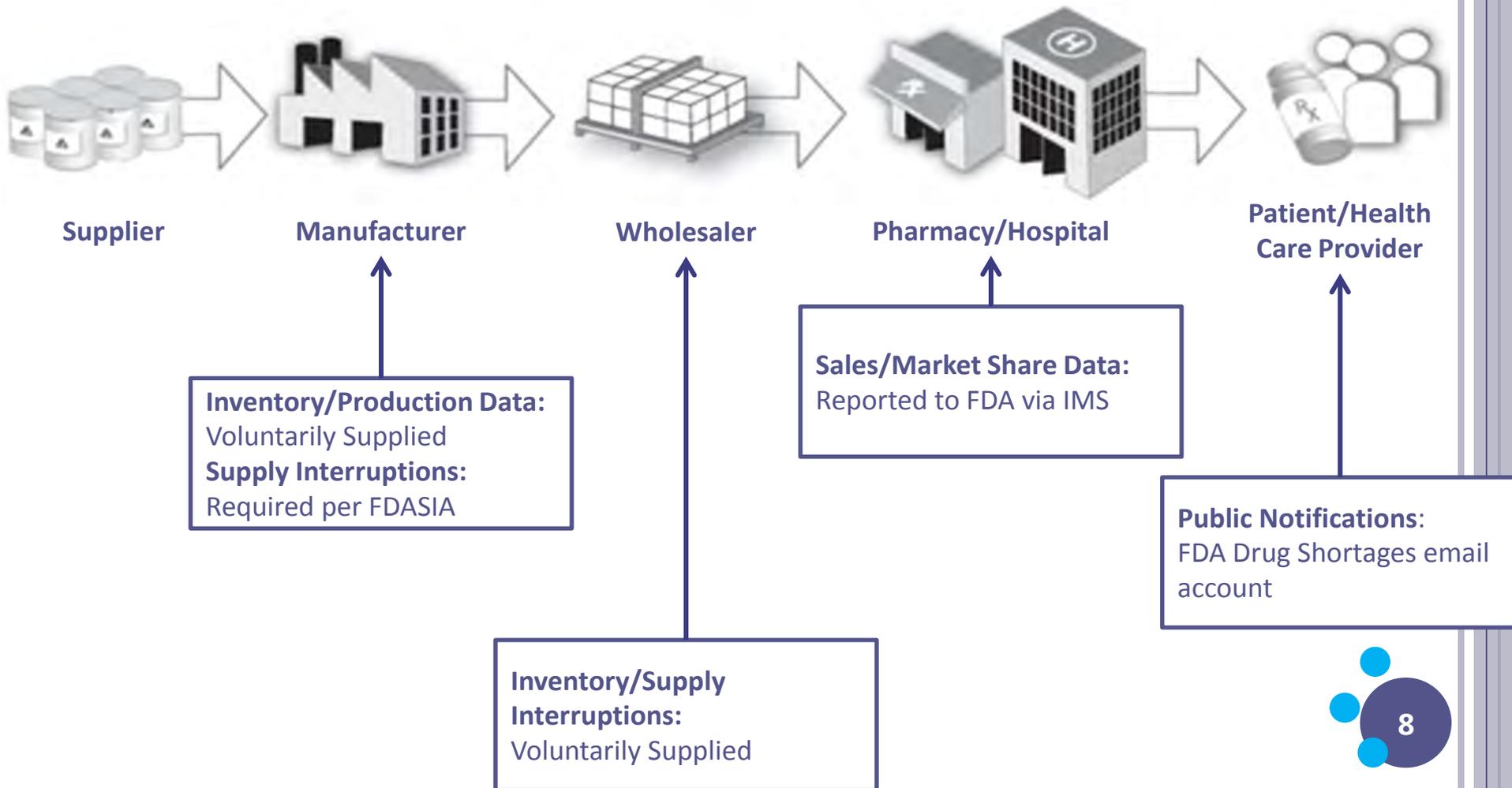
# DRUG SHORTAGE DATA SOURCES

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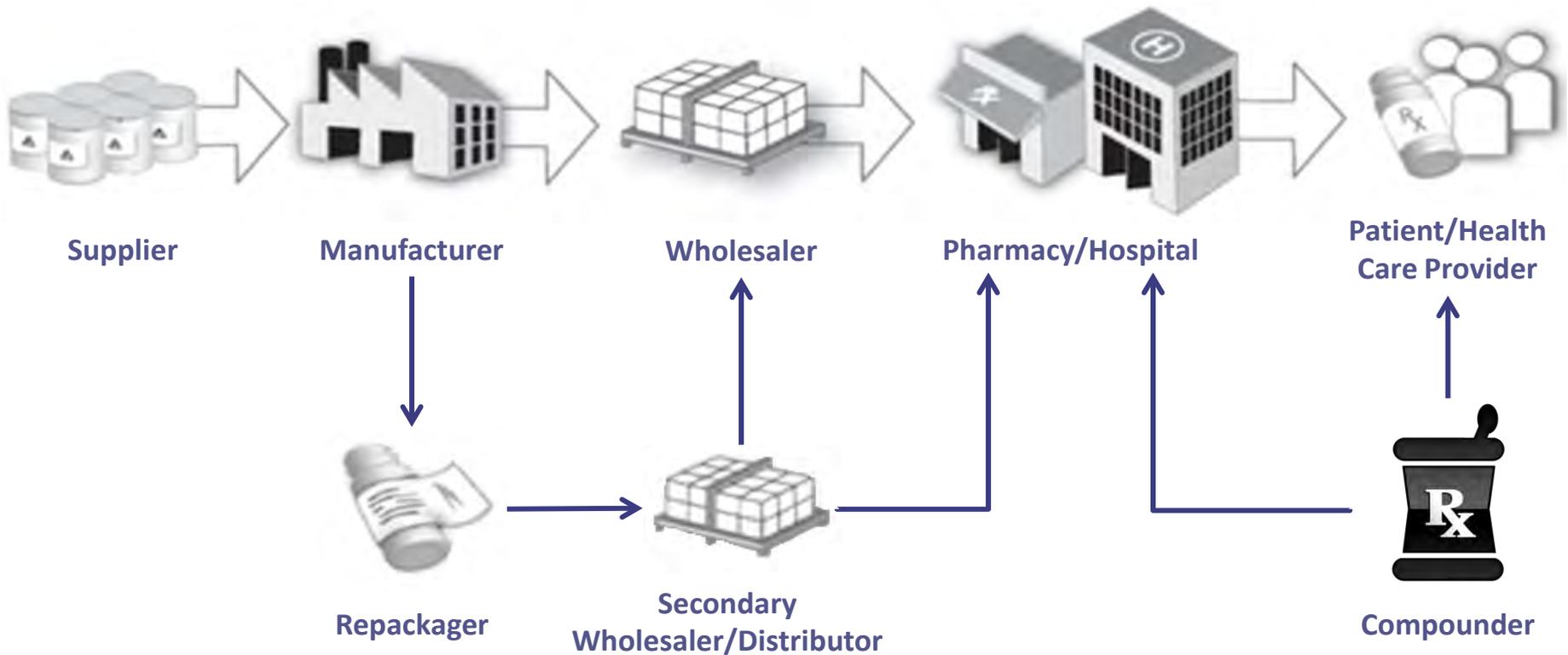
- Data about drug shortages comes from points all across the supply chain:
  - FDASIA required reporting
  - Voluntary information supplied by industry
  - Publically reported shortage tips
  - FDA personnel (e.g. district offices)
- Not all points in the supply chain are required to report supply data per FDASIA



# DRUG SUPPLY CHAIN – 1<sup>ST</sup> TIER



# DRUG SUPPLY CHAIN – 2<sup>ND</sup> TIER



Very limited to no data available to FDA regarding these 2<sup>nd</sup> tier supply sources.

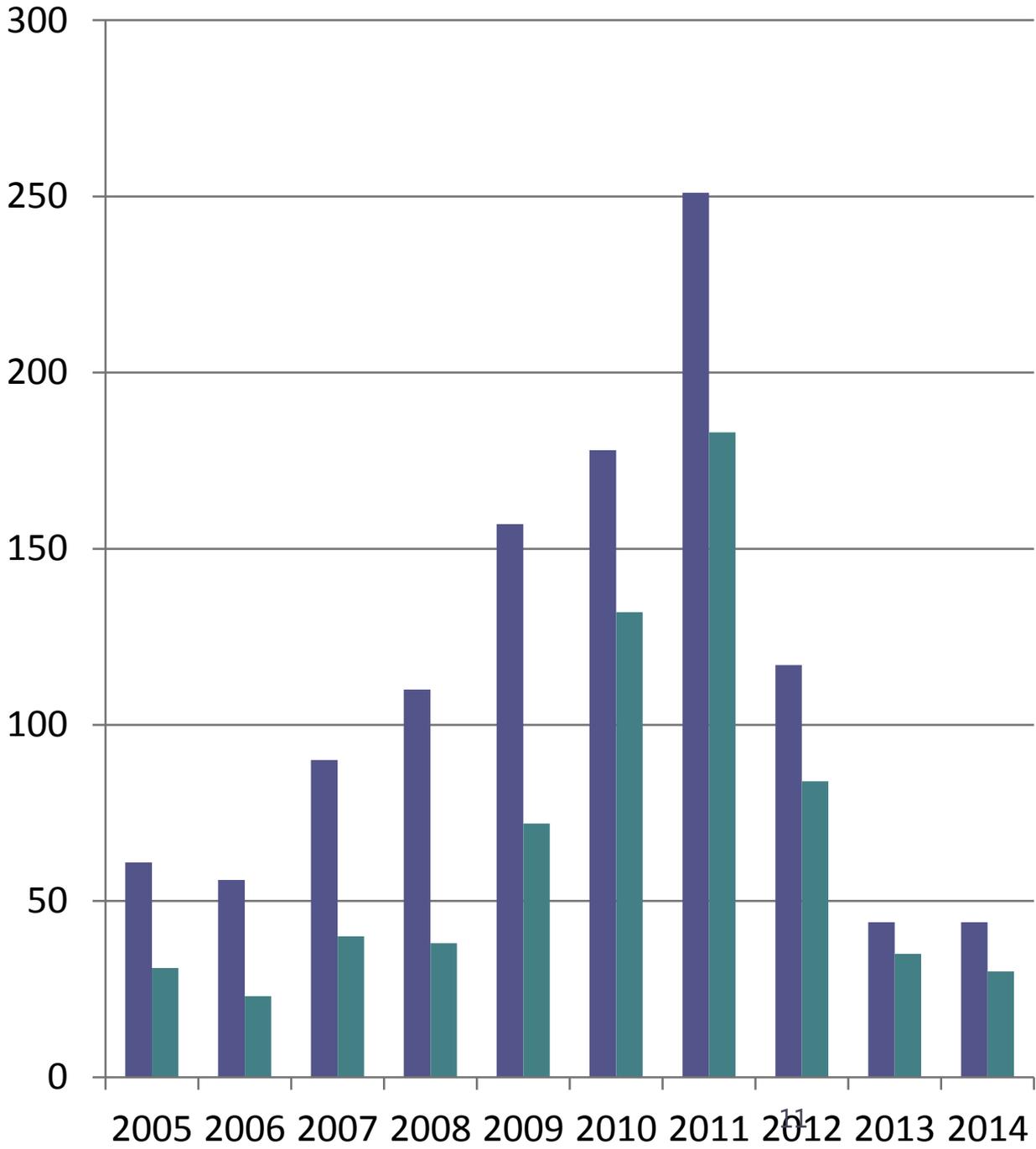
# DRUG SHORTAGE DATA

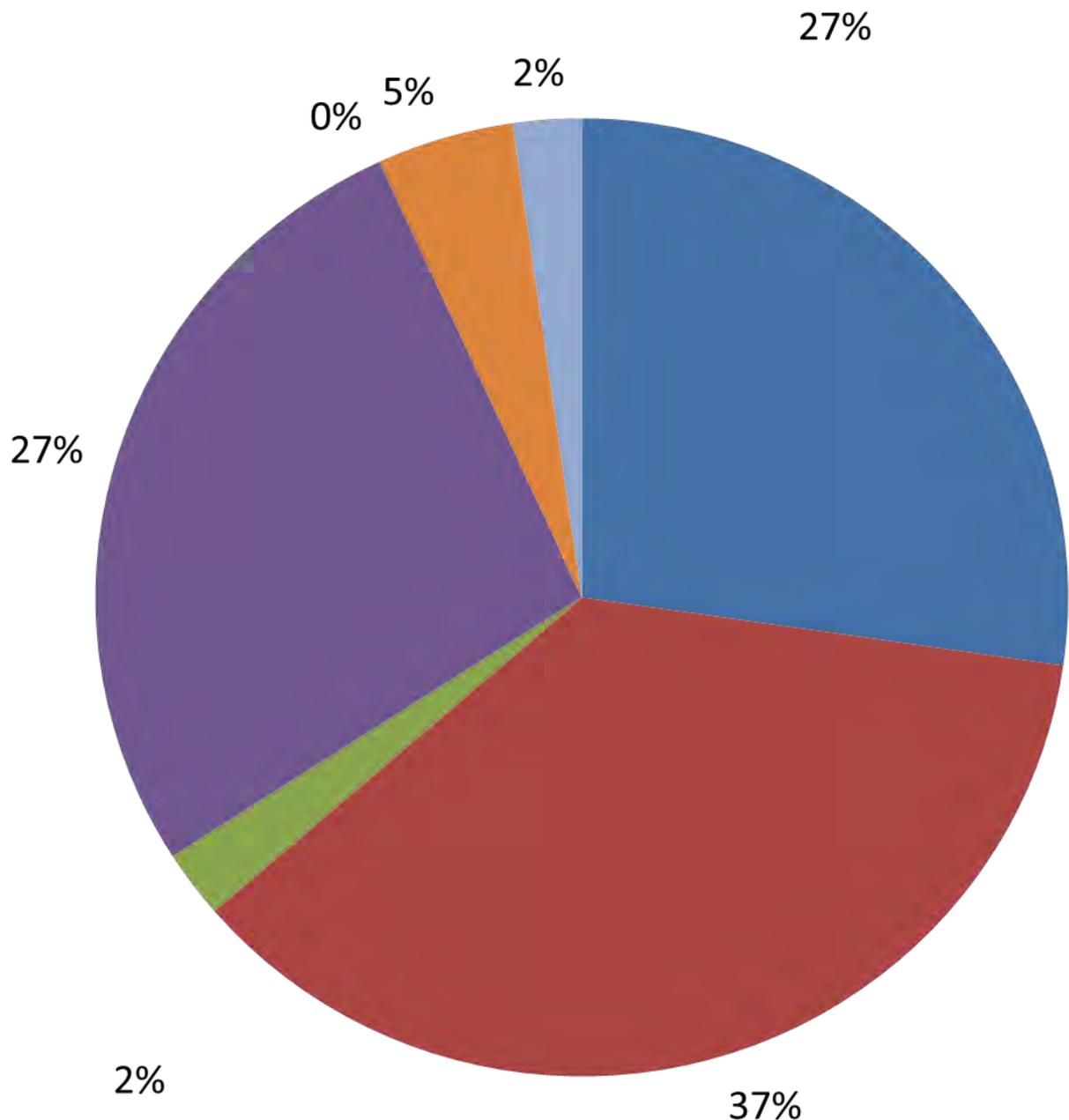
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- There were 251 shortages reported in 2011; 117 shortages were reported in 2012; 44 shortages were reported for both 2013 and 2014
- A high percentage are sterile injectables
  - Chemotherapy, anesthesia, injectable nutritional medications, and other 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

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- 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



# CAUSES OF SHORTAGES: STERILE INJECTABLES

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## ○ From the report by the Assistant Secretary for Planning & Evaluation, 2011:

- State of the Industry
  - Seven (7) 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 redundancy
  - Multiple products made on existing manufacturing lines
  - 24/7 production with no time cushion



# CAUSES OF SHORTAGES: STERILE INJECTABLES

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- From the 2011 report (cont.):
  - Complex manufacturing processes
    - No simple fix as these are complex molecules
    - 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?



# SHORTAGES OF CONTROLLED SUBSTANCES

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- Normally occur for same reasons as other drugs (predominantly quality issues)
- No shortages reported that are due to quota in over 4 years
- When quota needs are reported to potentially result in shortage for a medically necessary drug, FDA and DEA collaborate closely

# SHORTAGES AND THE FDA RESPONSE

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- Collaborating on system fixes and root problem resolution by working with various stakeholders:
  - Manufacturers
  - Industry groups



# SHORTAGES AND THE FDA RESPONSE

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## ○ 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

# HOW DOES THE FDA FIT?

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- **Patient care is our #1 concern**
- We get involved when we are informed
  - Early notification is critical
- The FDA seeks ways to prevent and mitigate shortages
  - Secondary response to an industry problem
  - Find a root cause and get manufacturer back on track

# HOW DOES THE FDA FIT?

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- Only some shortages can be prevented
  - Unforeseen breakdown in manufacturing line
  - Longstanding quality manufacturing problems
  - API sourcing problems
  
- Some can be addressed quickly while others require more time
  - Risks to the patient are always considered



# THE FDA'S APPROACH TO PREVENTION AND MITIGATION

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- Prioritize products that are medically necessary
- Risk/Benefit of the drug in question
- 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!!
- Be flexible, creative and fast!

# MEDICAL NECESSITY

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“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 TOOLBOX

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## ○ 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; 3<sup>rd</sup> party oversight of production; special instructions for safe use

## ○ **Request** other firms to increase production

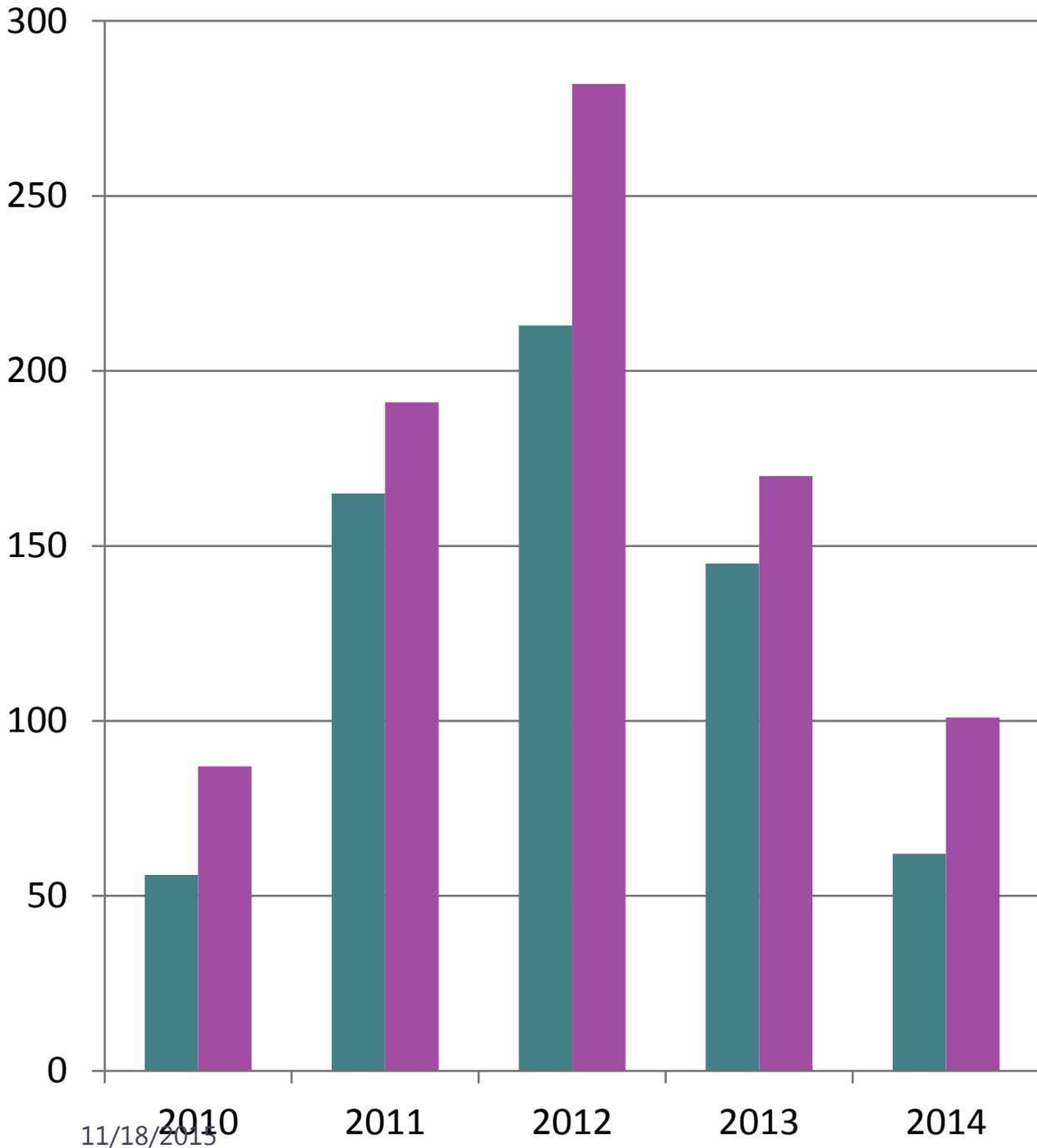


# FDA TOOLBOX

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- 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: forscarnet, ethiodol, thiotepa, norepinephrine, Xeloda, levoleucovorin, leucovorin
  - 2012: methotrexate, doxorubicin liposomal, propofol, phentolamine
  - 2013: sodium bicarbonate, 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

**AVERTED DRUG SHORTAGES: 2010-2013**



- Injectables
- All Forms

11/18/2015

# DRUG SHORTAGE

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- 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

# ROLE OF INDUSTRY

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- Communicate early about potential shortages
- Provide Shortage Information for posting on FDA Website When Shortage 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

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- 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



# LONG-TERM GOAL: PREVENTION OF DRUG SHORTAGES

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- Focus on the underlying causes of production disruptions to prevent drug shortages
  - Develop Methods to Incentivize and Prioritize Manufacturing Quality Systems
    - Drug Shortage Award Program
  - Use Regulatory Science to Identify Early Warning Signals of Shortages
    - Office of Pharmaceutical Quality
  - Increase Knowledge to Develop New Strategies to Address Shortages
    - Important data limitations exist

# FDA RESPONSE TO SHORTAGES: STRATEGIC PLAN

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- Taskforce of FDA personnel
  - Drug Shortage Staff, Office of Compliance, Office Pharmaceutical Quality, Office of Generic Drugs, Office of Regulatory Programs, CDER Office of Biologic Products, Center for Biologics, ORA
- Strategic Plan released October 31, 2013
  - 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

# THE FUTURE

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## ○ 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:

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## ○ 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



# THANK YOU FOR YOUR TIME!

**FDA Drug Shortages Homepage:**

<http://www.fda.gov/drugs/drugsafety/default.htm>

**To report drug shortages, email:**

[drugshortages@fda.hhs.gov](mailto:drugshortages@fda.hhs.gov)

**FDA Webinar on Prescription Drug Shortages of  
September 30, 2011:**

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

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THE AGENCY DEVELOPED THE DRUG SHORTAGES APP TO IMPROVE ACCESS TO INFORMATION ABOUT DRUG SHORTAGES, 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.”