

The Etiologies of Drug Shortages

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Learning Objectives

- At the conclusion of this discussion participants should be able to:
 - Describe US drug shortage trends
 - Describe reasons for drug shortages
 - Gain an understanding of the FDA's role in working with drug supply
 - Gain an understanding of the FDA's view of the future of drug supply

THE DRUG SHORTAGE PROGRAM

A high-level overview of the purpose and function of the drug shortages program.

Drug Shortage Program

- **Our mission is to prevent, mitigate and help resolve shortages**
- Part of the Center for Drug Evaluation & Research (CDER)
 - Drug Shortage Program began in 1999
 - CDER DSP to Drug Shortage Staff (2012)
 - CDER Immediate office-(2014)
- Drug Shortage Staff (DSS) also does outreach to professional organizations, patient groups, the public and other stakeholders

Drug Shortage Program

- 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

Shortages, Legislation, and the FDA Response



- Executive order to require early notification (2011)
- FDA Safety and Innovation Act (FDASIA) was signed into law 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 Issued July 8, 2015



Shortages, Legislation, and the FDA Response



- Current shortage information updated daily at fda.gov
- Drug Shortage Mobile APP
- Reporting shortages is encouraged:
 - Contact from the public about existing shortages
 - Contact from industry about potential shortages

Shortages, Legislation, and the FDA Response



- Collaboration on system fixes and root problem resolution by working with various stakeholders:
 - American Society of Health System Pharmacists (ASHP)
 - Industry groups:
 - GPHA
 - PhRMA
 - BIO
 - Other Government agencies:
 - CDC, CMS, etc

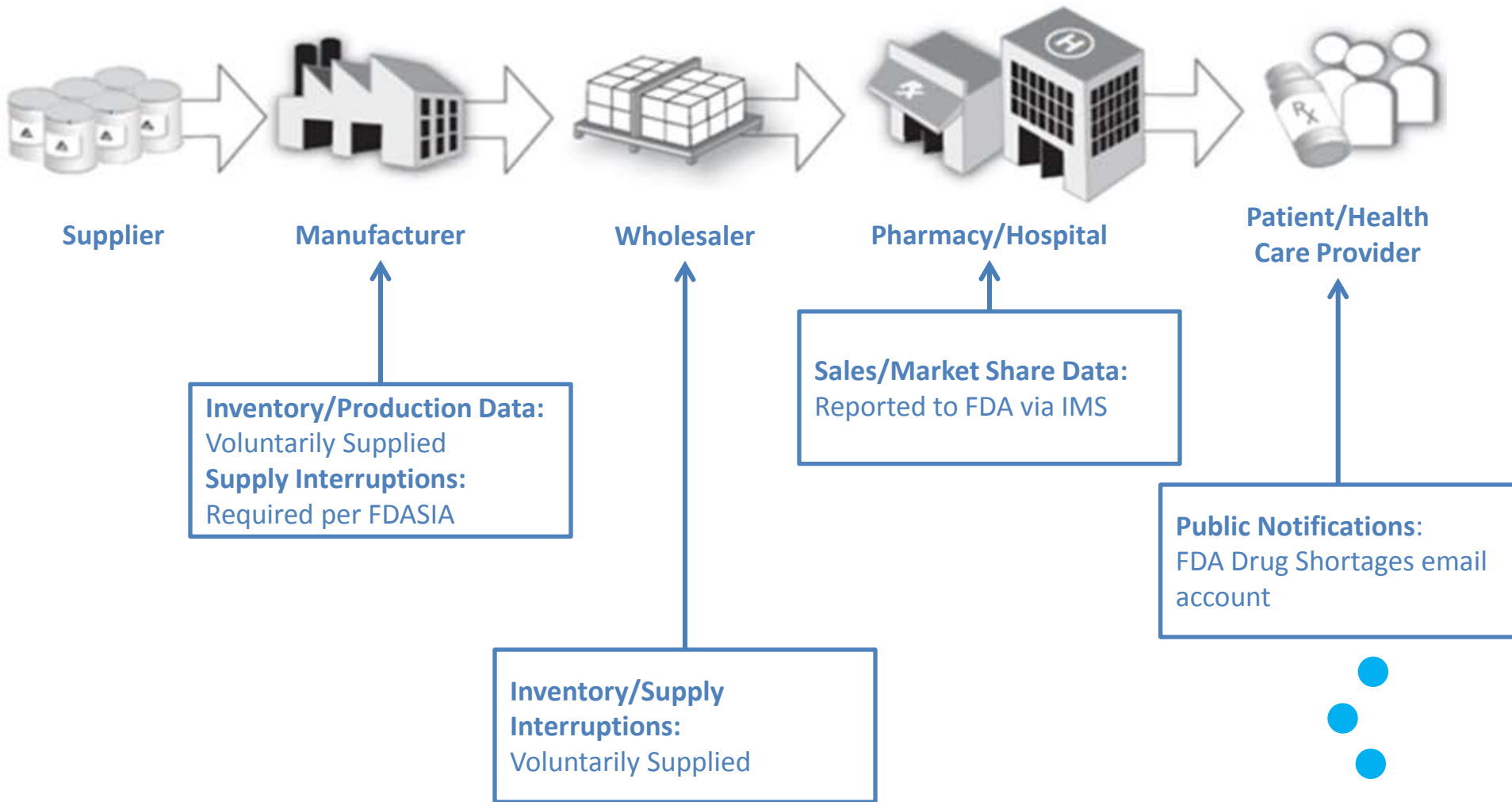


Challenge Question 1

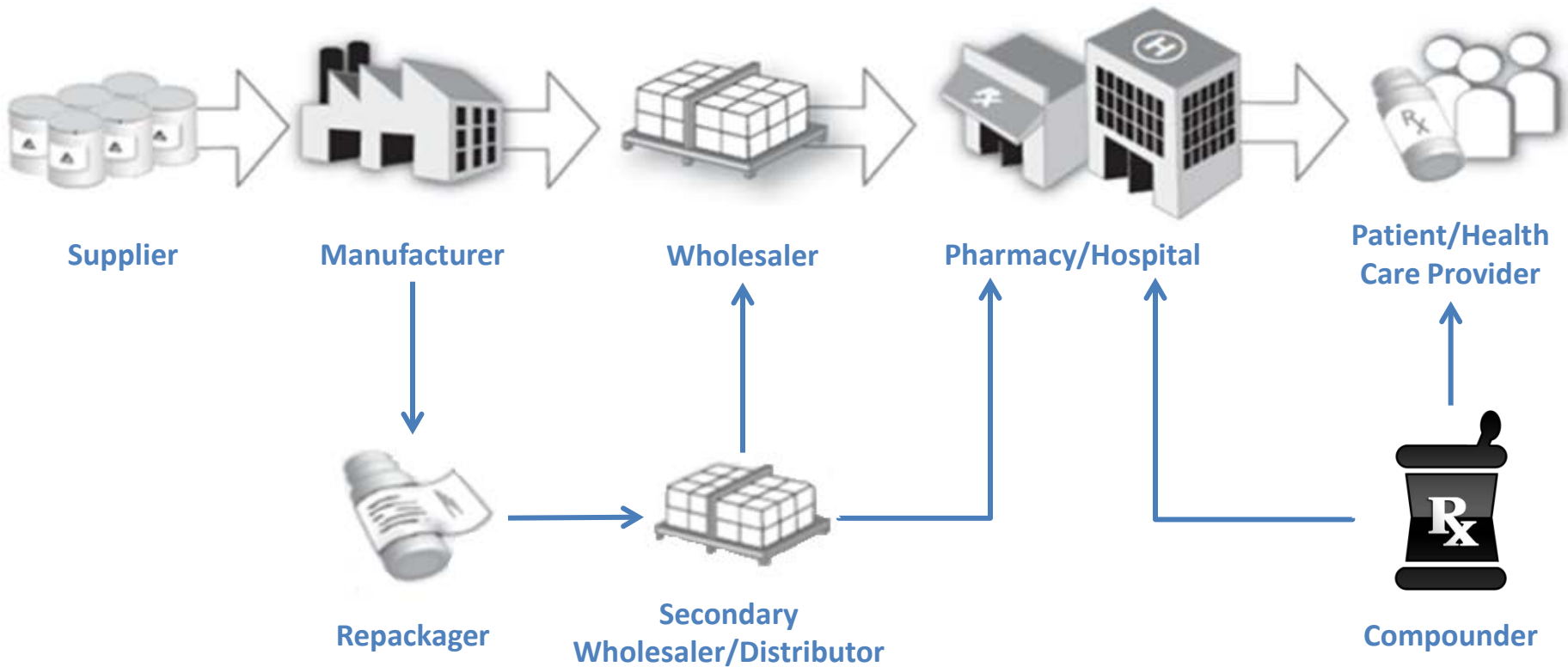
- Drug Shortage Staff works to prevent, mitigate and resolve shortages by working with all stakeholders below except:
 - A. Public
 - B. Centers for Disease Control and Prevention
 - C. FDA-Office of New Drugs
 - D. Federal Trade Commission
 - E. Manufacturers

DRUG SHORTAGE DATA SOURCES

Drug Supply Chain – 1st Tier



Drug Supply Chain – 2nd Tier



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

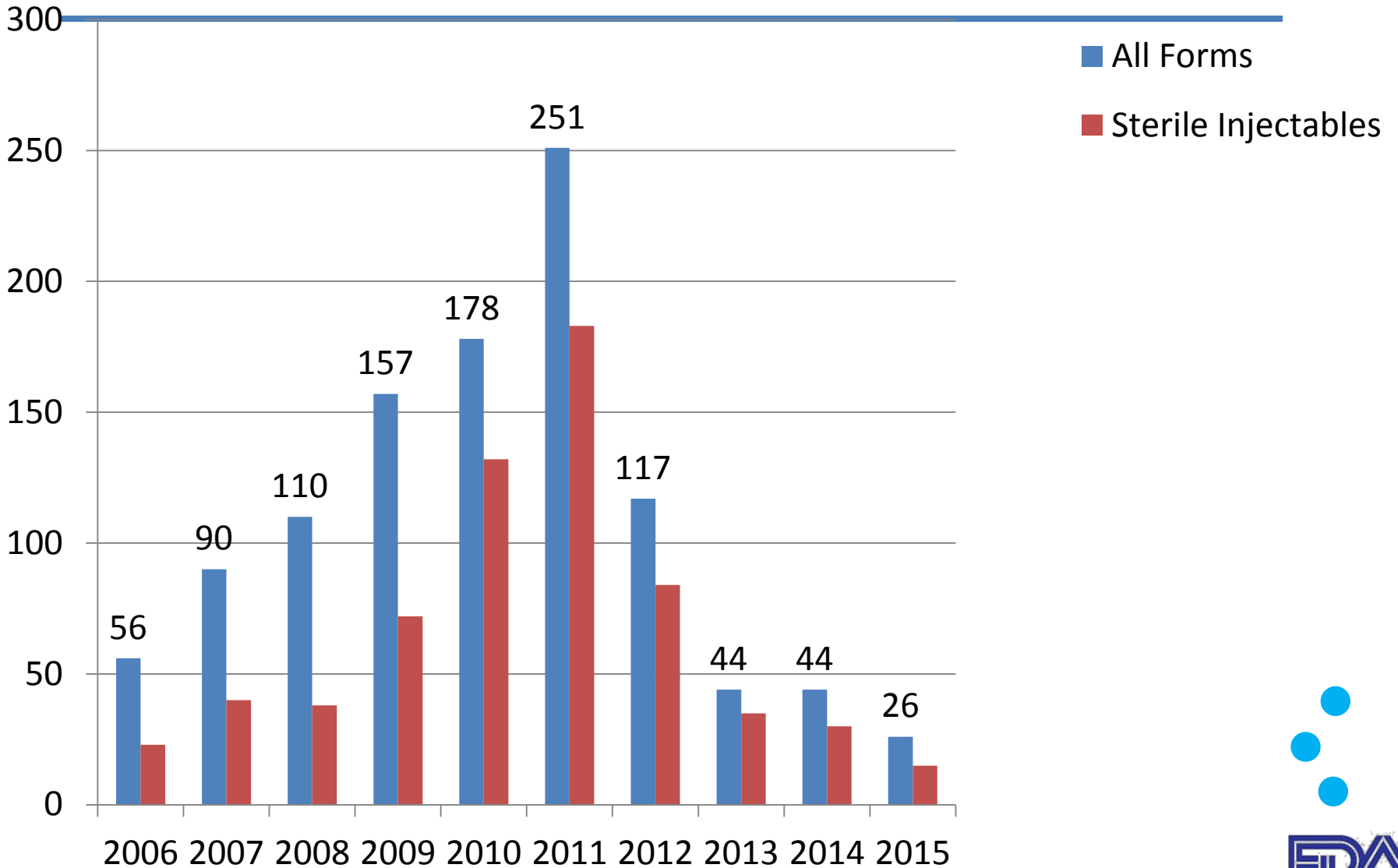


DRUG SHORTAGE DATA

Drug Shortage Data

- A high percentage are sterile injectable
 - 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



REASONS FOR DRUG SHORTAGES

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



Causes of Shortages: Sterile Injectables



- From the report by the Assistant Secretary for Planning & Evaluation, 2011:
 - State of the Industry
 - Seven (7) manufacturers make up most of the generic 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



- 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?



Challenge Question 2

- When there are quality issues with sterile injectable, this almost always results in a shortage. (True or False)
 - A. True
 - B. False

MITIGATING DRUG SHORTAGES

How the FDA and the Drug Shortages Staff work to alleviate and prevent drug shortages in the US.

How Does the FDA Fit?

- **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
 - Quick responses to shortage notifications to collaborate with industry to prevent supply disruptions.
 - Work with Industry to get manufacturing and distribution back on track

The FDA's Approach To Prevention and Mitigation



- Only some shortages can be prevented
 - Unforeseen breakdown in manufacturing line
 - Longstanding quality manufacturing problems
 - Natural disasters
- 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



- Drug shortages can not always be prevented
 - Unanticipated events occur
 - Manufacturing line breakdown or natural disaster (Tsunami)
 - Sometimes alternate 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 (*allocation*)
 - No easy way to do this well



The FDA's Approach To Prevention and Mitigation



- 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!



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

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.”

Drug Shortage Defined

Drug shortage:

A period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug. In general, the DSS focuses on shortages of medically necessary products that have a significant effect on public health.

Challenge Question 3

- What is the FDA's chief concern when it comes to drug shortages ?
 - A. Consistent supply of drug products
 - B. Medical necessity
 - C. Patient care
 - D. All of the above

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 at plant; 3rd party oversight of production; special instructions for safe use
- Communicate possible shortage concerns on a market shortfall to other suppliers.
 - Prompts firms to look at demand and supply

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: 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 injection
 - 2016: tretinoin capsules, bleomycin injection, L-cysteine injection

Role of Industry

- Communicate early about potential shortages
- Provide shortage information for posting on FDA website when a 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

ANATOMY OF A DRUG SHORTAGE

Anatomy of a Drug Shortage: Propofol

Teva Pharmaceuticals

Q3 2009 –
Discontinue
production of
propofol

Hospira

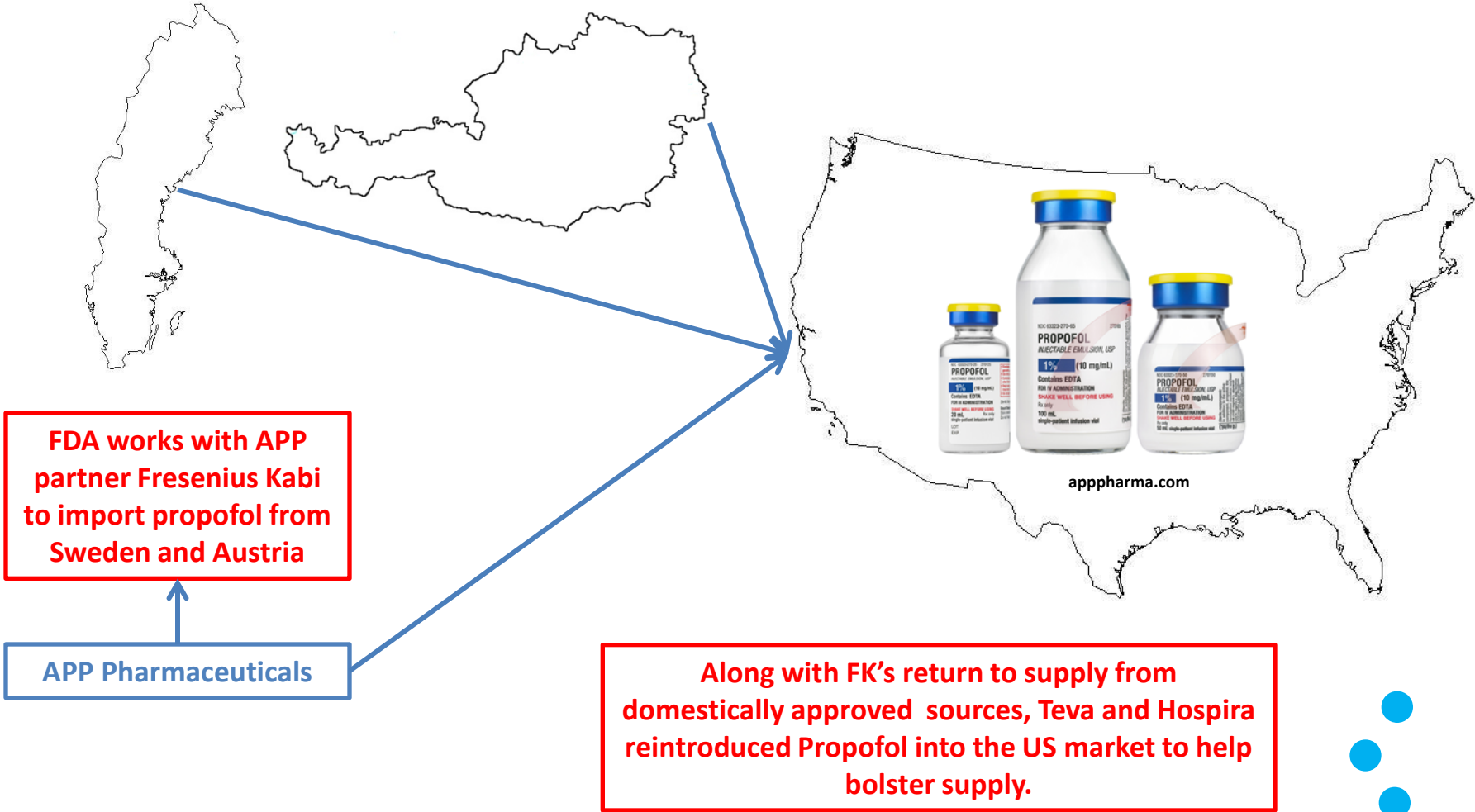
Q1 2010 –
Production quality
issues force
production
shutdown

(2010) APP was now the
sole producer and there
was a shortage of
propofol in the United
States!

APP Pharmaceuticals



Anatomy of a Drug Shortage: Propofol



DATA COMPARISON FDA VS ASHP

Data Comparison: FDA vs ASHP

- Contrasting the websites
 - FDA receives information provided by manufacturers
 - ASHP receives information from practitioners unable to get product
 - FDA does not consider a product to be in shortage if one or more manufacturers are able to supply the full market demand for the product
 - ASHP's Drug Shortage website provides information about which manufacturers have the drug available and which ones do not, since supply chain disruptions may occur when all previous manufacturers are not yet back on the market



Q. Is the drug product information listed on the FDA's Drug Shortage website the same as on the American Society of Health-System Pharmacists (ASHP) Drug Shortage website?

Both FDA and ASHP sites provide drug shortage information, however, there are some differences.

- FDA receives information provided by manufacturers regarding their ability to supply the market as well as market sales data and a product is listed on FDA's Drug Shortage website once it has been confirmed with information provided by manufacturers and market sales research that overall market demand is not being met by the manufacturers of the product.
 - FDA does not consider a product to be in shortage if one or more manufacturers are able to supply the full market demand for the product.
 - In contrast, ASHP's Drug Shortage website provides information about which manufacturers have the drug available and which ones do not.
- For more information on the differences see the following websites:
<http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm#q1>
<http://www.ashp.org/DocLibrary/Policy/DrugShortages/FDA-versus-ASHP.pdf>
 - Regardless of these differences, FDA and ASHP will continue working closely to share information and provide the most updated information possible on our websites.



The Gray Market

- Sources that have or hoard extra product sell it at inflated prices
 - Close link to “local stockpiling” with blurred margins
- Extent is the grey market is unknown but many complaints are received
- FDA reports these complaints to the Department of Justice
- Raises FDA concern about potential for counterfeit drugs filling in the gaps

Challenge Question 4

- FDA posts shortages on their website the same time they become aware of product availability concern . (True or False)
 - A. True
 - B. False

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 quality manufacturing processes, methods, and testing
 - 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

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

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

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



Questions ?

