

Clinical Implications of Drug Shortages: FDA Perspective

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Pharmaceutical Knowledge



Disclosure Statement

I have no financial relationships with proprietary entities that produce health care goods and services

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Outline

- Shortages as significant public health threat
 - Sources of drug shortages
- FDA role in drug shortages
 - Role and impact of early notification by manufacturers
- Recent Activities
 - Expanded International Work
 - Recognition of manufacturer contributions to shortage issues
- Future Directions
 - Continued Cooperation
 - Support for Quality Manufacturing

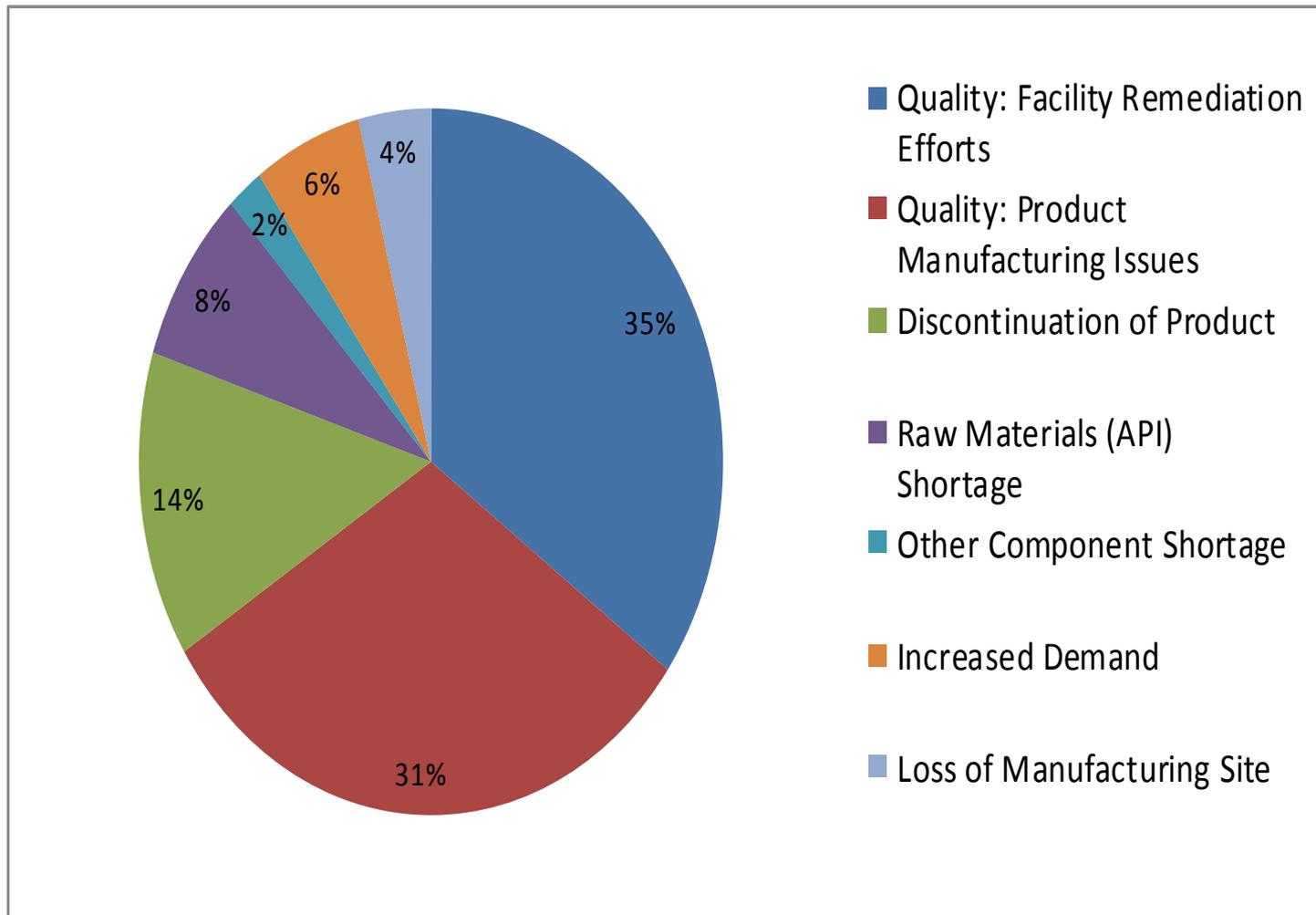


Public Health Importance of Drug Shortages

- Tretinoin capsules for acute promyelocytic leukemia (APL)
- Erwinaze for children with acute lymphoblastic leukemia (ALL)
- Sucraid for genetic sucrase-isomaltase
- IV Normal Saline for hydration
- Zinc for parenteral nutrition in neonates/premature infants
- Doxorubicin for ovarian cancer and other cancers



Sources of Drug Shortages: Quality Manufacturing Issues



Examples of Quality Manufacturing Issues

- Sterility: Bacterial and fungal contamination
- Particulates: Glass, metal or fiber in vials
- Crystallization: Drug may form crystals
- Precipitation: Reaction between drug and container or diluent
- Impurities: Can be toxic (heavy metals)
- Degradants: Lead to less effective drug product
- Equipment breakdown, need for remediation
- Natural Disasters

Sources of Shortages: Sterile Injectables

- State of the Industry
 - Small number of 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 redundant manufacturing
 - Multiple products made on existing manufacturing lines
 - 24/7 production with no time cushion

Sources of Drug Shortages: Sterile Injectables (cont)

- Complex manufacturing processes
 - 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?

FDA and USG Response to Drug Shortages: Early Notification



Early Notification

- October 31, 2011
 - Executive Order from President Obama directing FDA to use its authorities to encourage early notification of potential shortages
- December 19, 2011
 - Interim Final Rule published to improve advance notification of potential shortages
- July 9, 2012
 - FDASIA broadens scope of early notification requirements
 - Requires Strategic Plan and Annual Report on Drug Shortage Efforts

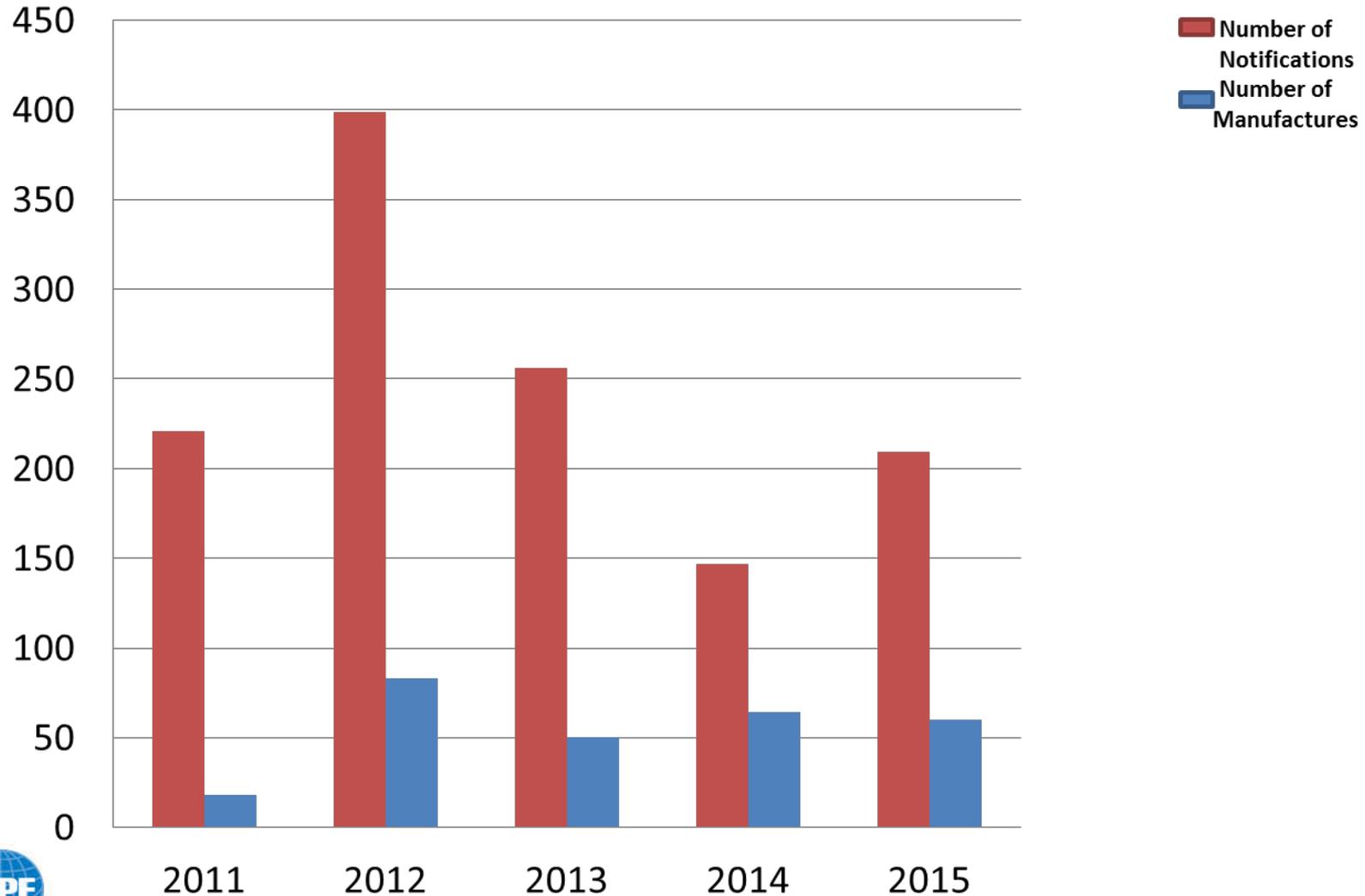


Early Notification

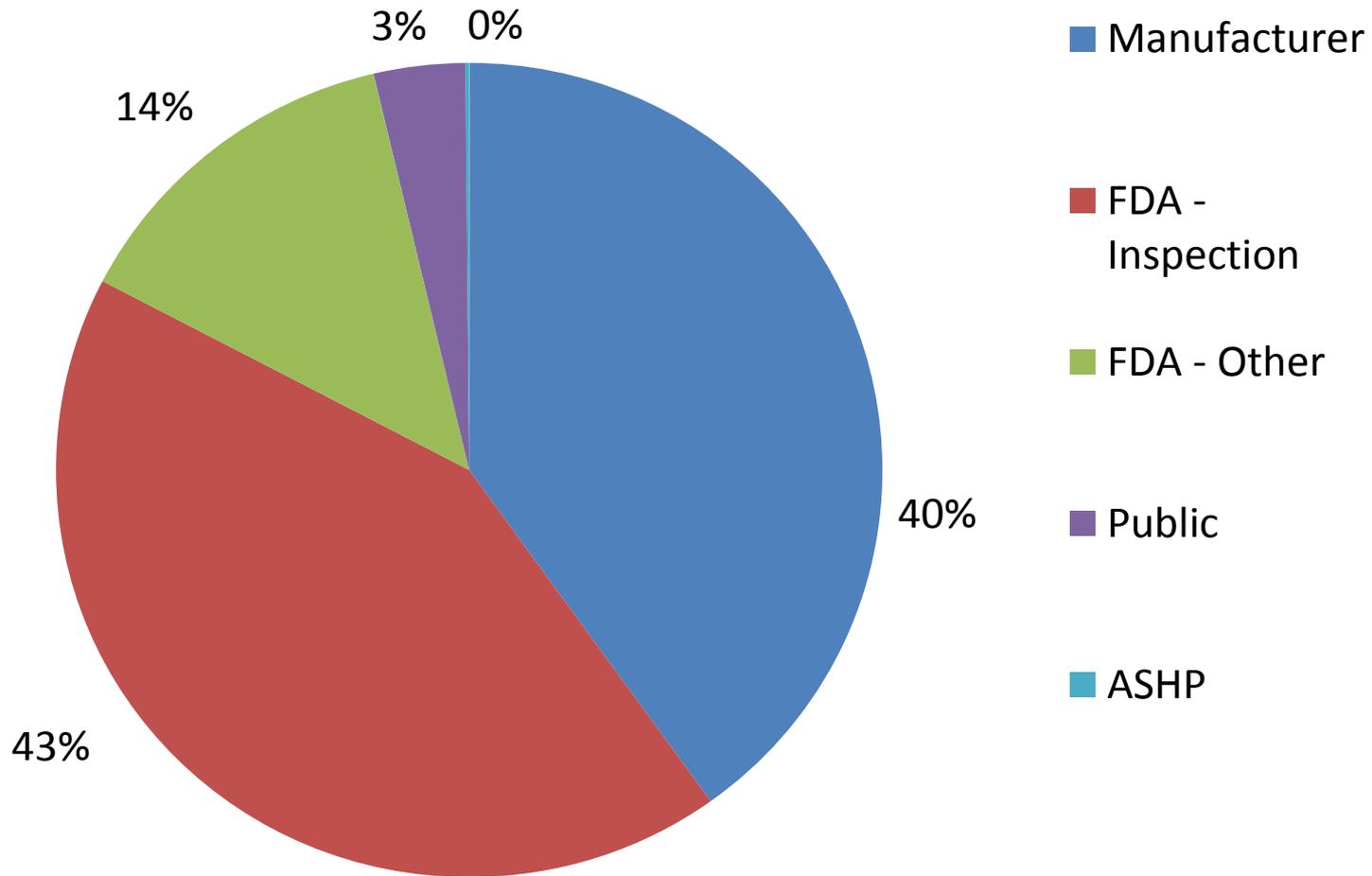
- Early notification is key
- The sooner FDA knows about a potential disruption in supply the better chance of resolution
- Failure to notify will result in a non-compliance letter to the manufacturer
- Four non-compliance letters issued to date for failure to notify



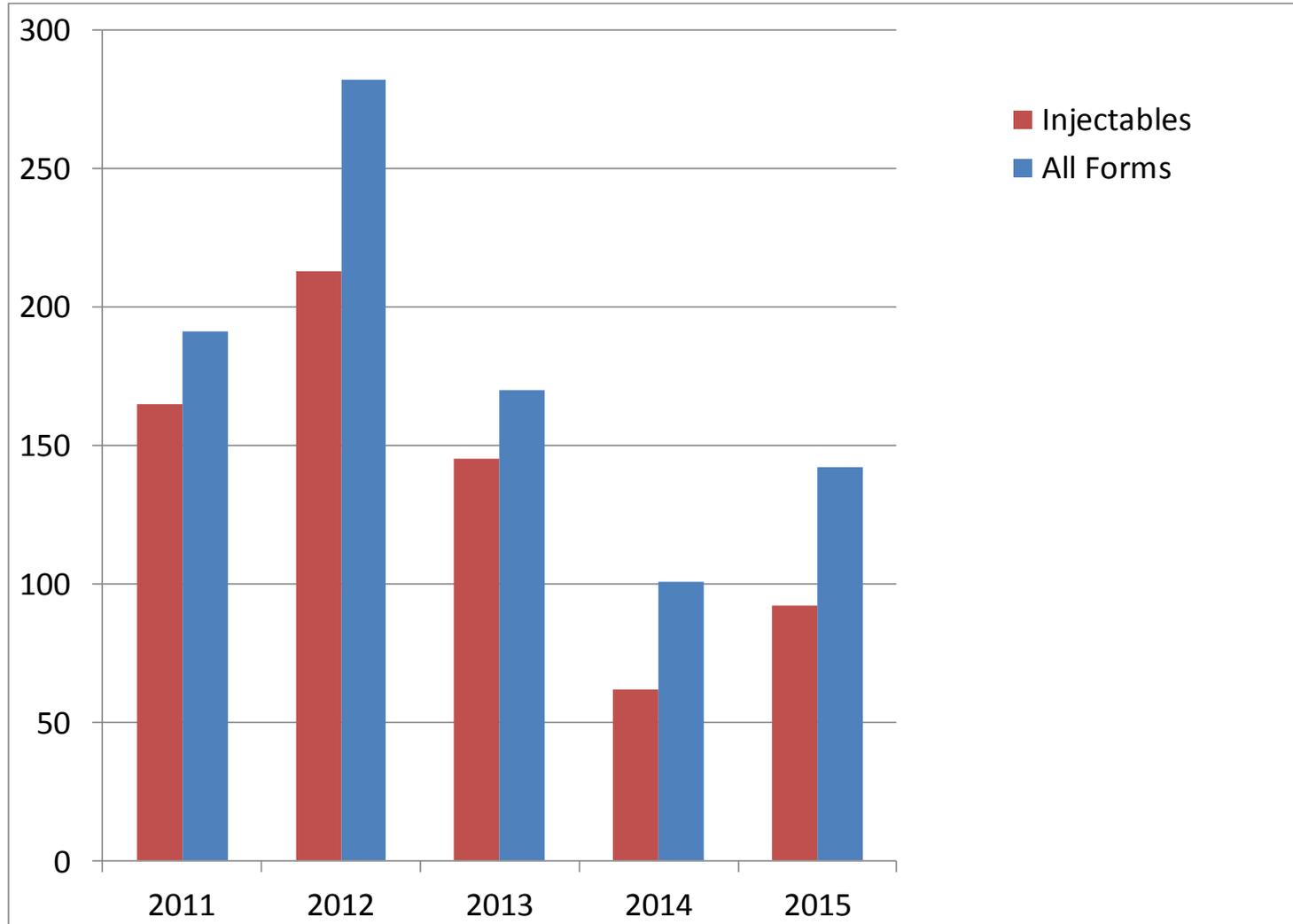
Manufacturer Notifications of Potential Supply Disruptions



Notification Source: Sterile Injectable Drug Shortages: 2013



Averted Drug Shortages: 2010-2015



FDA Response to Drug Shortages: Strategic Plan

- Created by Taskforce of FDA personnel
 - Drug Shortage Staff, Office of Compliance, Office of Generic Drugs, Office of Regulatory Programs, Center for Biologics Evaluation and Research, ORA
- Strategic Plan released October 31, 2013
- Two Overarching Goals:
 - 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



Strengthening FDA's Response to Potential Shortage: FDA Actions

- Respond promptly and efficiently to notification of a shortage
- Perform risk-based analysis to determine ways to address shortage
 - Determine if other manufacturers can increase production
 - Expedite inspections and reviews of submissions
 - Exercise temporary enforcement discretion for new sources of medically necessary drugs
 - Work with the manufacturer to ensure adequate investigation into the root cause of the shortage
 - Review possible risk mitigation measures for remaining inventory
- Communicate effectively to stakeholders





Strengthening FDA's Response to Potential Shortage: FDA Actions

- Current shortage information updated daily at fda.gov
 - http://www.accessdata.fda.gov/scripts/drugs_hortages/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



Strengthening FDA's Response to Potential Shortage: FDA Actions

- 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

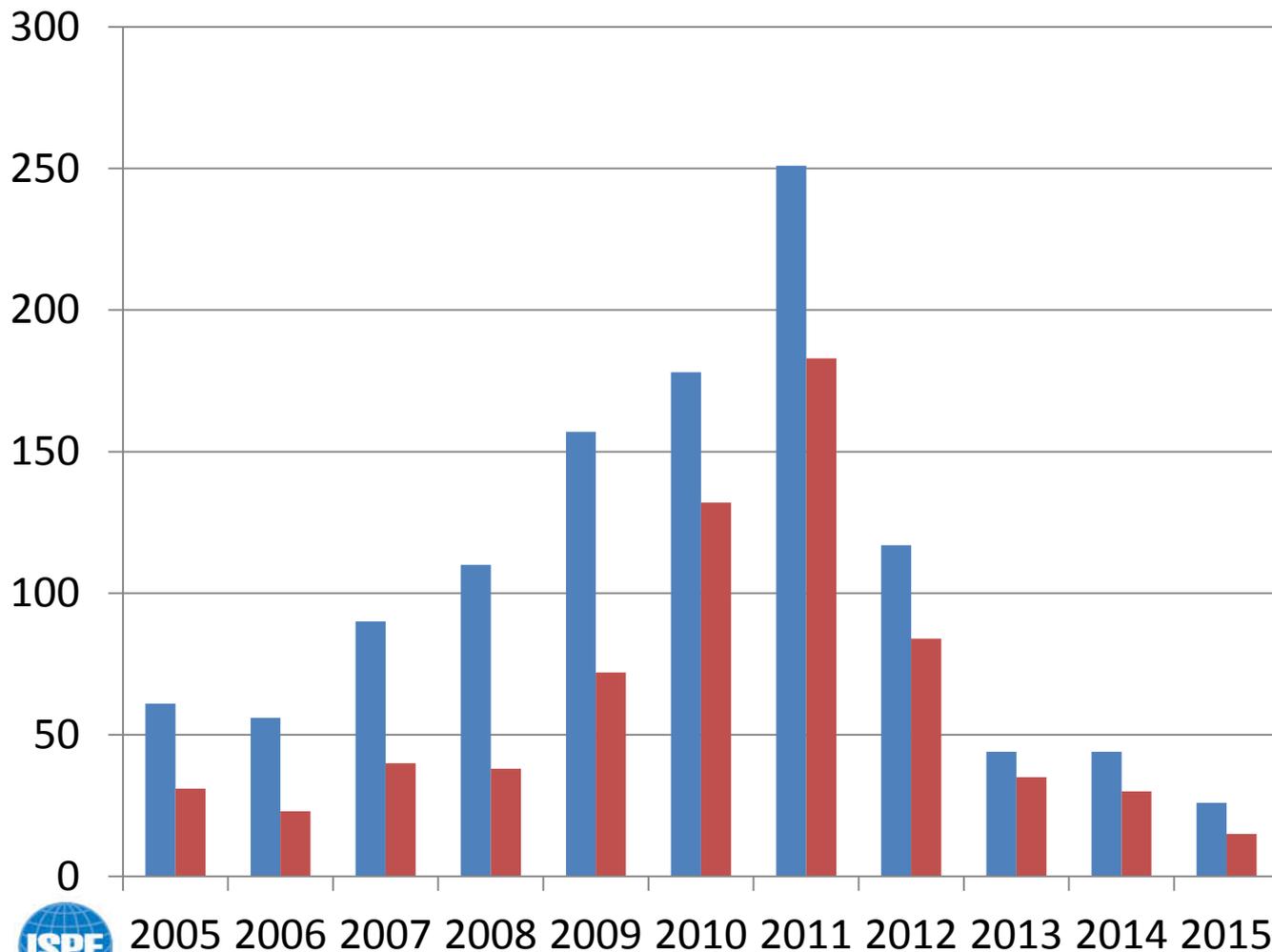
- Data about drug shortages comes from points all across the supply chain:
 - FDASIA required reporting – enacted July 2012
 - Industry required to supply information
 - Wholesalers voluntarily supply inventory and interruptions
 - Pharmacy Hospital sales provided via IMS sales/marketing data
 - Public 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



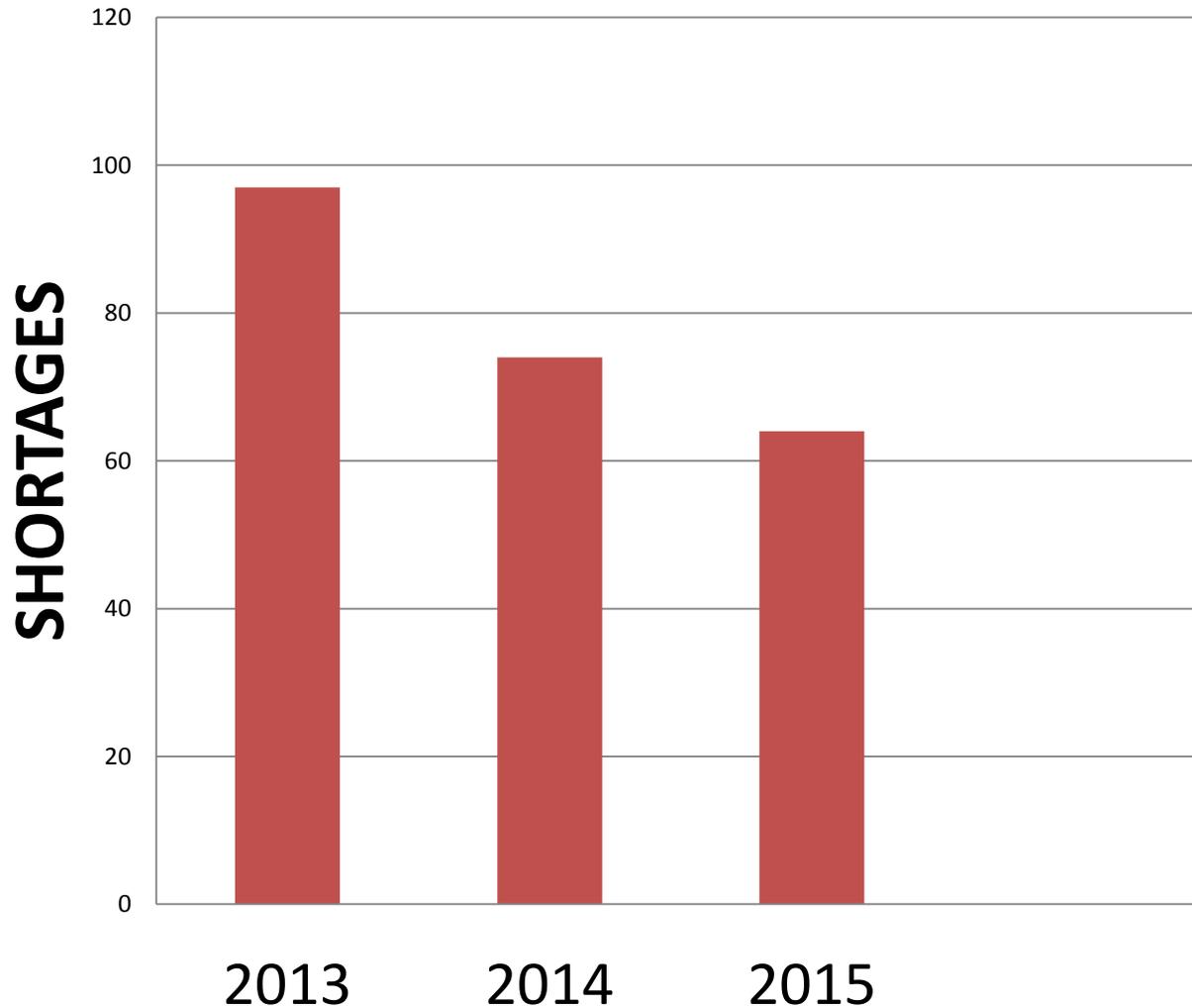


Current State: Drug Shortages

- All Forms
- Sterile Injectables



Current State: Ongoing Shortages at End of Calendar Year



The Future of Drug Shortages

- FDA
 - Drug Shortages are a continued priority for FDA resources and attention
 - Ongoing FDA focus on internal agency processes
 - Ongoing FDA focus on cooperation with manufacturers, patients, patient groups, international regulators, other stakeholders
 - Ongoing FDA focus on improved communications
 - Ongoing FDA focus on data quality and transparency

The Future of Drug Shortages

- Focus on Cooperation: no one party can solve drug shortages
 - FDA can only prevent shortages we know about
 - Role for international regulatory cooperation
- Focus on Industry commitment to a culture of quality manufacturing
 - Work to support improved manufacturing practices, methods and quality testing
 - Role for acknowledging critical contributions
 - Promptly report and correct even small production and quality problems
 - Continued discussions with FDA about ways to support quality manufacturing

Focus on International Collaboration

- Expanded international interactions
- Quarterly meetings held between FDA and other regulatory authorities (EMA, TGA, HC, and others). Six meetings held to date
- Information sharing about shortages experienced in the various countries and any other activities related to shortages
- Has been beneficial for all parties in shortage situations to explore potential alternate sources



Recognizing Manufacturing Excellence: Drug Shortage Assistance Award

- Recognizes companies for their efforts in preventing or alleviating a drug shortage
- Brings attention to companies that assist in addressing a drug shortage and prioritizing quality manufacturing
- Serves as an incentive for companies to assist in addressing drug shortages



Drug Shortage Assistance Award

- To date, three companies have been recognized and given this award
 - Guerbet for its efforts related to the shortage of Ethiodol (ethiodized oil) injection
 - Clinigen for its efforts related to the shortage of Foscavir (foscarnet sodium) injection
 - Euroheal, a subsidiary of Hikma Pharmaceuticals, for its efforts related to the shortages of thiotepa for injection and phentolamine mesylate for injection



Long-term Goal: Prevention of Drug Shortages

- Focus on the underlying causes of production disruptions to prevent drug shortages.
 - Develop Methods to Incentivize and Prioritize Manufacturing Quality
 - Use Regulatory Science to Identify Early Warning Signals of Shortages
 - Proposed Office of Pharmaceutical Quality
 - Increase Knowledge to Develop New Strategies to Address Shortages
 - Important data limitations exist
 - ISPE survey an important tool to aide in this work!



Summary: FDA Role In Drug Shortages

- Working 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

THANKS

- CDER staff who work on drug shortage issues
 - Drug Shortage Staff (Captain Valerie Jensen and her staff)
 - Office of Compliance
 - Office of New Drugs
 - Office of Pharmaceutical Quality
 - Office of Generic Drugs
 - Office of Regulatory Programs
 - Office of Communications

