Understanding and Minimizing the Impact of Current Drug Shortages

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DISCLOSURE

- This presentation represents my own opinions.
- University of Utah Drug Information Service receives some funding from Vizient™ to provide drug shortage content.

LEARNING OBJECTIVES

- Explain current trends in drug shortages and the most recent data on causes of drug shortages.
- Describe how recent manufacturing and drug quality trends relate to drug shortages.
- Evaluate progress towards drug shortage solutions.
- Identify best practices for minimizing the impact of drug shortages.

NATIONAL SHORTAGES AND UNIVERSITY OF UTAH DRUG INFORMATION SERVICE

- UUDIS provides drug shortage content to ASHP and Vizient™
- Public website at www.ashp.org/shortages
  - Partners since 2001
  - Receive voluntary reports submitted via web
  - Collaboration is key to success
  - Frequent communication with FDA drug shortage team

DIFFERENCES BETWEEN WEBSITES

ASHP

- **www.ashp.org/shortage**
- Drugs impacting clinical practice (biologics, devices, dosage forms)
- How to access
- Frequent updates
- Alternatives, safety

FDA

- **www.fda.gov/cder**
- Fewer products
- No biologics or devices
- Information from manufacturer

https://www.ashp.org/Drug-Shortages/Current-Shortages/FDA-and-ASHP-Drug-Shortages

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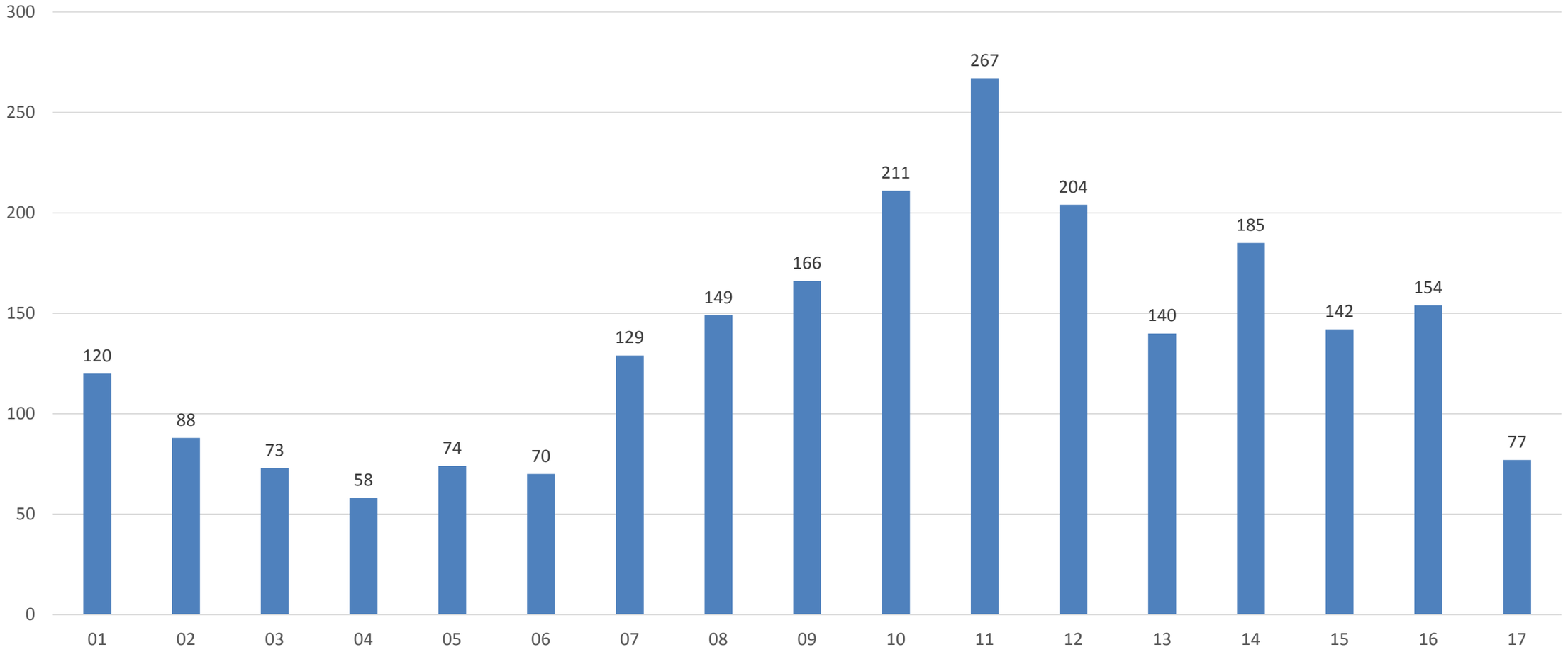
CURRENT TRENDS

NATIONAL DRUG SHORTAGES BY YEAR
JAN 1, 2001 TO JUNE 30, 2017



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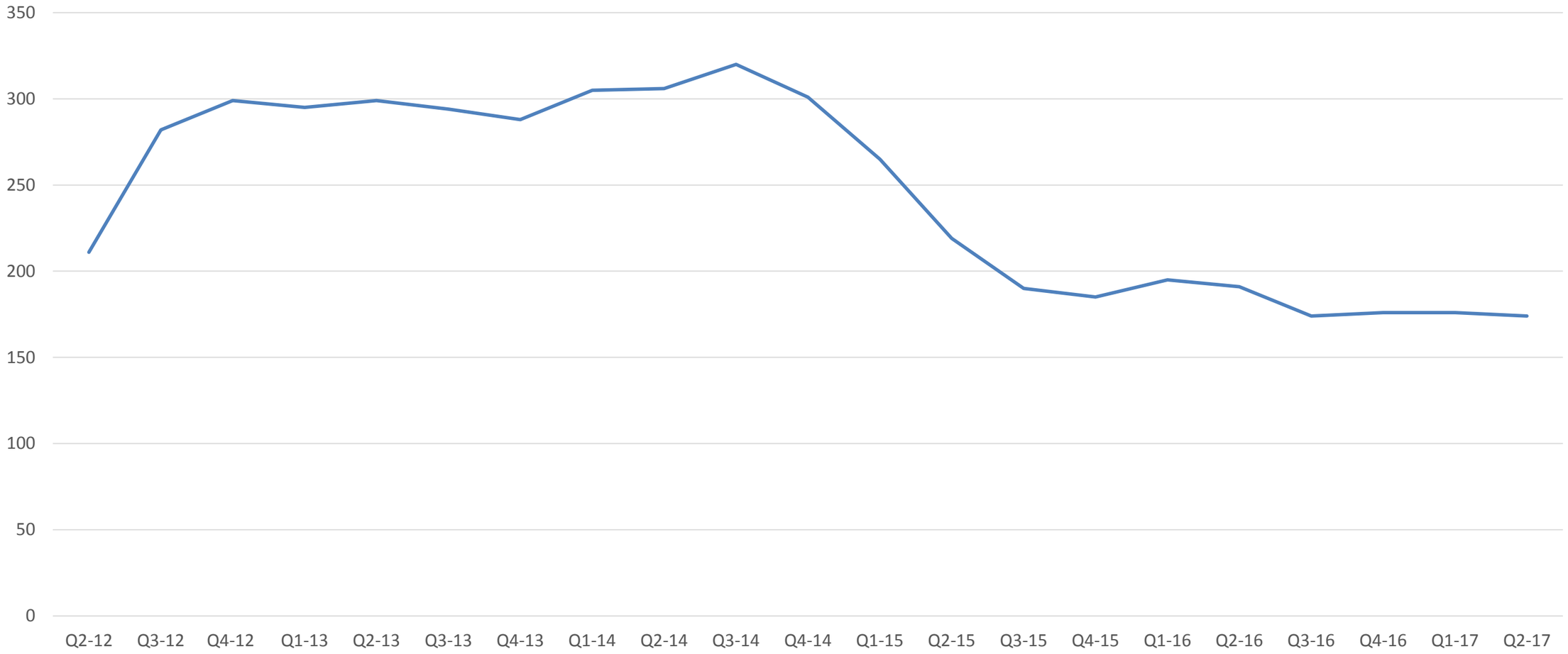
ACTIVE AND ONGOING SHORTAGES – 5 YEAR TREND



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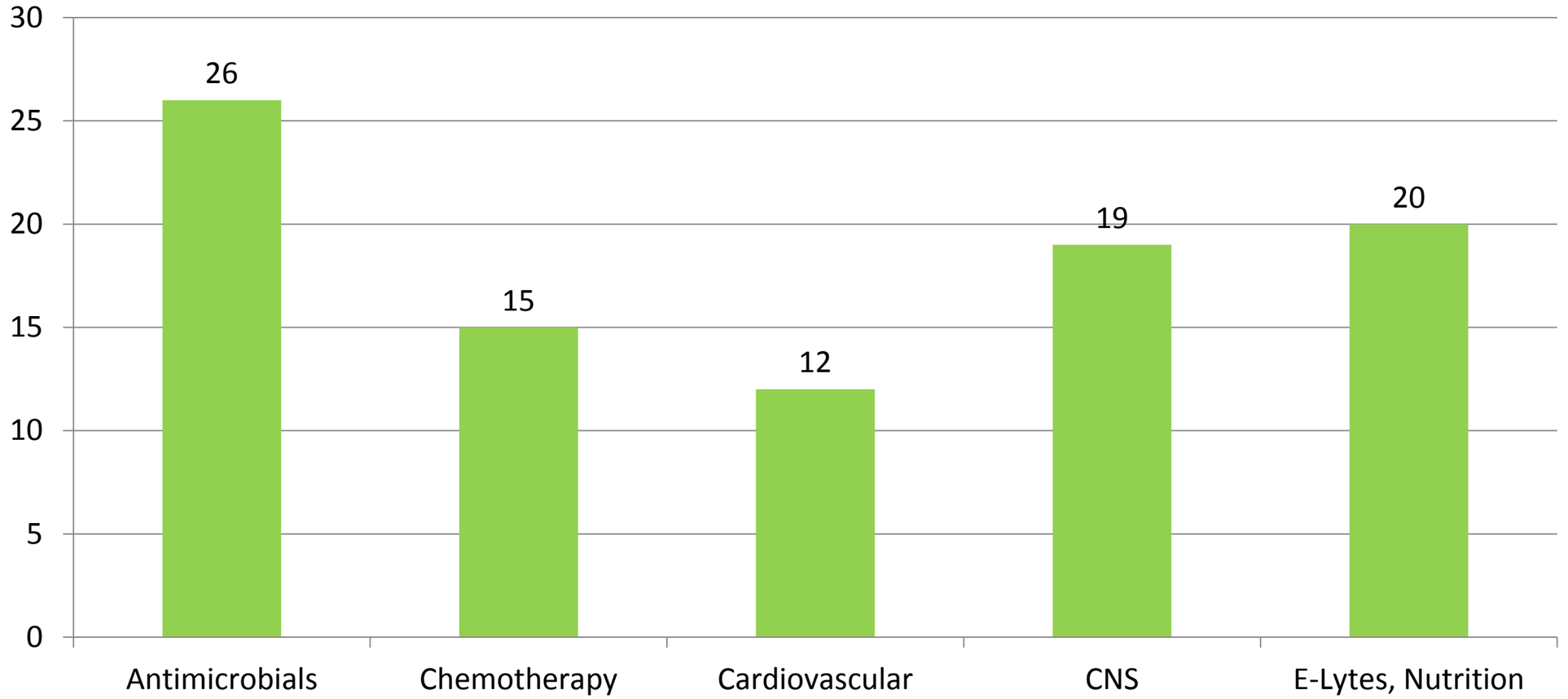
ACTIVE SHORTAGES
TOP 5 DRUG CLASSES



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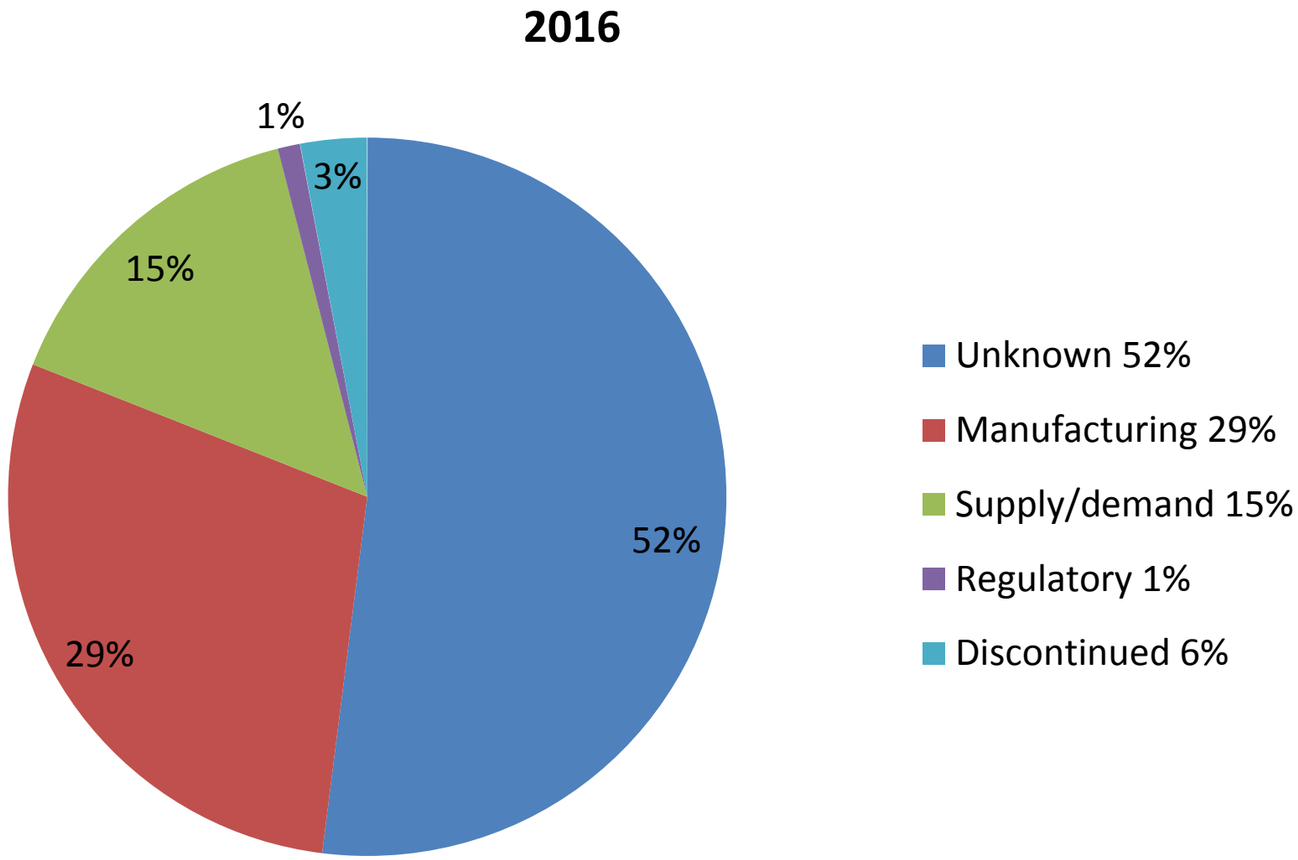
REASONS FOR SHORTAGES AS DETERMINED BY UUDIS DURING INVESTIGATION



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WHAT DO THESE NUMBERS MEAN?

- The rate of new shortages has decreased
- Long-term active and ongoing shortages are not resolving
- Shortages of basics like sodium bicarbonate, emergency syringes, antibiotics, electrolytes, and cardiovascular agents still impact large numbers of clinicians and patients

http://www.gao.gov/products/GAO-16-595

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WHY IS THIS HAPPENING?

WHAT ARE KEY CAUSES OF DRUG SHORTAGES?

a. Raw material issues
b. Counterfeit products
c. US manufacturing moving overseas
d. None of the above

SHORTAGE REASONS – MYTHS VS. REALITY CHECK

- US problem only
- Raw materials
- Foreign manufacturing
- Imports are the fix
- Counterfeits cause shortages in US
- One single reason for shortages

- Europe, Canada, US
- Rare cause
- Issues at US facilities
- No product to import
- Rare cause, global problem
- Complex problem

JUNE 2016 GAO ANALYSIS

- GAO reviewed UUDIS, FDA data
- Factors associated with shortages – 2012 to 2015
  - Fewer suppliers with at least 1 with a warning letter for not following CGMP
  - Generic products – lower profit margins
  - http://www.gao.gov/products/GAO-16-595

ARE SHORTAGES FDA'S FAULT?

a. True

b. False

ARE SHORTAGES FDA'S FAULT?

NO

- FDA shortage team is extremely collaborative
- Violations must be extreme for a shut-down (safety first!)
- Work diligently to prevent shortages

YES

- Enforcement actions can cause shortages
- Manufacturers may have trouble complying with regulations
- Regulatory discretion = unintended consequences?

FDA’S STRATEGY

- Prioritize medically necessary agents (determined on a case by case basis)
- Evaluate risks and benefits for patients
- Offer assistance and advise, but up to the manufacturer to fix
- Success hinges on early notification

A Review of FDA's Approach to Medical Product Shortages. October 31, 2011.

HOW DOES FDA PREVENT SHORTAGES?

- Regulatory discretion
  - Require filters, double checks
- Ask others to increase production
- Expedite reviews (new product, longer expiration, new raw material, new manufacturing sites)
- Imports

A Review of FDA's Approach to Medical Product Shortages. October 31, 2011.

IMPORTS

- Multiple examples since 2010
  - propofol, foscarnet, ethiodol, thiotepa, norepinephrine, capecitabine, leucovorin, levoleucovorin, methotrexate, doxorubicin liposomal, phentolamine, sodium bicarbonate, nitroglycerin, saline, bleomycin
- Limited by quantity available to share with US market
  - May be difficult to access or use
  - May not be an option for some clinical trials

FDA STRATEGIC PLAN

- Mandated as part of FDASIA law
- 2 key goals
  - Enhance mitigation efforts
  - Develop long-term prevention
- Suggestions for external stakeholders
  - Manufacturing incentives
  - Use quality data when purchasing
  - Capacity, redundancy

http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf

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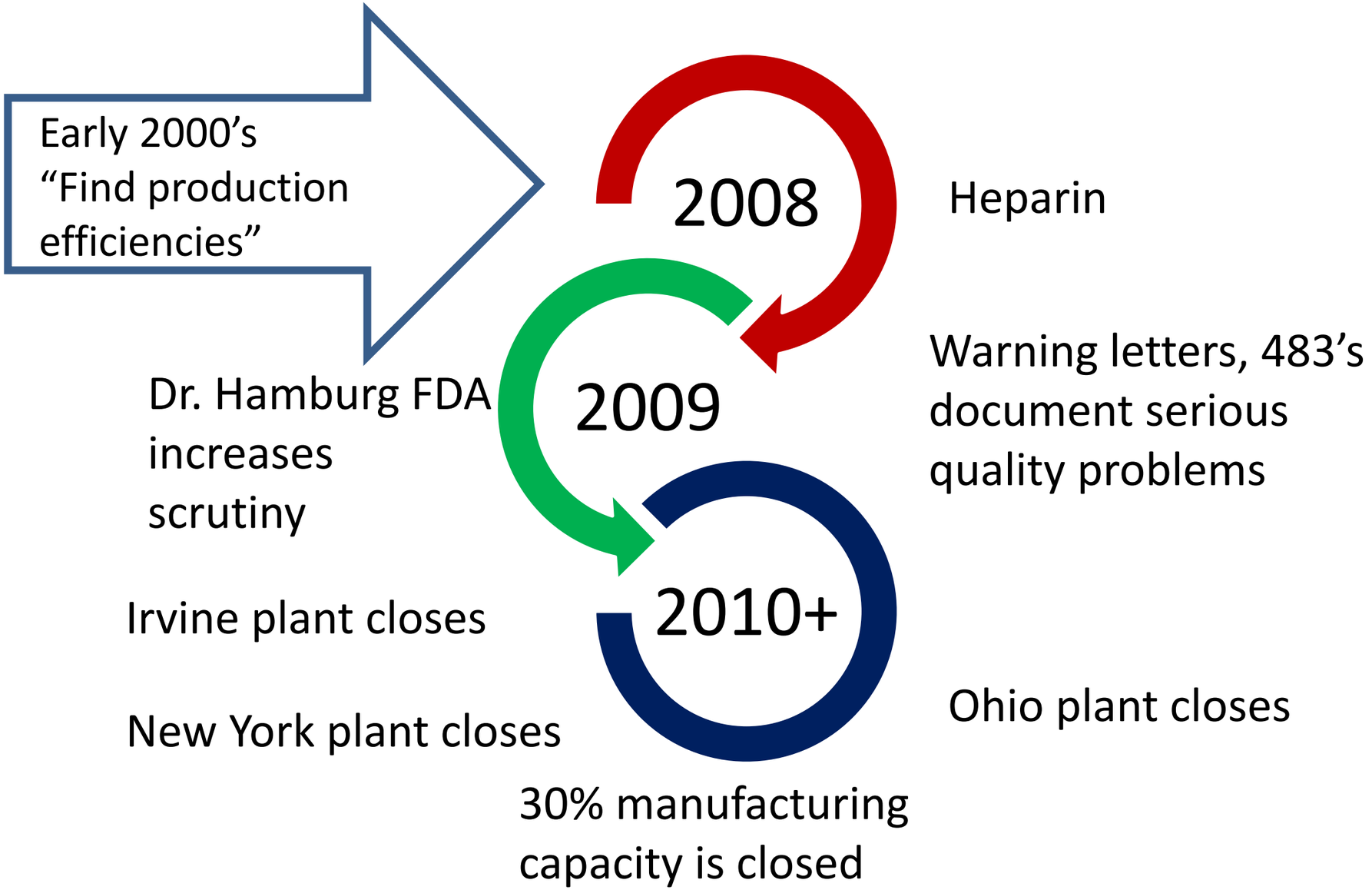
HOW DID WE GET HERE?

CASCADE OF EVENTS



FORM 483 AND WARNING LETTERS

- 483 - documents inspection findings
- Warning letters – significant issues
- Worth reading – even with redactions
  - Metal particles, mold, contamination
  - Insects, animals
  - Urine
  - Manipulating data, mixing good with failed API

FRAGILE SUPPLY CHAIN GENERIC INJECTABLES

- Few suppliers
  - 3 manufacturers supply 71% of market
  - Only 1 or 2 manufacturers for > 1/3 products
- Capacity is limited
  - Concentrated, “just in time” production
  - Multiple products made on single line
  - No back up manufacturing lines

Clin Pharmacol Ther. 2013;93:170–176
Mayo Clinic Proc.2014.89(3):361-373

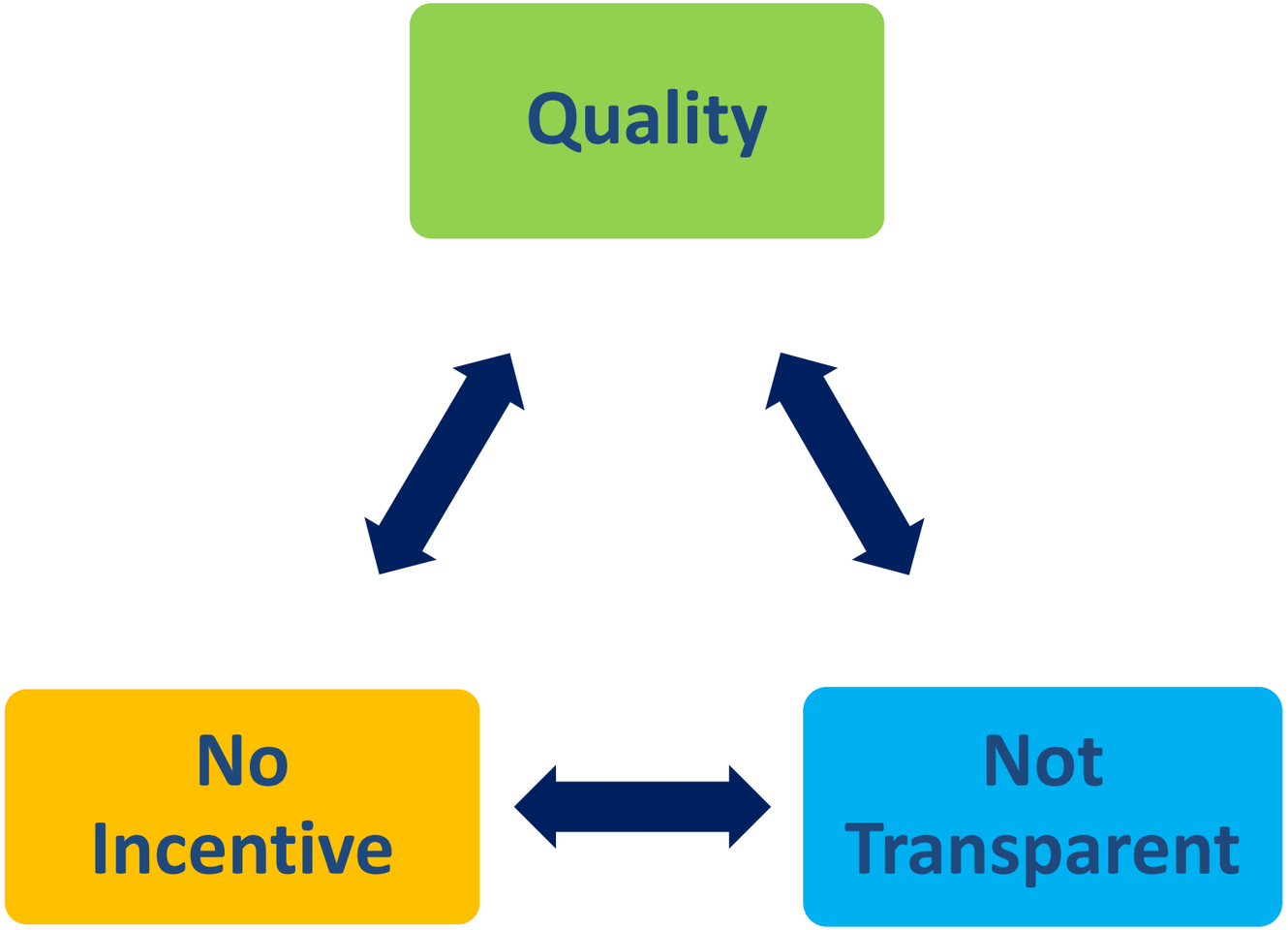
DRUG MANUFACTURING IS A BUSINESS

- Profitability
- Manufacturing fixes
- Capacity – most factories running 24/7
- Prioritization (new opportunities)
- Forecasting (contracts)
- Aging facilities

NO QUICK AND EASY FIX

- Complex manufacturing process
  - Quality problems are difficult to fix
  - Investigation of root cause takes time
  - Changes take time
  - Capacity or redundancy not available

ECONOMIC DRIVERS OF DRUG SHORTAGES



Clin Pharmacol Ther. 2013;93:170–176
Mayo Clinic Proc.2014.89(3):361-373

WHAT DOES QUALITY MEAN?

- Difficult to observe
- Microbial contamination difficult to detect (non-uniform, patients already sick)
- Purchasers rely on FDA to ensure quality
- FDA inspects, but relies on manufacturer to self-report between inspections
- Does quality = availability?

NO REQUIREMENT TO REPORT MANUFACTURER OF PRODUCT

- Contract manufacturing means we don't always know who makes the product
- No requirement to disclose manufacturer (or location) in product label (or 483)
- Your brand product may be manufactured by a generic company

ISN'T THIS A FREE MARKET ISSUE?

- Supply and demand doesn't work - choice, market entry not easy
- How to purchase for quality?
- Shortages generally don't impact profits
- Patients and clinicians impacted, not suppliers

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FIXING THE SHORTAGE PROBLEM

INDUSTRY BASED EFFORTS

- Accelerated Recovery Initiative (2011)
  - GPhA developed plan
  - Partnership between IMS and generic manufacturers
  - No case studies yet – capacity

Karlin S. Generic Rx Shortage Initiative Stuck: Too Few Manufacturers to Pick Up Slack. The Pink Sheet. July 8 2013: #00130708013.

INTERNATIONAL SOCIETY FOR PHARMACEUTICAL ENGINEERING

- Survey -2013
  - Key deficits in quality systems, aseptic processing equipment
- Shortage initiative
  - Root causes of manufacturing problems
- Prevention Plan (October 2014)
  - 6 dimension plan
- Quality Metrics

International Society for Pharmaceutical Engineering (ISPE). http://www.ispe.org/drugshortages. 2013.

About the Center for Drug Evaluation and Research

CDER Offices and Divisions

Drug Safety Oversight Board

Jobs at the Center for Drug Evaluation and Research (CDER)

Meeting Presentations (Drugs)

CDER Exclusivity Board

FAQs about CDER

Reports & Budgets (CDER)

Manual of Policies & Procedures

Office of Pharmaceutical Quality

CDER's Office of Pharmaceutical Quality's (OPQ) mission is to assure that quality medicines are available for the American public.

What OPQ Does

OPQ is a new office within CDER that creates a single unit dedicated to product quality. The new structure, which stood-up in January 2015, provides better alignment among all drug quality functions at CDER, including review, inspection, and research.

OPQ combines non-enforcement-related drug quality work into one super-office, creating one quality voice and improving our oversight of quality throughout the lifecycle of a drug product. OPQ creates a uniform drug quality program across all sites of manufacture, whether domestic or foreign, and across all drug product areas – new drugs, generic drugs, and over-the-counter drugs.

QUALITY METRICS GOALS

- Modernize drug quality oversight
- Risk based inspection scheduling, predictive of drug shortages
- Objective criteria including:
  - Lot acceptance rate
  - Product quality complaint rate

NEW IDEAS FOR MANUFACTURING

- Janet Woodcock advocates continuous manufacturing for:
  - Faster, improved quality, lower prices, fewer shortages
  - Domestic plants – fully integrated from API to finished product

Cox B. FDA Talks Up Continuous Manufacturing, Offers Assistance. The Gold Sheet. July 29 2014: # 08140724006.

CONTINUOUS MANUFACTURING

- Traditional manufacturing = batch process
  - At every step, product is assessed and collected
  - Off-line labs test finished product
  - Days to weeks processing time
- Continuous manufacturing = monitoring throughout
  - Minutes to hours processing time

BEST PRACTICES TO MINIMIZE IMPACT

DISASTER PLANNING FRAMEWORK

Rationing Salt Water — Disaster Planning and Daily Care Delivery

John L. Hick, M.D., Dan Hanfling, M.D., Brooke Courtney, J.D., M.P.H., and Nicole Lurie, M.D., M.S.P.H.

NEJM , March 19, 2014

- Mitigation
- Preparedness
- Response
- Recovery

MANAGING MEDICATION SHORTAGES

- No single emergency – daily emergencies
- Pharmacists and other clinicians successfully manage shortages every day
- Best practice = **Have a Plan**
- Best practice = **Make a Team**

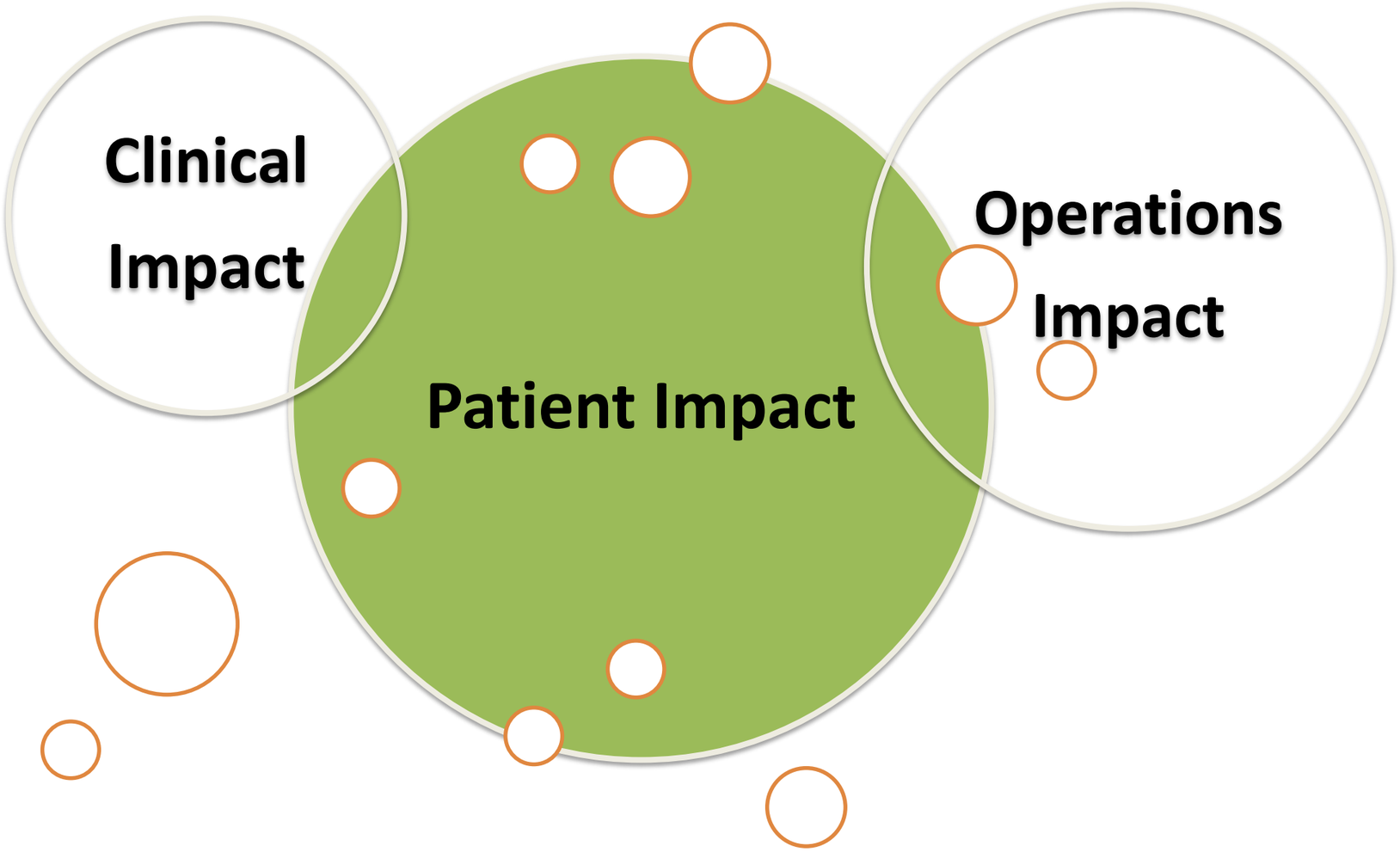
TEAM CHECKLIST – WHO WILL…

- ✓ Gather data, monitor the shortage?
- ✓ Make purchasing decisions?
- ✓ Make storage, preparation, and dispensing change decisions?
- ✓ Make rationing decisions?
- ✓ Change technology?
- ✓ Communicate information?

SHORTAGE MANAGEMENT TEAM COMMUNICATIONS

- Make sure each member understands their role and shares back information
- Situations can change quickly
- Efficient management relies on good team communication
- Timeliness is essential

COMPLEX PROBLEM SOLVING



MANAGEMENT STRATEGY

- Customize – what type of shortage?
  - Some drug available
    - Ration vs. use until gone
  - No drug available, use alternatives
  - No drug available, no alternatives
    - Postpone therapy vs. no therapy
- Must customize for acuity / impact
  - (IV fluids vs. chemotherapy vs. vaccine)

MOST COMMON SITUATION
WE CAN GET SOME BUT…

- It’s a different strength
- It’s in different packaging
- It’s a different size
- It’s from a different manufacturer
- It’s imported
- It’s not enough!

WHICH SITUATION COULD LEAD TO THE GREATEST HARM?

a. Same drug – different strength
b. Same drug – different packaging
c. Imported drug
d. No drug available

ANSWER

- It depends....
- Different strength most concerning according to failure modes and effects analysis
  - SALA errors possible with different packaging, manufacturers
  - Imported product (lack of bar code, NDC, packaging differences)
  - Range of patient impact

Hospital Pharmacy. 2011;46(12):943-951

RATIONING AND ETHICS

- Don’t ration alone
- Example tools available by drug class
- Chemotherapy

  J Oncol Pract. 2013 Mar;9(2):e21-3

  Arch Intern Med. 2012 Oct 22;172(19):1494-9.

  Oncologist. 2014;19(2):186-92.
- Antimicrobials

  Infect Control Hosp Epidemiol. 2012 Jul;33(7):745-52

MESSAGING

- Balance timeliness and completeness.
- Initial plan and ongoing status updates:
  - Will product look different – pictures!
  - Alternative agents - include dose, drug interactions, safety issues.
  - Conservation strategy – which patients are eligible?
  - Decision making process transparency.

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SELF ASSESSMENT QUESTIONS

THE TREND IN DRUG SHORTAGES FOR 2016 IS ONE OF:

a. Decreasing new shortages and increasing active shortages
b. Increasing new shortages but decreasing active shortages
c. Slight increase in new shortages and decreasing active shortages
d. Decreasing new shortages and a gradual decrease in active shortages

THE REASON FOR MOST SHORTAGES IS:

a. Raw material shortages
b. Natural disasters
c. Manufacturing or quality problems
d. Corporate decisions

PACKAGE INSERTS MUST INCLUDE:

a. Name of the company that manufactured the drug
b. Location of the factory
c. Country of origin for the active pharmaceutical ingredient (API)
d. None of the above

FDA CAN PREVENT SOME SHORTAGES BY:

a. Prioritizing approvals of new products
b. Forcing companies to increase production
c. Forcing companies to continue to produce a drug
d. Decreasing drug prices

DETERMINING POTENTIAL CLINICAL IMPACT OF A SHORTAGE INCLUDES:

a. Whether an alternative is available
b. Identifying which patients will be most impacted
c. Determining if the product is life-saving or curative
d. All of the above

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FINAL THOUGHTS

IT MAY GET WORSE BEFORE IT GETS BETTER….

- FDA increasing inspectors in India, China
- Factories with past problems sold – will $$ be spent to truly fix?
- Focus on biosimilars
- Who will make the basics that we need?

BUT THERE IS SOME HOPE

- Trend of decreasing new shortages is real
- Action is moving towards prevention, early identification of manufacturing issues

CONTACT

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