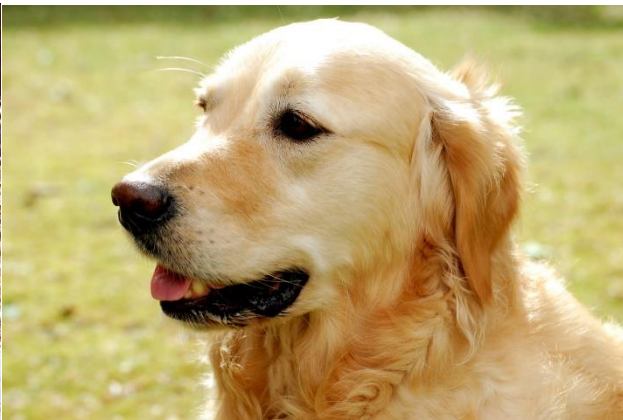


Animal Pharmaceutical Supply Chain Interruptions



J. Greenwald
September 26, 2019

OVERVIEW

Introduction

- Why Care?
- Current Status in the US
- Supply Chain
- Disruptions versus Shortages

Background Information From Human Health

- Drug Supply Interruptions are Not New
- FDA Efforts to Prevent/Mitigate Human Drug Shortages
- Industry Perspective
- Tools

Conclusions

VETERINARY DRUG INTERRUPTIONS: WHY CARE?

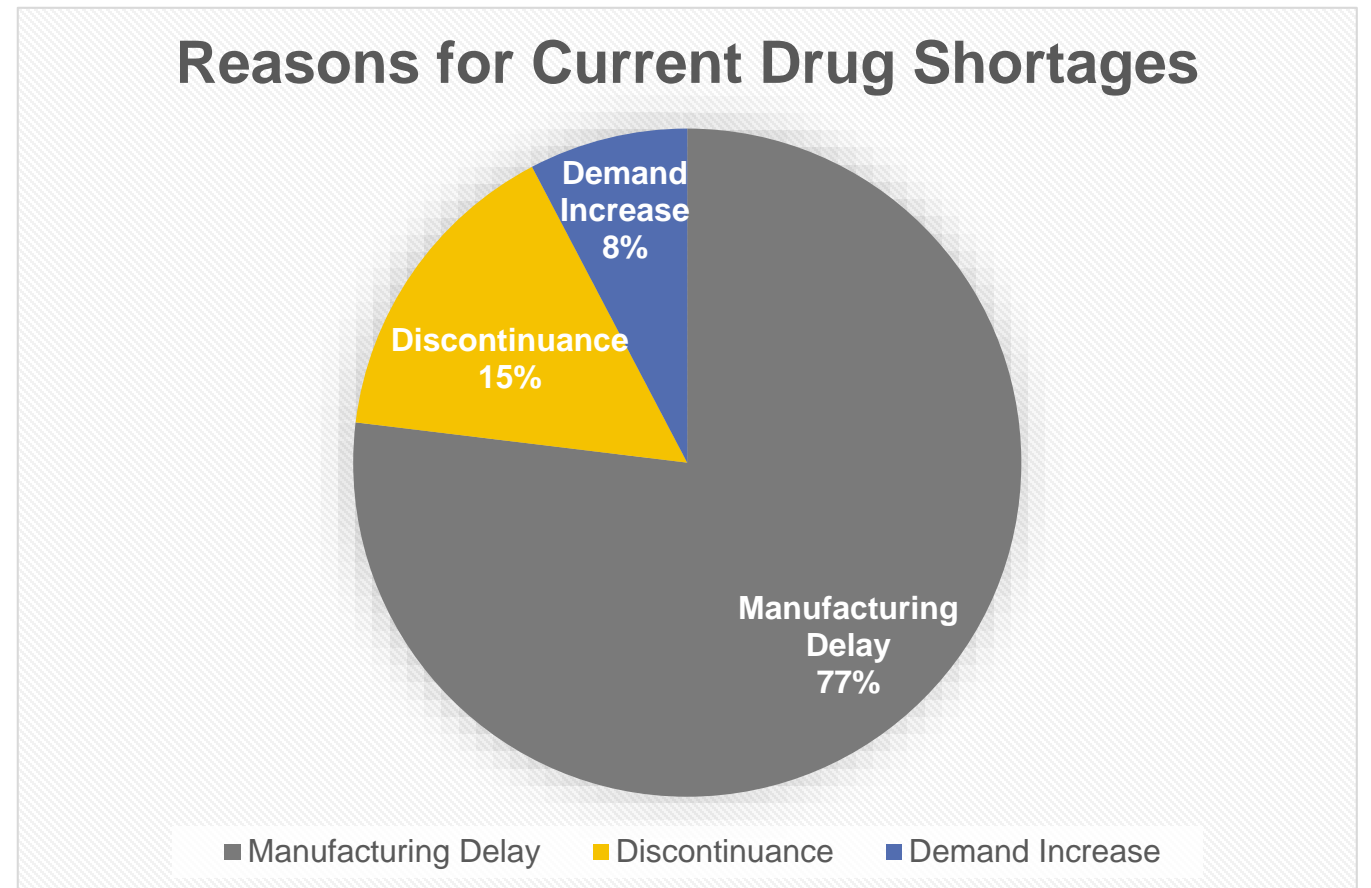
Note - human drug shortages affect veterinarians and animals too!

Animals	may suffer
Veterinarians	may struggle to provide safe and effective care in a timely manner
Animal Producers	may have losses
Pet Owners	may experience emotional and financial stress
Regulators	may face difficult choices
Manufacturers	may lose revenue, market share, and reputation

US VETERINARY DRUG SHORTAGES

13 Current Drug Shortages on CVM's website

12 resolved Drug Shortages on CVM's website dating back to 2011



Note - CVM only tracks shortages of medically necessary veterinary products (MVNP).



Drug Shortages in Veterinary Medicine: Why Pets Get the Short End of the Stick

August 08, 2015

FDA working to resolve flunixin shortage

19 Aug 2016 | NEWS

by Sian Lazell | sian.lazell@informa.com

THE BLOG

Confronting Pet Drug Shortages

As with all things, knowledge is power and so there are several proactive things you can do to find out if recent prescription drug shortages will affect you, your family or the animals in your life.

By Dr. Richard Palmquist, Contributor

Chief of Integrative Health Services at Centinela Animal Hospital, Inglewood California

01/24/2012 02:10pm EST | Updated March 25, 2012



Shortage of Apoquel, new veterinary pruritus drug, to continue until 2015

Zoetis: Existing patients can continue treatment but no new orders are being accepted.

May 20, 2014
By dvm360.com staff
DVM360 MAGAZINE



FDA: Vetsulin in short supply; veterinarians called on to seek alternatives

Feb 07, 2011
By dvm360.com staff
DVM360 MAGAZINE



Drug Shortage Making Heartworm Disease Treatment Much Tougher

AUGUST 17, 2011

JAVMAnews

November 15, 2010

FDA veterinary group addressing large-animal fluid shortage

Agency working with drug companies to import large-volume IV solution from other countries.

Apr 14, 2015
By dvm360.com staff
DVM360 MAGAZINE



Key veterinary euthanasia drugs in short supply

FDA takes steps to ease the problem

October 20, 2017
By Phyllis DeGioia

Adequan Canine 'extremely limited' due to plant renovations

Production of canine arthritis treatment stopped in May; unclear when production will resume.

Jun 18, 2013
By dvm360.com staff
DVM360 MAGAZINE

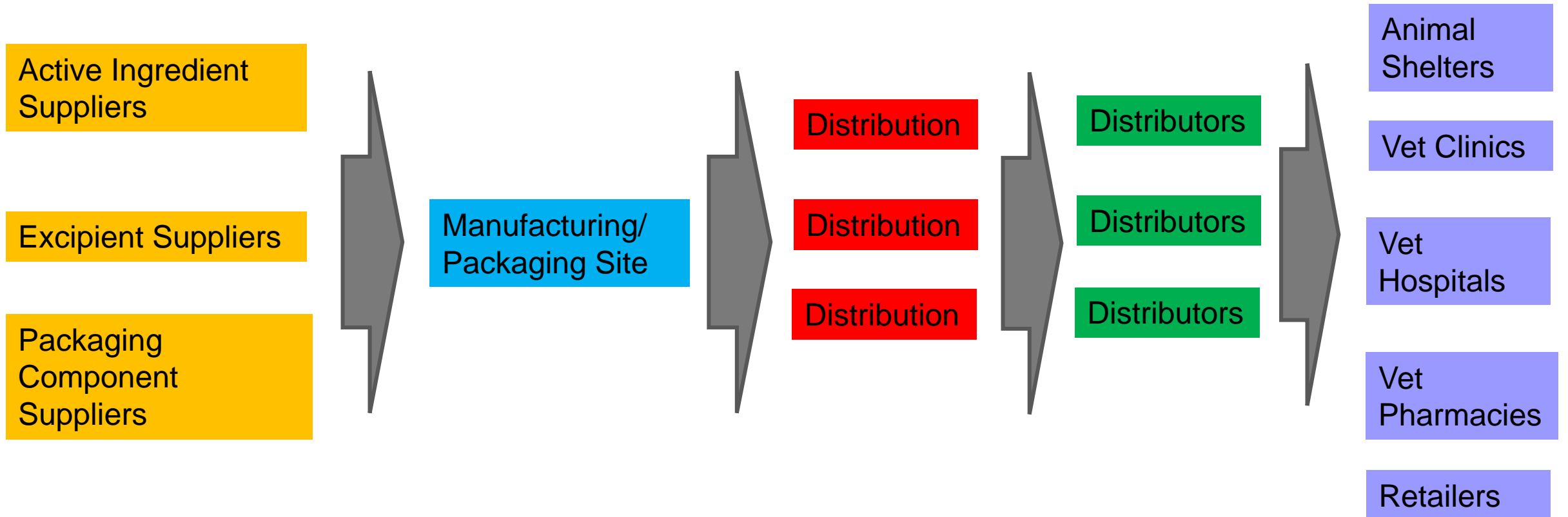


On back order

Drug shortages seem to be increasing in veterinary medicine

By Katie Burns
Posted Nov. 1, 2010

GLOBAL ANIMAL HEALTH PHARMACEUTICAL SUPPLY CHAIN



Disruption:

- any occurrence which has **negative consequences** and causes some **confusion or disorder** on routine supply chain operations (Vakharia and Yenipazarli, 2008)

DISRUPTIONS VERSUS SHORTAGES

Shortage:

- a situation that causes providers to have to make changes to medications or choose alternative drugs due to a supply issue (ASHP, 2018)
- a period of time when the demand or projected demand for a drug within the United States exceeds the supply of the drug. (FDSEA Act, Title X)

DRUG SUPPLY INTERRUPTIONS ARE NOT NEW

Actions were taken to prevent shortages during World War I (JAMA, 1917)

Penicillin G shortage (Science, 1976)

• More Penicillin G Shortages (1994, 1999)

Cause

- API supplier stopped production
- Drug product manufacturer recalled and stopped production due to GMP deficiencies

Cause

- Site Transfer due to new GMP requirement

Mitigation

- FDA recommended using Penicillin G Potassium as an alternative
- Emergency Stock of Product allocated on emergency basis by manufacturer
- FDA approved a temporary supplier in Austria

**FDA Efforts to
Prevent and Mitigate
Human Drug
Shortages**

FDA DRUG SHORTAGE PROGRAM

In 1999, FDA CDER established a small drug shortage program (DSP)

- supported manufacturers and pharmacies through year 2000 (“Y2K” problem)
- many requests received, mostly regional, coordination was beneficial and simple

However, more significant shortages became apparent

- root causes related to manufacturing issues, broader implications
- FDA investigated...

FDA ECONOMIC ANALYSIS

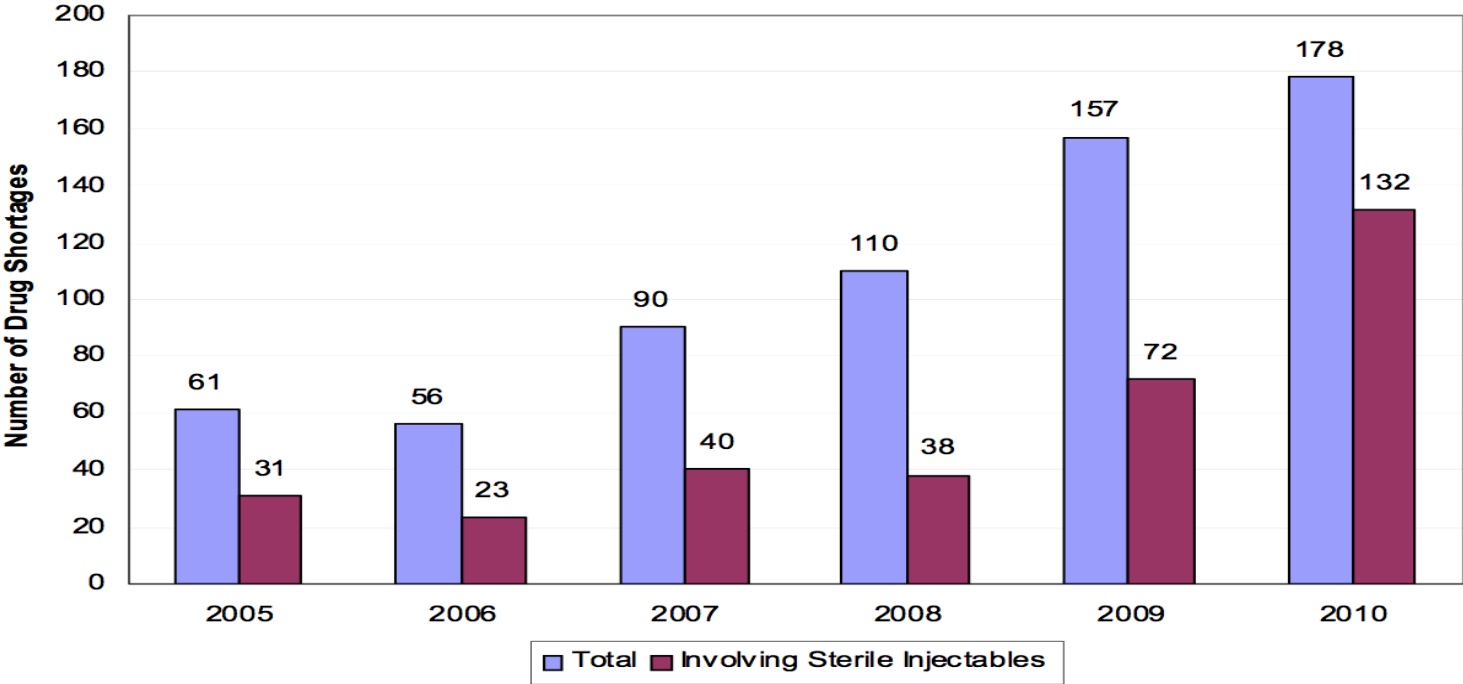
2011: FDA attributed the class wide shortages of sterile pharmaceutical injectables to:

- ↑↑ scope and volume of products produced by industry not matched by ↑↑ manufacturing capacity.
- high rate of patent expirations and increasing generic competition.

The FDA economists thought the issue would resolve itself as new suppliers entered and competed more effectively.

FDA 2011 REPORT

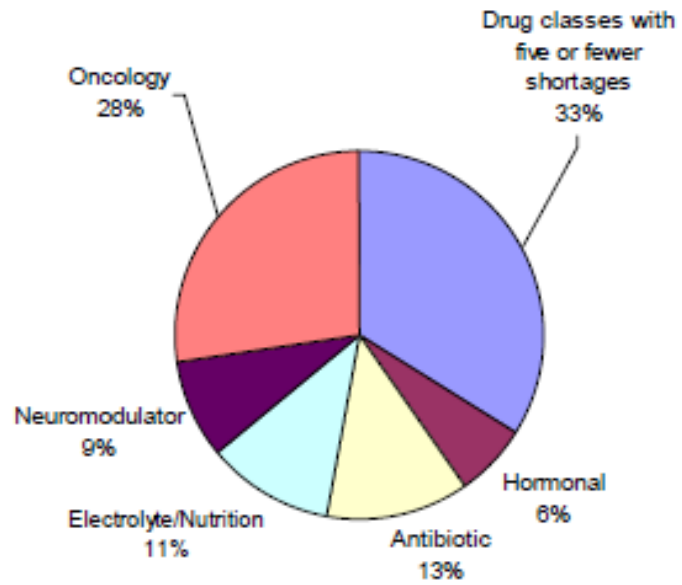
Figure 1: Number of U.S. Drug Shortages FDA's Drug Shortage Program Helped Address, 2005-2010



(Source: CDER Drug Shortage Program)

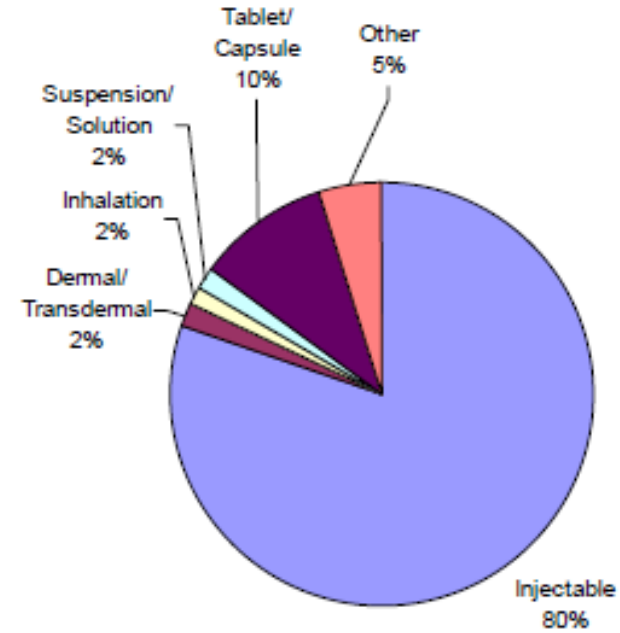
FDA 2011 REPORT

Figure 3: Drug Shortages by Drug Class, 2010-2011



(Based on 127 drug shortages between January 1, 2010 and August 26, 2011)

Figure 2: Drug Shortages by Route of Administration, 2010-2011



(Based on 127 drug shortages beginning between January 1, 2010 and August 26, 2011)

FDA 2011 REPORT

Figure 4: Drug Shortages by Primary Reason for Disruption in Production and Supply, 2010-2011

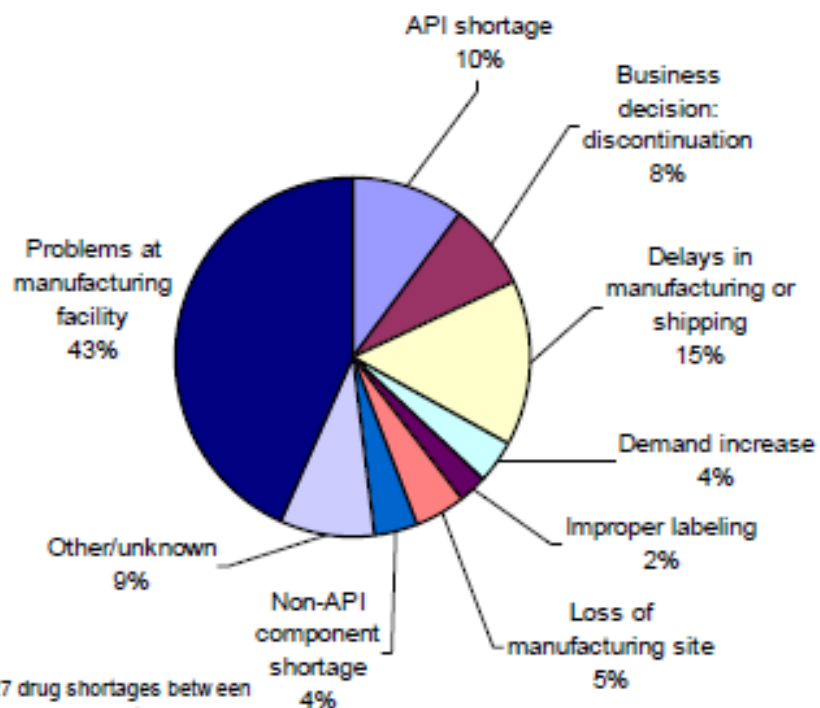
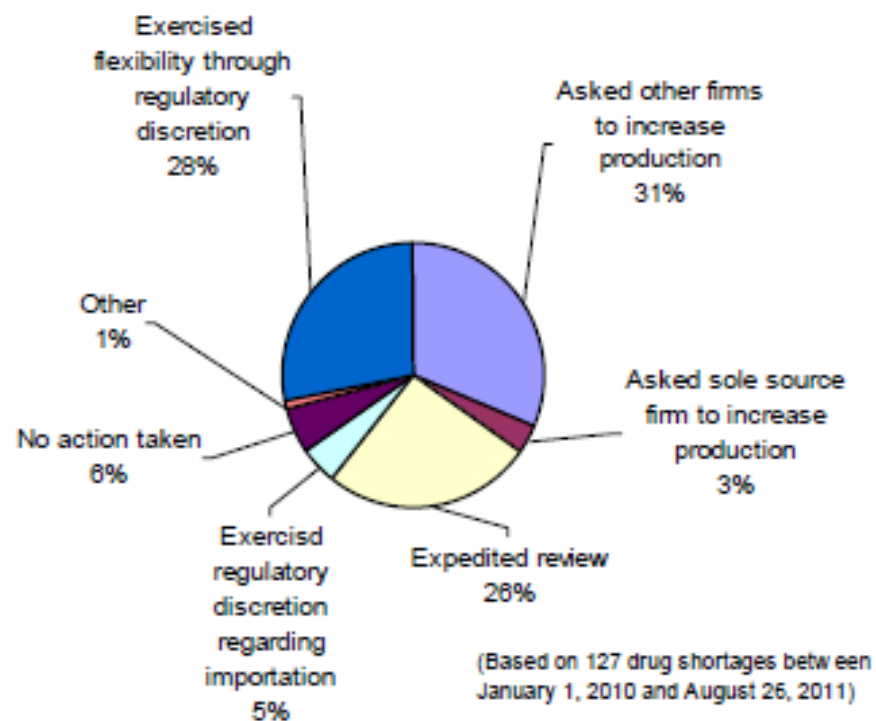


Figure 5: Drug Shortages by Primary FDA Action Taken, 2010-2011



FDA 2011 REPORT

Short-Term

- Urge manufacturers to notify FDA in advance of a shortage
- Develop guidance for industry on reporting
- Increase FDA drug shortage staffing
- Maintain a drug shortage database
- Support legislation (notification and FDA enforcement power)

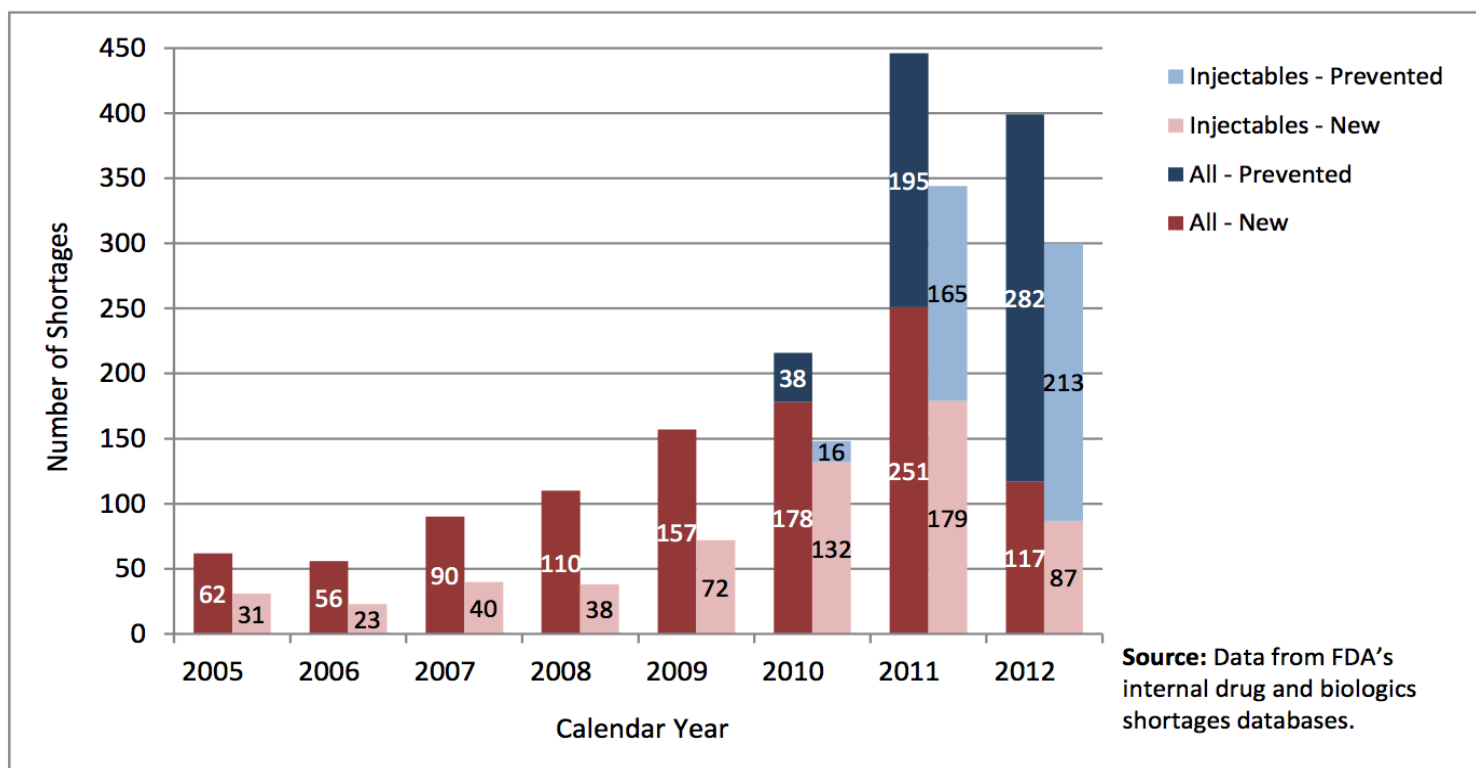
Long-Term

- Assess mitigation and prevention strategies and new approaches
- Determine cause of quality issues and develop approaches to address
- Encourage manufacturers to create back up plans
- Assess a “sentinel reporting network” for early warning
- Communicate drug shortages to the public (website)
- Improve internal FDA communication
- Urge transparency of distributor practices
- Develop a model to predict drug shortages

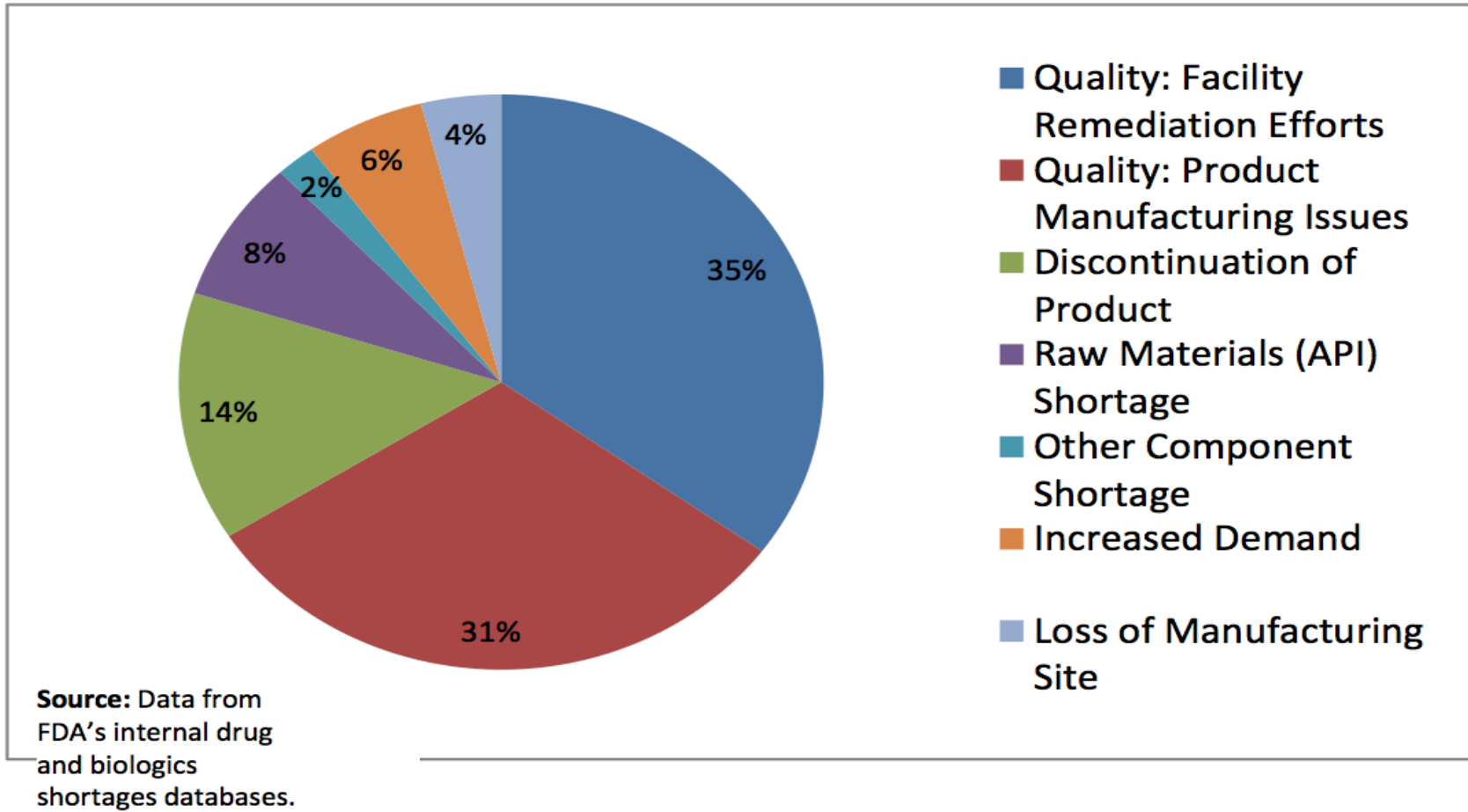
LEGISLATION

- Prior to 2011, sole manufacturers of human drugs had to report discontinuances of medically necessary drugs to FDA
- Executive Order 13588, signed in 2011
 - Empowered FDA to “help prevent and reduce current and future disruptions in the supply of life saving medicines”
 - All manufacturers now must notify FDA of potential disruptions and discontinuations of critical medicines in advance
- Food and Drug Safety and Innovation Act (FDASIA), signed July 2012
 - Title X – manufacturers of life supporting or sustaining drugs, or drugs intended for use in the prevention or treatment of a debilitating disease or condition, must notify FDA if these drugs will be discontinued or disrupted at least 6 months in advance or as soon as possible
 - FDA enforcement
 - FDA required to make annual reports to Congress, maintain a list of drug shortages, form a task force, and execute a strategic plan
 - FDA required to assess risk of shortage prior to issuing warning letters

FDA STRATEGIC PLAN FOR PREVENTING AND MITIGATING DRUG SHORTAGES – 2013



FDA STRATEGIC PLAN FOR PREVENTING AND MITIGATING DRUG SHORTAGES - 2013



FDA STRATEGIC PLAN FOR PREVENTING AND MITIGATING DRUG SHORTAGES - 2013

Strengthen Mitigation Response

- Develop and/or Streamline Internal FDA Process
- Improve Data/Response Tracking
- Clarify Roles and Responsibilities of Manufacturers
- Enhance Public Communications

Develop Long Term Prevention Strategies

- Develop Methods to Incentivize and Prioritize Manufacturing Quality
- Identify Early Warning Signals of Shortages
- Increase Knowledge to Develop New Strategies to Address Shortages

FDA STRATEGIC PLAN FOR PREVENTING AND MITIGATING DRUG SHORTAGES - 2013

Create
Allocation
Plans

Communicate
with Contract
Manufacturers

Manage
Inventory

Develop Short
and Long Term
proposals

Communicate
with FDA

Investigate
Root Causes

**Roles and
Responsibilities
of Manufacturers**

Consider
Clinical Trials

QUALITY INCENTIVE INITIATIVE

Woodcock and Wosinska (2013)

“Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages”

Shortages of generic sterile injectable drugs are due to:

- manufacturing-quality issues and disincentives to improve quality
- aging, specialized, dedicated facilities
- capacity constraints
- cost savings initiatives
- increased price competition
- just-in-time inventory levels
- focus on price rather than quality
- reactive rather than proactive manufacturers (no reward for quality)

QUALITY INCENTIVE INITIATIVE

•Manufacturers voluntarily submit quality metrics data

FDA uses metrics data to detect signals

FDA rewards participation by publicly posting manufacturer name on the Quality Metric Reporter List

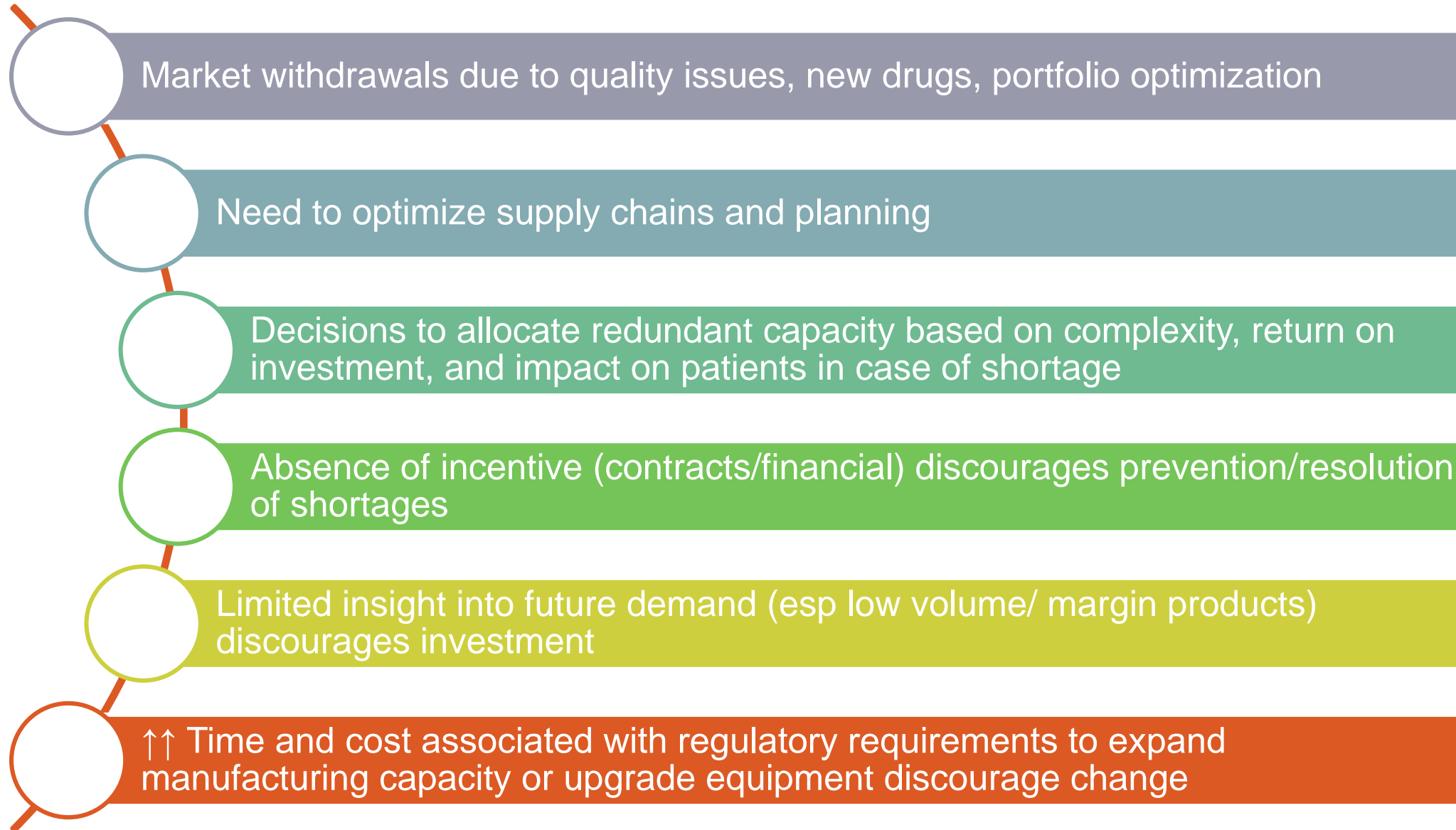
The Quality Metric List is used for supplier selection and purchasing decisions

FDA draft Guidance for Industry

Submission of Quality Metrics Data

**Industry
Perspectives on
Human Drug
Shortages**

ISPE ECONOMIC ANALYSIS 2017 (SURVEY OF 10 COMPANIES)



ISPE DRUG SHORTAGES SURVEY - JUNE 2013

The Survey assessed:

- Quality Records
- Facilities and Equipment
- Packaging and Labeling
- Production Equipment
- Production System (Sterile/Non Sterile)
- Material Systems (Sterile/Non Sterile)
- Lab Controls (Sterile/Non Sterile)

Major Findings:

- Aseptic processing equipment was identified as a significant factor
- Production system issues leading to drug shortages or near misses were present during technology transfers or product development according to a small but significant number of respondents

ISPE DRUG SHORTAGES SURVEY - JUNE 2013

Success Factors in Preventing Drug Shortages

Strong Quality System/Compliance/GMP

Corporate Goal to Avoid/Prevent Drug Shortage

Ability to React

Strong Relationship with Health Authorities

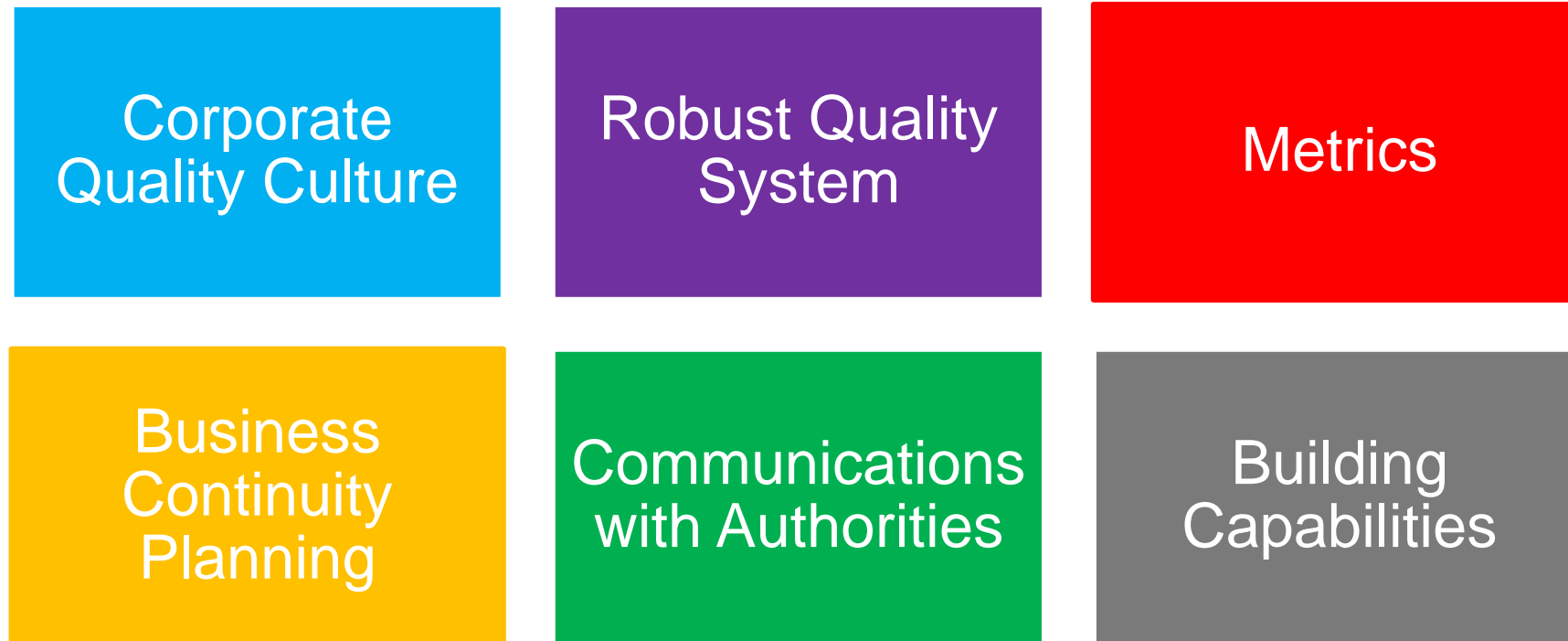
Dedicated Resources

Incentives

Metrics

ISPE DRUG SHORTAGE PREVENTION PLAN - 2014

Global plan (or toolkit) presented in the following framework:



The plan includes information based on interviews with industry and includes detailed discussion, case studies, and examples.

ISPE Drug Shortage Prevention Plan - 2014

Corporate Quality Culture

- Assess quality culture
- Establish decision-making procedures
- Proactively manage trends and signals
- Establish a process for problem escalation
- Supply chain evaluation of robustness and resilience
- Develop management capability related to managing crises
- Establish cross functional rapid response teams
- Conduct regular quality review meetings with cross functional attendance

ISPE Drug Shortage Prevention Plan - 2014

Robust Quality System

- Establish a life cycle management business process
- Continuously validate manufacturing processes
- Ensure management review of deviations, look for trends
- Ensure investigations surface root causes and effects
- Ensure timely completion and effectiveness of CAPAs
- Set up knowledge management system and establish subject matter experts
- Use sound scientific and risk-based approaches
- Perform a drug shortage focused risk assessment of facilities and equipment
- Maintain lists of critical materials used in manufacturing and establish risk mitigation strategies for these materials

ISPE Drug Shortage Prevention Plan - 2014

Metrics

- Establish a variety of drug shortage metrics related to quality, supply chain, and culture as a basis for continuous improvement

Business Continuity Planning

- Achieve a healthy supply chain through integration of supply chain and quality systems with governed by effective management
- Build redundancy based on risks as needed
- Proactively establish crisis management and disaster recovery plans

ISPE Drug Shortage Prevention Plan - 2014

Communications with Authorities

- Develop an internal supply risk escalation process
- Rapidly communicate potential supply risks to the regulatory authorities
- Develop plans to resolve the issue
- Discuss regulatory submission content and timing
- Foster cross functional training and interaction
- Create an environment of continuous learning and sharing
- Utilize mentorship to maximize learning and development

Building Capabilities

PDA AND ISPE TOOLS

Parenteral Drug Association (PDA) Technical Report 68, Risk-Based Approach for Prevention and Management of Drug Shortages (2014)

- Product level risk based framework
- Uses a risk triage model
- Includes Templates

ISPE Drug Shortage Assessment and Prevention Tool (2015)

- Uses framework from the 2014 ISPE Prevention Plan
- Intended to help manufacturer's make a roadmap to the "desired state"
- Uses gap assessment approach
- Takes into account – maturity levels

CONCLUSIONS

- There are supply disruptions of veterinary drugs which may impact animals, veterinarians, producers, pet owners, regulators, and manufacturers.
- Supply disruptions are not new.
- FDA and ISPE have taken significant steps toward prevention and mitigation of human drug shortages and some of this information may be useful to consider for veterinary drugs
- Open Questions:
 - How many veterinary drug disruptions are there?
 - What is the impact of animal drug disruptions?
 - What are the causes of animal drug shortages?
 - What are we currently doing to prevent/mitigate disruptions?
 - Is there a need to do more to prevent/mitigate disruptions?