

Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions

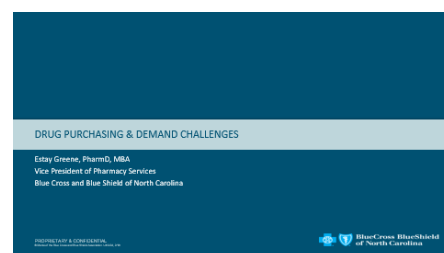
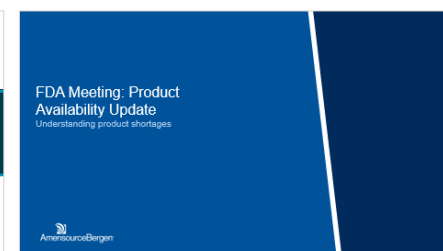
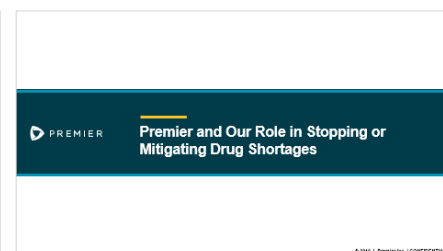
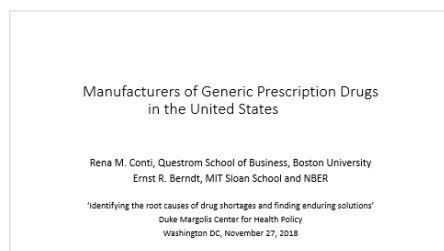
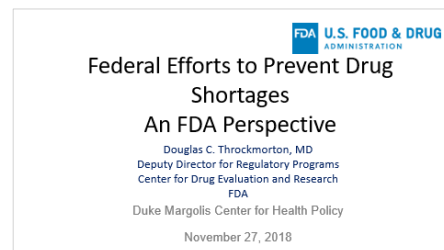
Washington Marriott Metro Center

November 27, 2018

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Contents



Session 1: Federal Efforts to Prevent Drug Shortages

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DRUG SHORTAGE TASK FORCE

Keagan Lenihan

Task Force Leader

Associate Commissioner for Strategic Initiatives and External Affairs

U.S. Food and Drug Administration

TASK FORCE ACTIONS



- Announcement of Interagency Task Force (July)
- Open a Docket and announced Public Meeting (September)
- Hold Series of Listening Sessions (September and October)
- Public Meeting (November)

TASK FORCE MEMBERS



- Food and Drug Administration (CDER, CBER, CDRH, ORA)
- Center for Medicare and Medicaid Services
- The Office of the Assistant Secretary of Preparedness and Response
- The Department of Veterans Affairs
- The Department of Defense
- The Federal Trade Commission

LISTENING SESSION SERIES

- ✓ Experts and Think Tanks
- ✓ Adverse Consequences
- ✓ Pharmacies and Hospitals
- ✓ Manufacturing Groups
- ✓ Medical Groups
- ✓ GPO's and Distributors

THEMES FROM LISTENING SESSIONS*



Theme 1:	The impacts of drug shortages affect every level of the healthcare system, ultimately compromising the standard of care, producing waste, and increasing costs.
Theme 2:	Multiple market factors such as buyer and seller consolidation, low margins, and contracting practices contribute to drug shortages.
Theme 3:	It is unclear what the right level of transparency is based on manufacturing security concerns, and hospital, pharmacy, and GPO needs. The healthcare community would like more transparency throughout the supply chain.
Theme 4:	Multiple federal agencies such as FDA, DEA, and CMS, have different authorities on drugs - making it hard for industry/ hospitals to manage. Ideas have been put forth on how agencies can mitigate but may unintentionally exacerbate the issues.



U.S. FOOD & DRUG
ADMINISTRATION

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Federal Efforts to Prevent Drug Shortages

An FDA Perspective

Douglas C. Throckmorton, MD
Deputy Director for Regulatory Programs
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FDA

Duke Margolis Center for Health Policy

November 27, 2018

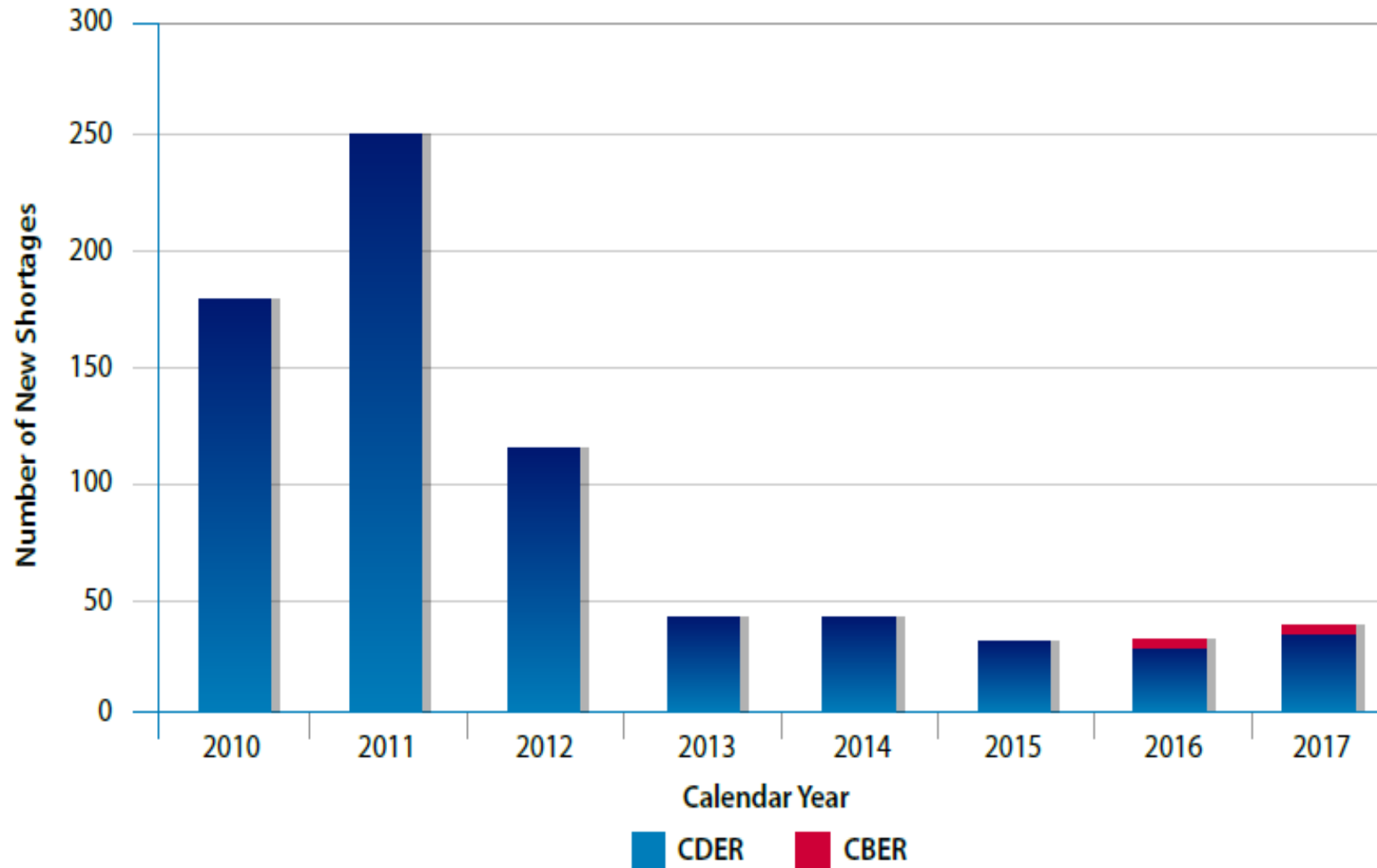
Definitions of Medical Product Shortage



- **Drug Shortage (FDA):** *A drug shortage* means a period when the demand or projected demand for the drug within the United States exceeds the supply of the drug.
- **Drug Shortage (ASHP*):** A drug product is in shortage:
 - once the shortage is verified with manufacturers
 - when supply issues affect how a pharmacy prepares or dispenses a drug product, or influence patient care requiring prescribers to use an alternative therapy

*ASHP: American Society of Health-System Pharmacists

Trends in New Drug Shortages 2010-2017



From FDA Drug Shortage Report to Congress, 2017

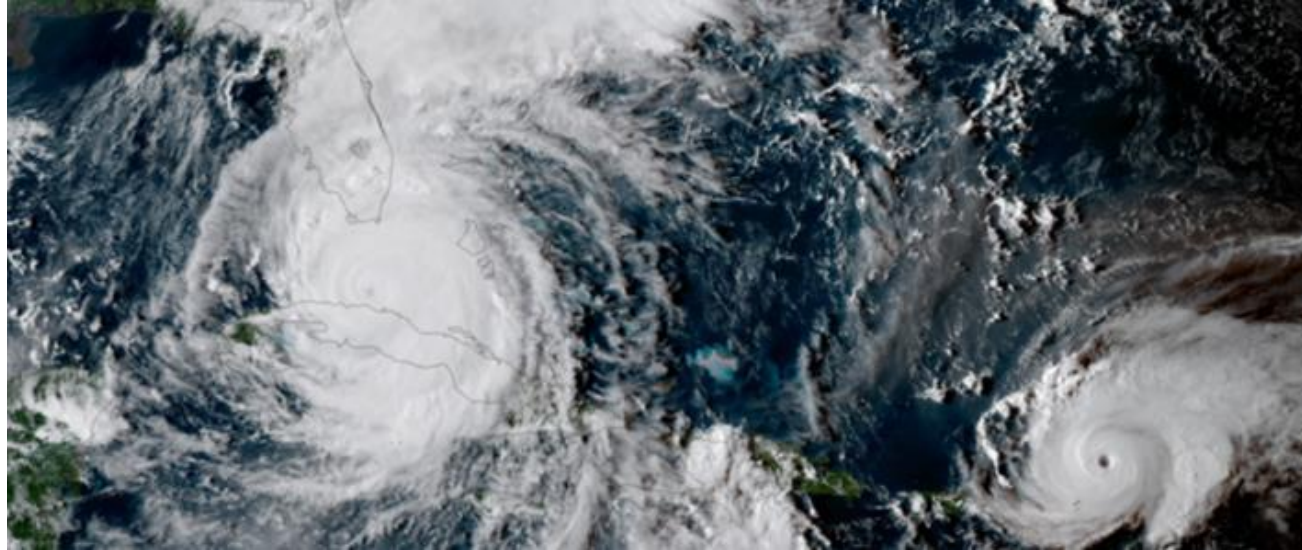
<https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM610662.pdf>

Sources of Shortages: Manufacturing Challenges



- Consolidation in manufacturing of sterile injectables
 - In Fall of 2017, interruption of manufacturing by a single firm led to shortages of multiple critical drugs including injectable narcotics, “caines” and others drugs
- Shortages of critical sterile injectable drugs from increased demand or manufacturing problems
 - IV electrolyte salts, Magnesium Sulfate, Calcium Gluconate and Potassium Chloride

Sources of Shortages: Natural Disasters



- Hurricane Maria affected multiple manufacturers in Puerto Rico
 - IV fluid shortages which began in 2014 were worsened due to Baxter facility impact in PR

What FDA Does to Address Drug Shortages



- Drug Shortage Staff focused on addressing drug shortages
 - Facilitate temporary and long-term strategies to address shortages
 - Coordinate timely and comprehensive risk/benefit decisions within FDA
 - Personnel across multiple FDA Offices involved in shortage response
 - Distribute information (web posting, professional organizations):
 - <https://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>
- Goal: Maintain availability while minimizing risk to patients

What FDA Cannot Do to Address Drug Shortages



FDA cannot require:

- A company to disclose details of why a shortage occurs
- A company to make a drug
- A company to make more of a drug
- How much and to whom the drug is distributed

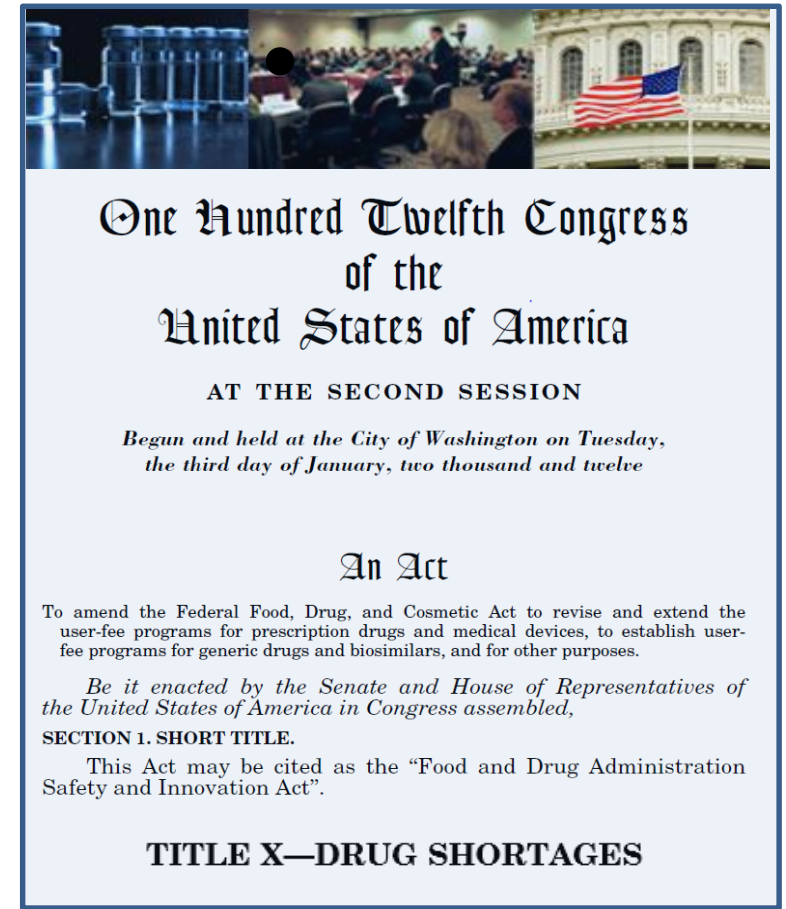
Lessons Learned

- Availability of drugs for patients is critical for healthcare
 - Interruptions of drug manufacturing due to any reason can lead to drug shortages with devastating impact on public health
- Sources of drug shortages include manufacturing challenges and natural disasters
 - FDA response tailored to address underlying cause(s)

Communications and information sharing are critical both to preventing and to mitigating shortages
- Recovery from shortages takes time. Prevention is critical to reducing the numbers of drug shortages

Communication is Critical

- **Requirements to Industry For Early Notification**
- Manufacturers are required to notify the FDA of a permanent discontinuance or interruption in manufacturing that is likely to lead to a meaningful disruption in the supply of a covered drug in the United States
- At least 6 months in advance of but in no case later than 5 business days after the interruption in manufacturing occurs
- Not limited to medically necessary products
- Regardless of market share, or number of companies marketing, or wholesaler volumes



Today's Meeting

- Discussion goals:
 - Root Causes of drug shortages
 - Economics of drug shortages
 - Measurement of shortages and their public health impact
 - Economic drivers underlying drug shortages
 - Manufacturing and Distribution
 - Anticipating vulnerabilities, eliminating barriers to adequate drug supply
 - Potential tools to address drug shortages
 - Market-driven actions
 - Governmental actions
 - Incentives to encourage adequate drug supply and manufacturing redundancy and resiliency

Thank you

FDA



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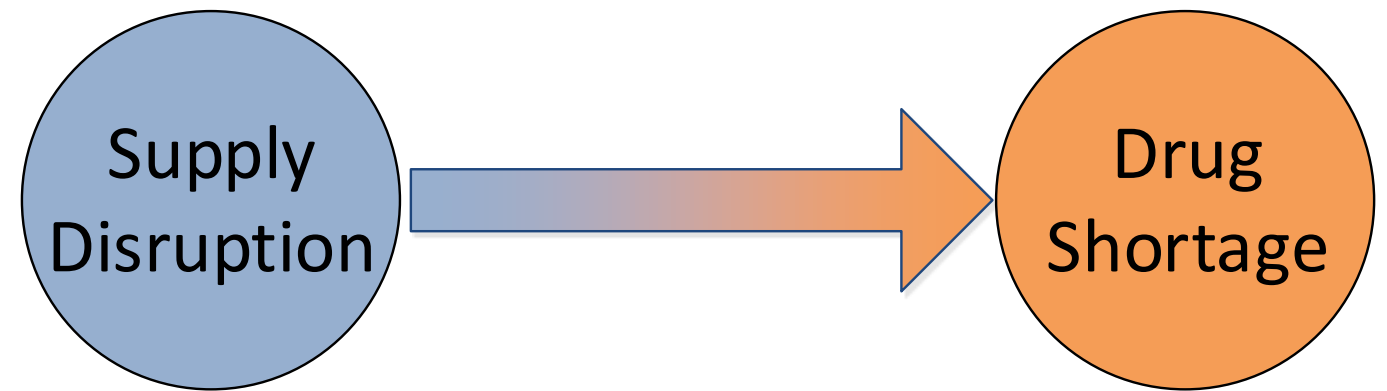
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Economic Drivers of Drug Shortages

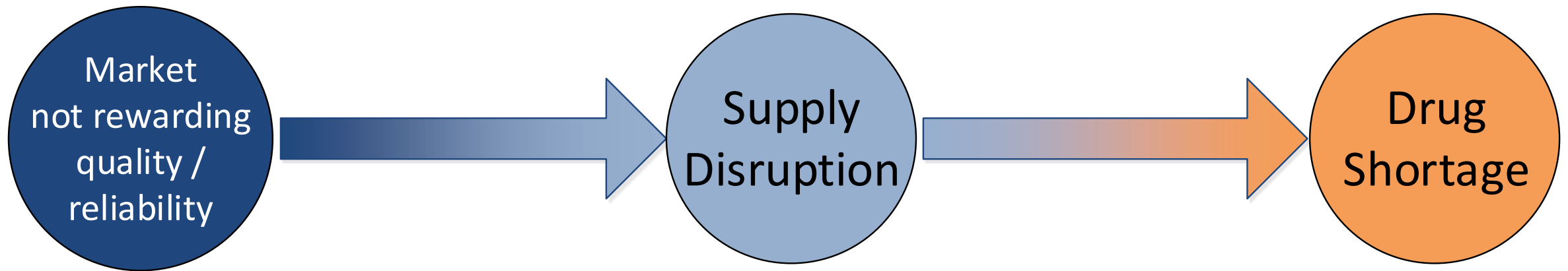


Framing Questions About Shortages

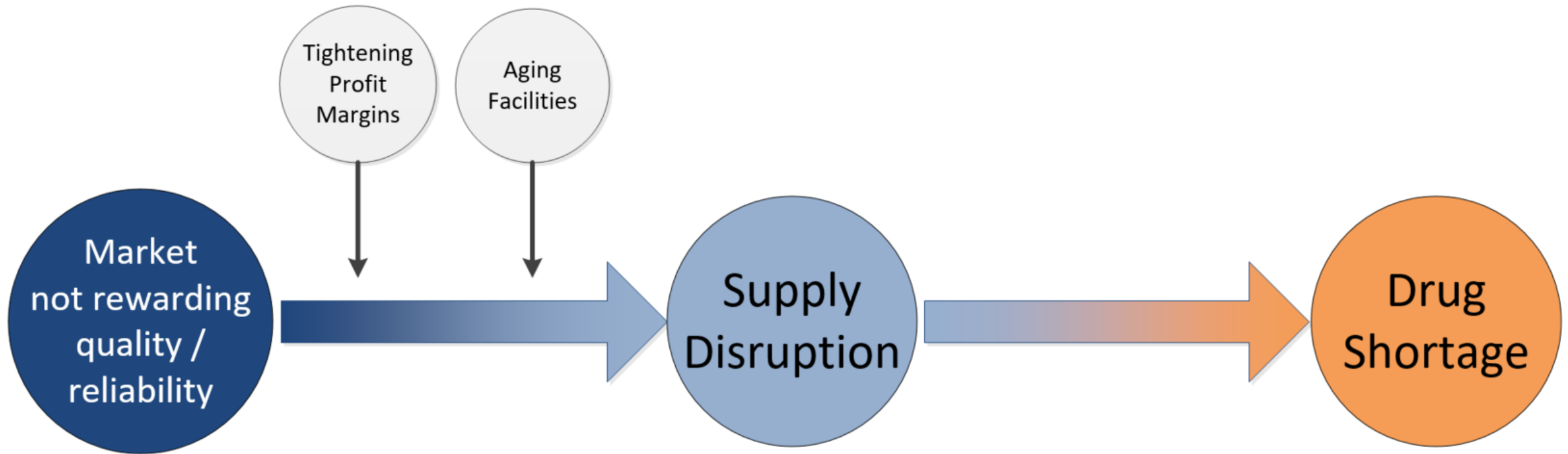
- 1** Why drugs?
- 2** Why these specific drugs?
- 3** Why now?



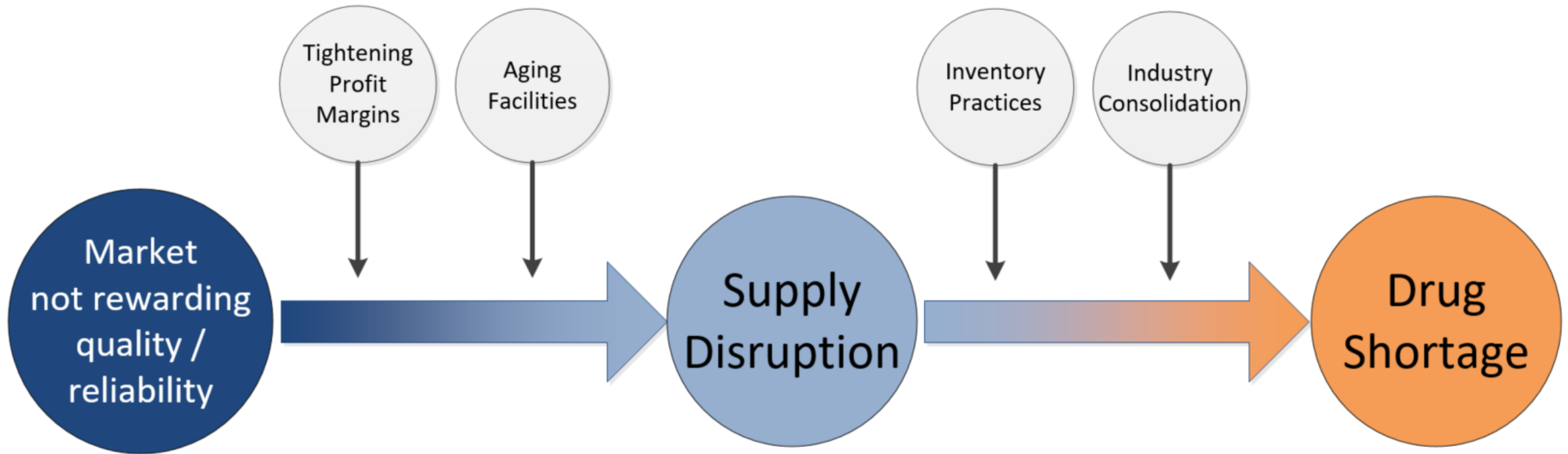
Adapted From: Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages, Volume: 93, Issue: 2, Pages: 170-176, First published: 07 November 2012, DOI: (10.1038/clpt.2012.220)



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What Do FDA Data Tell Us About the Scope and Scale of Drug Shortages?



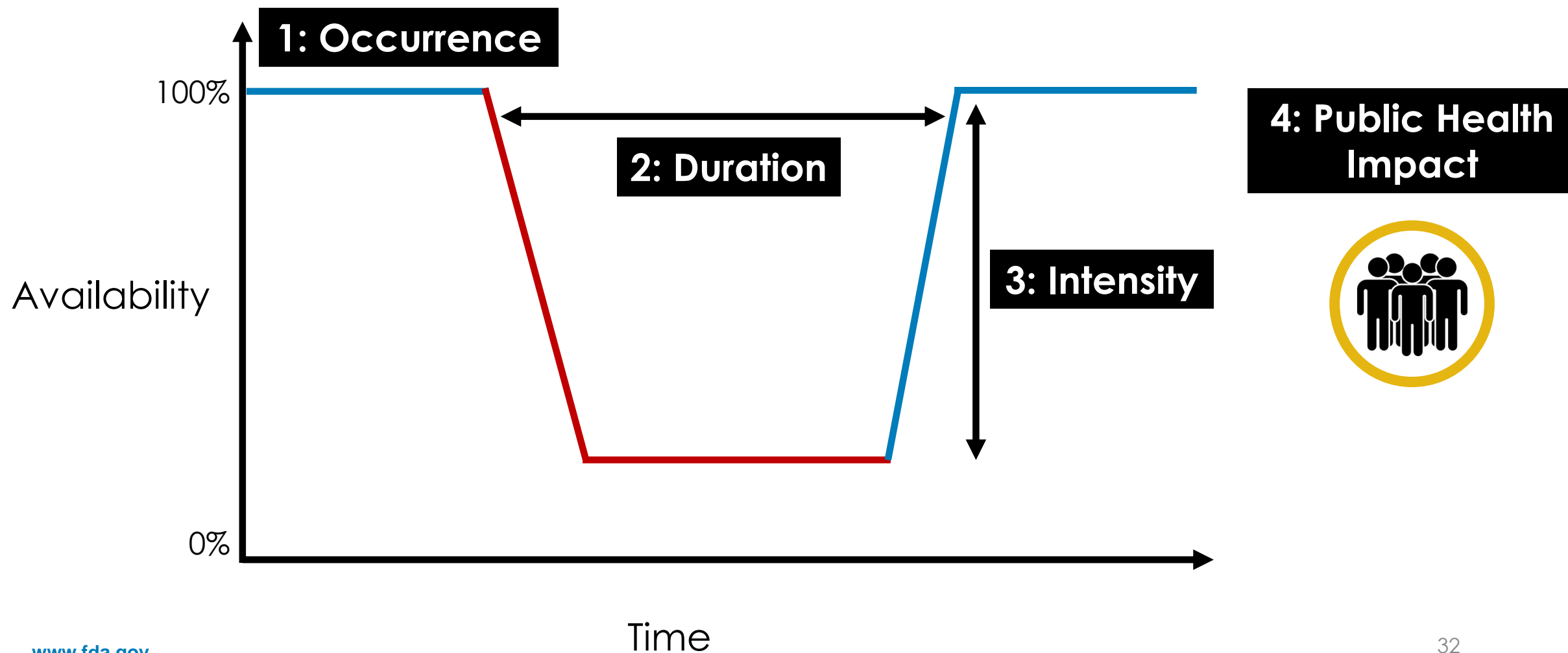
Matthew Rosenberg
FDA/CDER Economics Staff
November 27, 2018

Acknowledgements

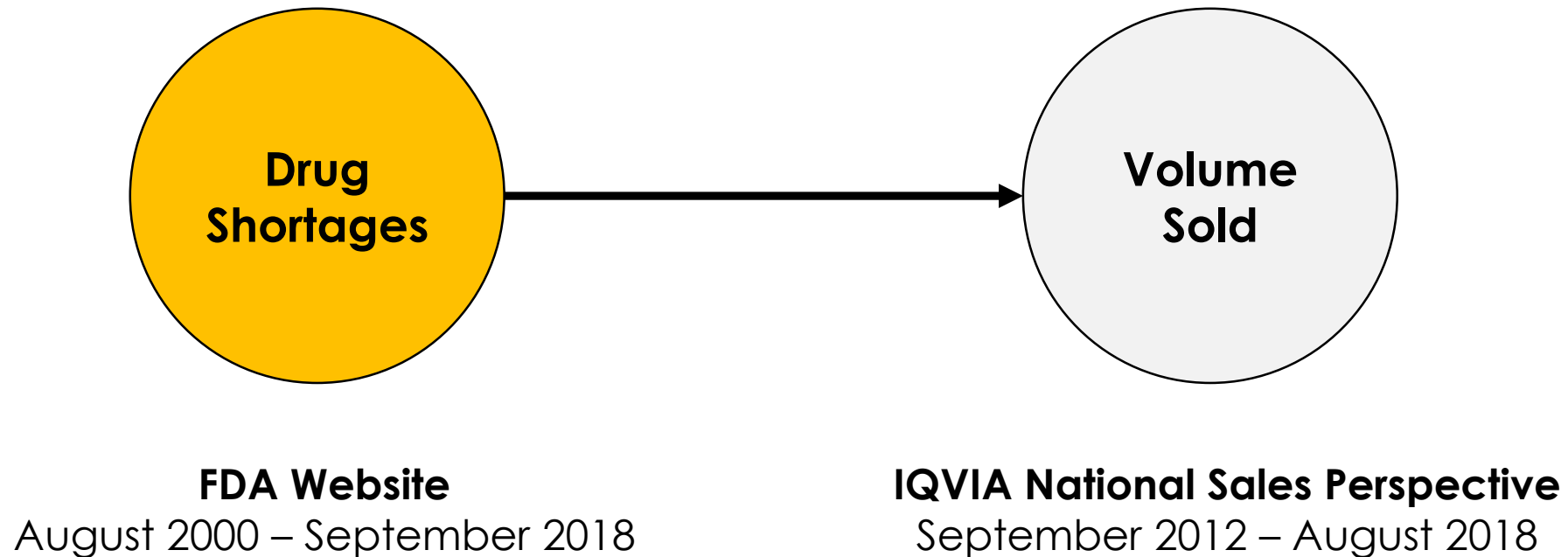
Thank you to CDER colleagues who contributed to this talk:

- Economics Staff
- Office of Surveillance
- Drug Shortage Staff
- Numerous Pharmacy Student Interns

How We Think About the **Severity** of Drug Shortages



We Use The Following Data Sources to Calculate These Measures



Preview of Findings

- 1** Occurrence: **Increasing**
- 2** Duration: **Longer**
- 3** Intensity: **High**
- 4** Public Health Impact: **High**

1: There Has Been a **Recent Increase** in Drug Shortages

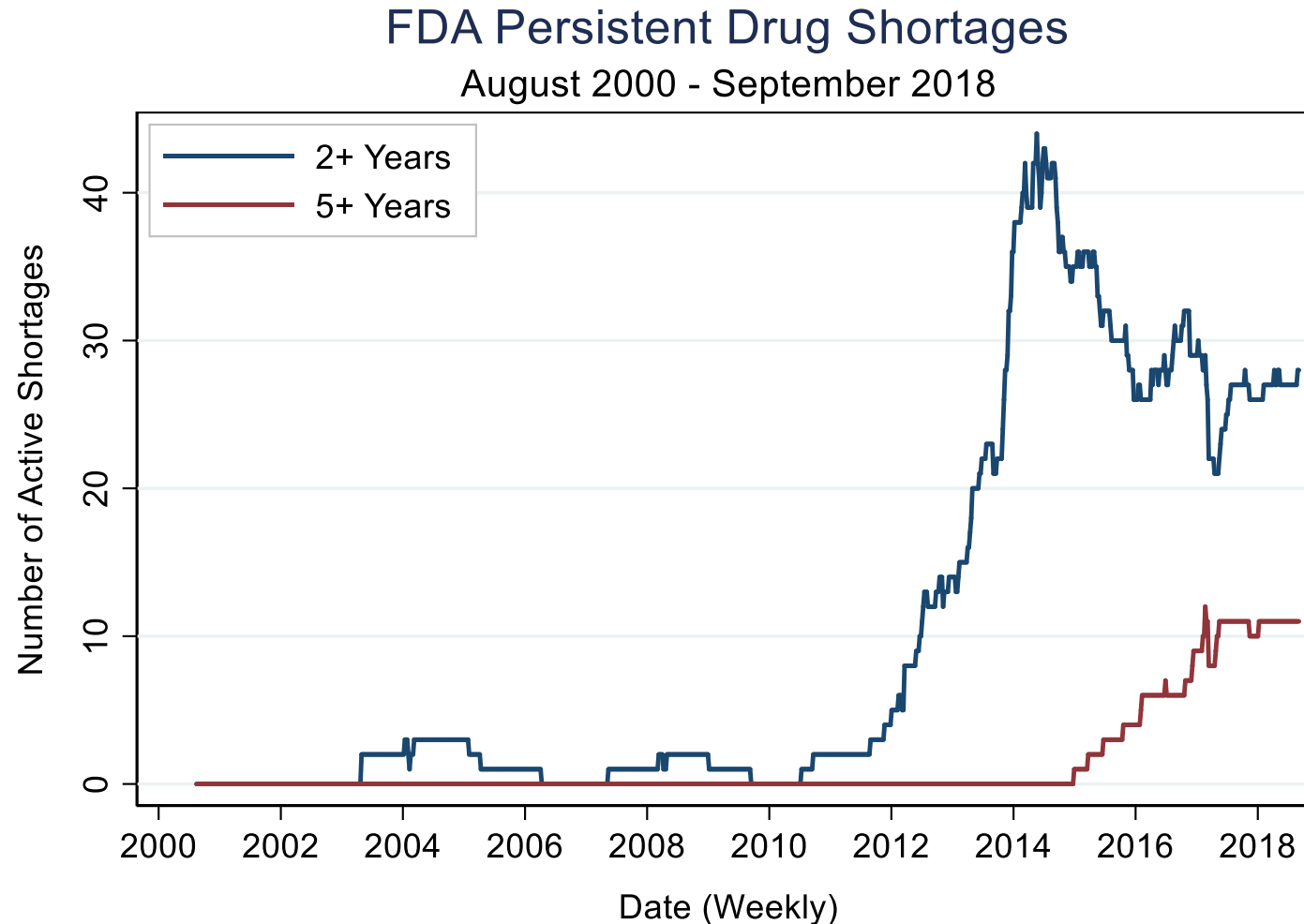


FDA Active Drug Shortages
August 2000 - September 2018



Source: FDA Website

2: Drug Shortages Have Grown **More Persistent**



Source: FDA Website

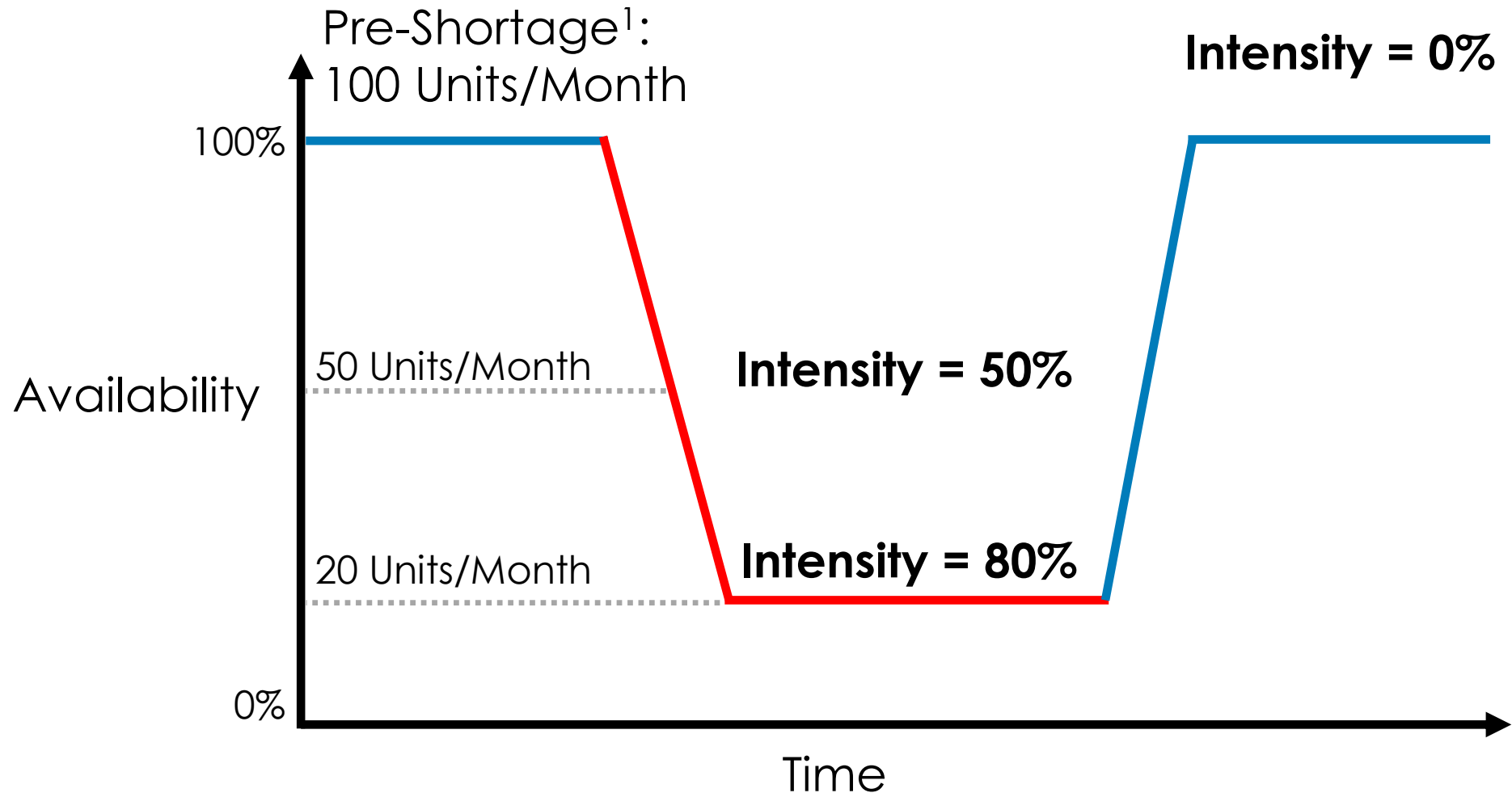
2: Some Active Drug Shortages Have Lasted For More Than **8 Years**

5 Longest Individual FDA Drug Shortages by Total Duration¹, August 15, 2000 to September 5, 2018

Drug Name	Years in Shortage	Still Ongoing?
Liotrix Tablets	8.7	Y
Multi-Vitamin Infusion	8.5	Y
Leucovorin Calcium Powder for Injection	8.2	Y
Sodium Chloride 23.4% Injection	7.6	Y
Fentanyl Citrate Injection	6.9	Y

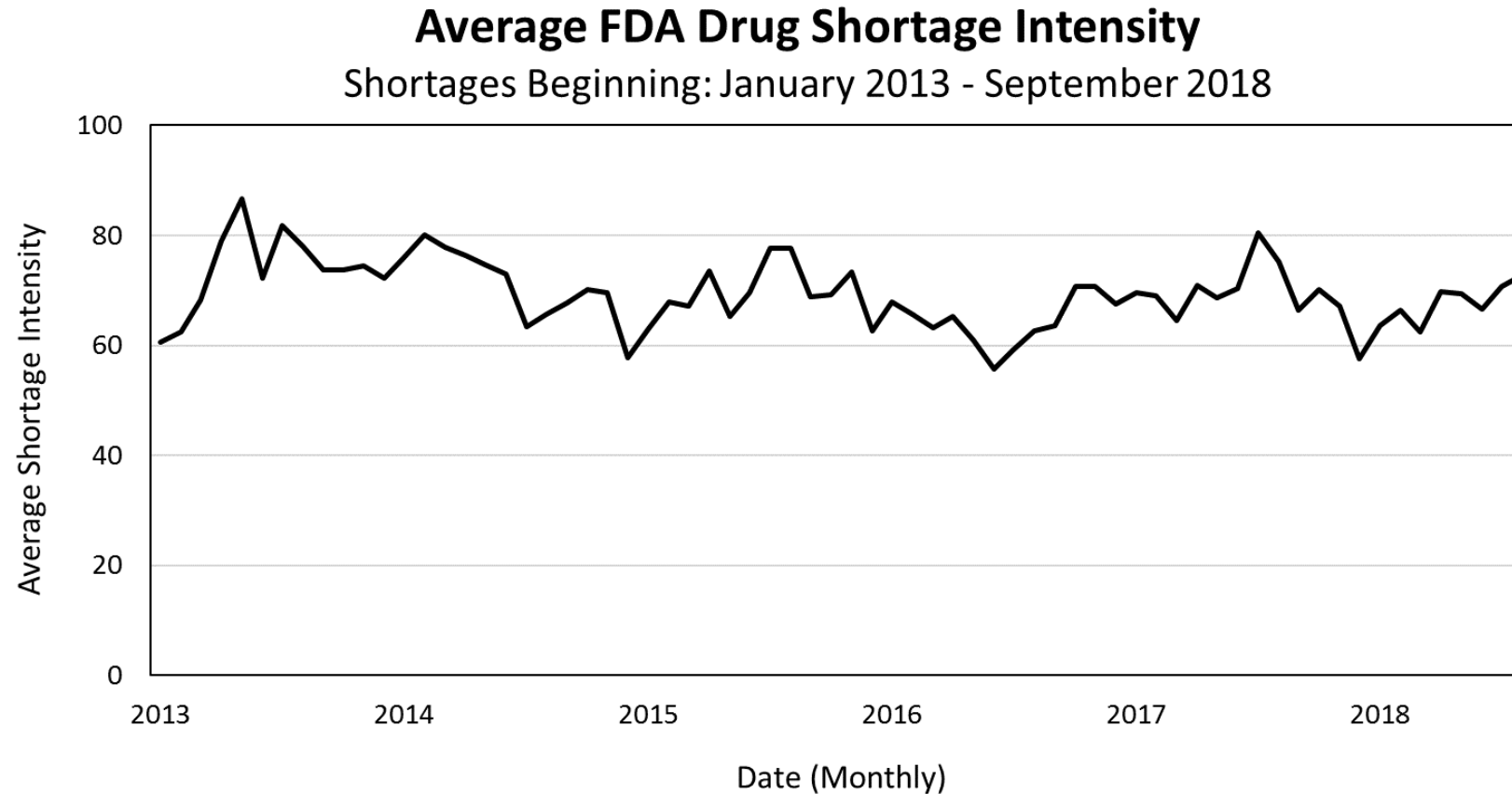
¹Note: If a shortage is still ongoing, we use September 5, 2018 as its end date
Source: FDA Website

3: We Calculated Intensity In Terms of Product Unavailability



¹Averaged over the 6 months prior to the shortage

3: The Average Intensity of Drug Shortages **Remains High**



Sources: FDA Website; IQVIA, National Sales Perspective, September 2012 to August 2018. Extracted: October 2018.

4: Public Health Impact of Shortages Is **High**



Norepinephrine Shortage Per FDA Website: Feb 2011 – Feb 2012 (*Average Intensity: 30.5%¹*)

2017 JAMA Study²: During the Shortage...

Patients switched to alternatives like phenylephrine

Deaths increased by **3.7 percentage points**

Nationally Projected Losses³: \$13.7 Billion

¹Sources: FDA Website; IQVIA, National Sales Perspective, September 2012 to August 2018. Extracted: October 2018

²Vail et al. Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock. JAMA. 2017.

³We project to all US septic shock admissions using Rhee et al. 2017 and Table 82 of Health, United States 2016. We assume a value of mortality risk reduction of \$10 million.

Summary of Findings

- 1** Occurrence: **Increasing**
- 2** Duration: **Longer**
- 3** Intensity: **High**
- 4** Public Health Impact: **High**

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Session 2: The Economics of Drug Shortages

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Drug Shortages

Erin R. Fox, PharmD, BCPS, FASHP



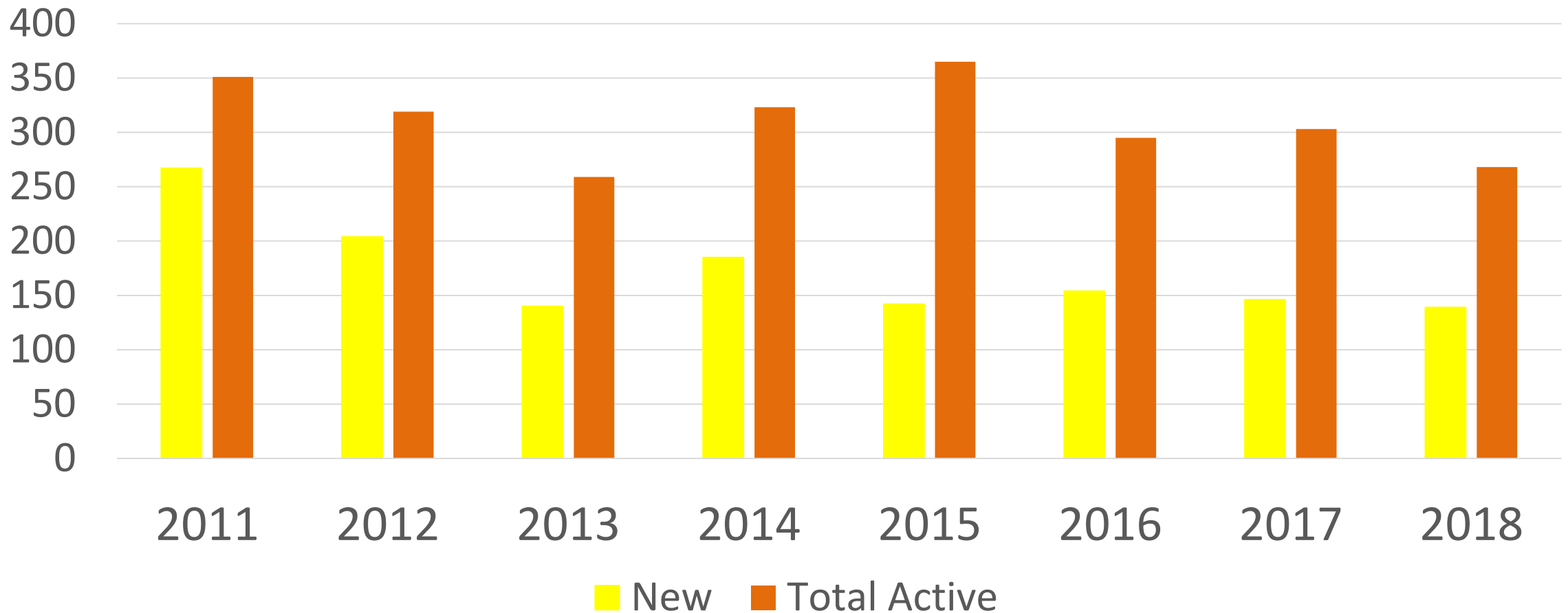
DISCLOSURE

- This presentation represents my own opinions
- University of Utah Drug Information Service has a contract with Vizient (a GPO) to provide drug shortage information. The total amount is < 5% of total budget.
- University of Utah Health is Vizient member

KEY CHALLENGES

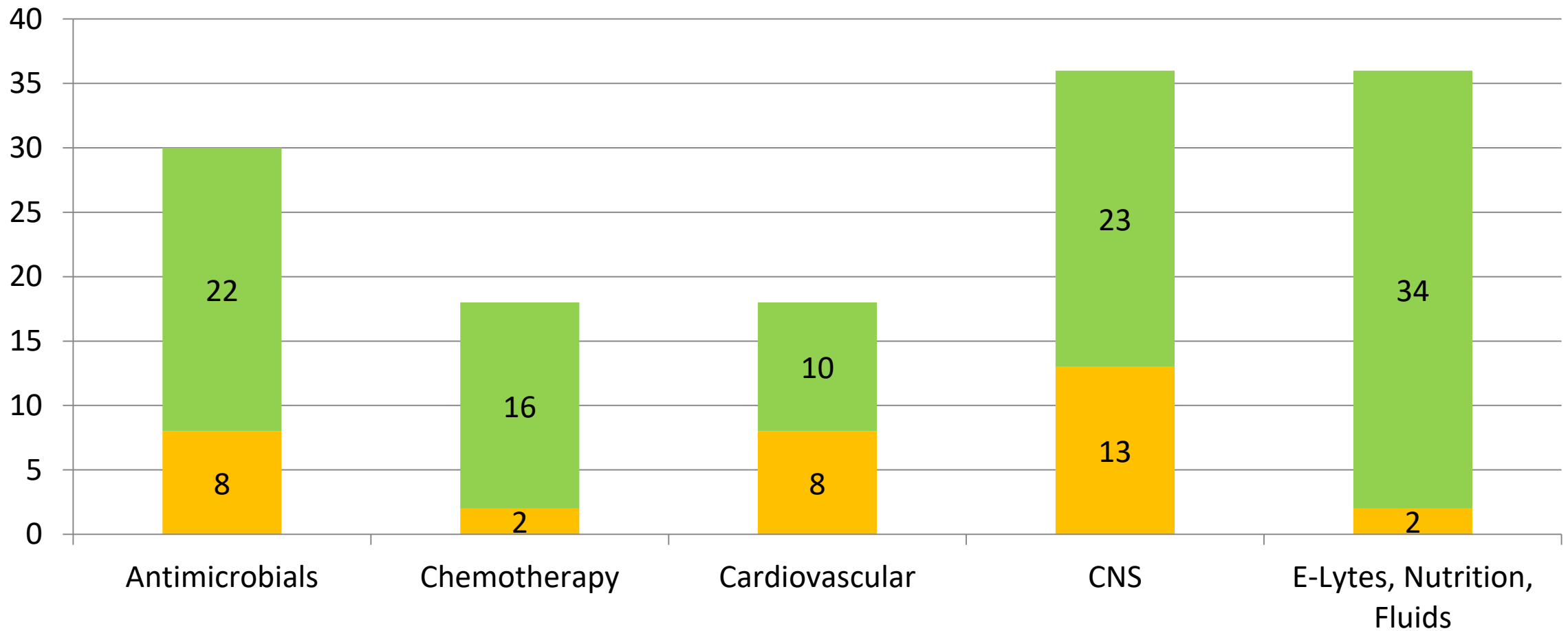
- Metrics
- Automation / Patient Safety
- Quality deficits
- Lack of Transparency

NEW SHORTAGES AND ACTIVE SHORTAGES BY YEAR 2011 – SEPTEMBER 30, 2018



ACTIVE SHORTAGES – SEPTEMBER 30, 2018

TOP 5 DRUG CLASSES



University of Utah Drug Information Service Erin.Fox@hsc.utah.edu, @foxerinr
Green = injectable, yellow = non-injectable

DIFFERENCES BETWEEN DATA SETS

UUDIS / ASHP

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

FDA

- **www.fda.gov/cder**
- Fewer products
- No devices
- Separate section (CBER) for biologics
- Information from manufacturer

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

SOLE SOURCE / NEAR SOLE SOURCE PRODUCTS

- Single firm often produces 90% of total supply – common to have sole source raw materials
- Market share not transparent
- What limits competition and new entrants?
 - Low use products
 - Practice changes
 - Approval backlog?
- FTC not required to consider FDA recommendations / public health when evaluating mergers
- Are essential medications critical infrastructure?

FORMULATION MATTERS

- Automation / Informatics for patient safety
- Requires use of exact same product / NDC
- Clinically unimportant changes (vial vs. syringe) require 100's of hours time

INCREASED LABOR

- Lose entire supply with a single recall
- Switching to IV push due to minibag shortage required review and changes to 700 electronic treatment plans (for just 2 drugs)



Photo credit: Erin Fox

Kaakeh R et al. AJHP. 2011;68:1811-1819

CAN YOU PURCHASE FOR QUALITY?

- FDA makes warning letters and 483 inspections public, but names of drugs are redacted
- No requirement to disclose which company actually makes a product, or manufacturing site
- Purchasers can't follow the data to spend their limited dollars wisely
- Few data available for higher risk 503b compounders

<https://www.fda.gov/downloads/drugs/guidances/ucm455957.pdf>

API QUALITY CRISIS

- Ongoing contamination of ‘sartans’
- Health impact estimates don’t include pediatric use
- Recalls began July 13 – last update was Nov 21 with additional recalls – when will we know which products are safe?

TAKEAWAYS

- Shortages mean hospitals don't have critical medications needed for patient care
- Purchasers have few choices due to sole suppliers and consolidation
- Quality problems are concerning, but not transparent
- Drug supply may not be safe

Session 2: The Economics of Drug Shortages

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Manufacturers of Generic Prescription Drugs in the United States

Rena M. Conti, Questrom School of Business, Boston University
Ernst R. Berndt, MIT Sloan School and NBER

‘Identifying the root causes of drug shortages and finding enduring solutions’
Duke Margolis Center for Health Policy
Washington DC, November 27, 2018

Acknowledgements and Disclaimers

- Research discussed today benefited from data provided by the FDA, IQVIA and University of Utah Drug Information Service and discussions with officials from these institutions.
- Mr. Berndt acknowledges research support from the National Institute on Aging, Grant R01AG043560, to NBER. Ms. Conti acknowledges research support from The Commonwealth Fund and the American Cancer Society.
- Mr. Berndt was appointed an FDA special government employee in March 2018. Ms. Conti is awaiting appointment as an FDA special government employee.
- Any opinions and findings expressed here are those of the authors, and are not necessarily those of the institutions with whom they are affiliated, or the research sponsors.

Agenda organized around critical questions for understanding market, formulating responses

1. What is a shortage?
2. What is a drug 'manufacturer'?
 - What are current characteristics of 'generic' drug manufacturers?
3. How competitive is the supply of generic drugs in the US?

What is a 'shortage'?

An economic perspective

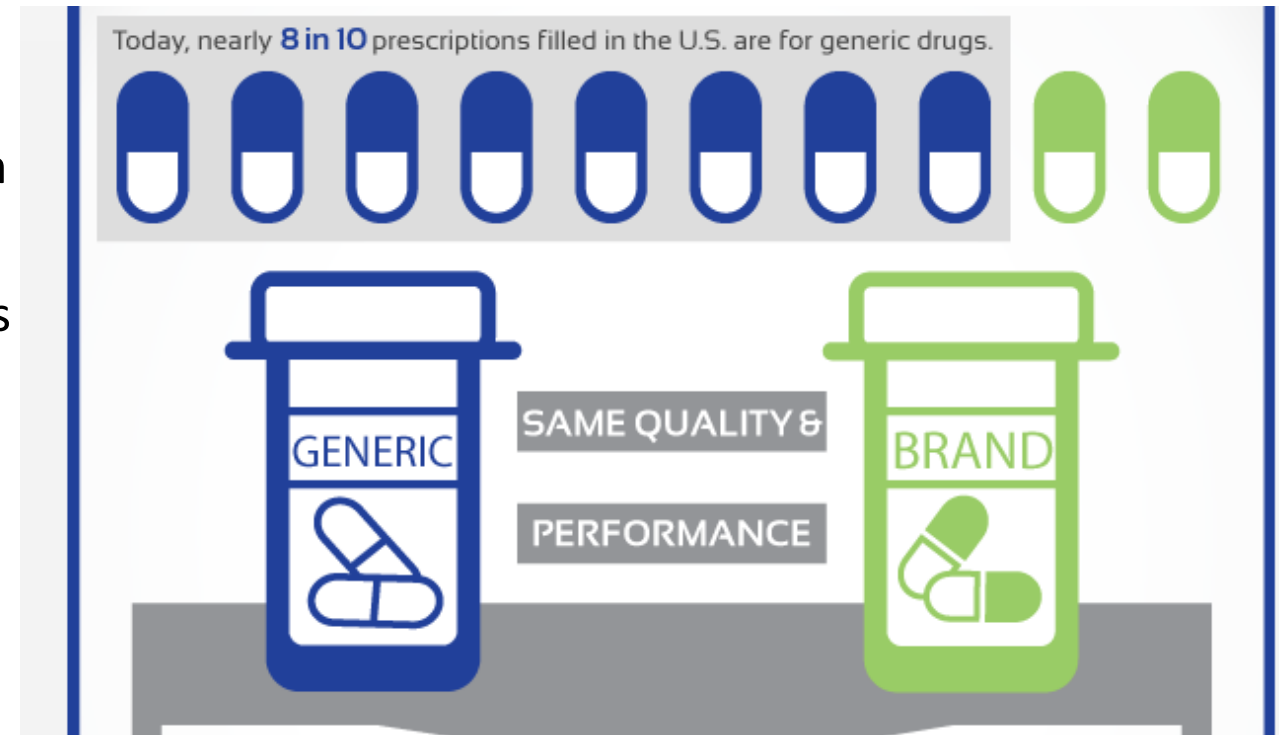
- “Ran out of a drug, can’t get adequate replacement supply unless I deal with unlicensed suppliers”
- Economic perspective:
 - A shortage exists when, at any given market price, the quantity demanded by purchasers exceeds the quantity supplied by manufacturers.
 - In response to a shortage, profit-maximizing firms raise prices, the quantity demanded falls, new suppliers enter or existing suppliers increase quantity because of expected profitability, and over time the combination of increased quantity supplied and reduced quantity demanded as prices increase eliminates the shortage.
 - i.e. If demand is stable, ‘shortages’ should be transitory in a ‘competitive’ market.

Initial observations on root causes of most “classic” drug shortages

- Existing drug shortages appear to be quite persistent and incident shortages appear to share periodicity.
- Likely something about the demand, supply and/or pricing of these drugs that does not allow the US market to ‘equilibrate’.

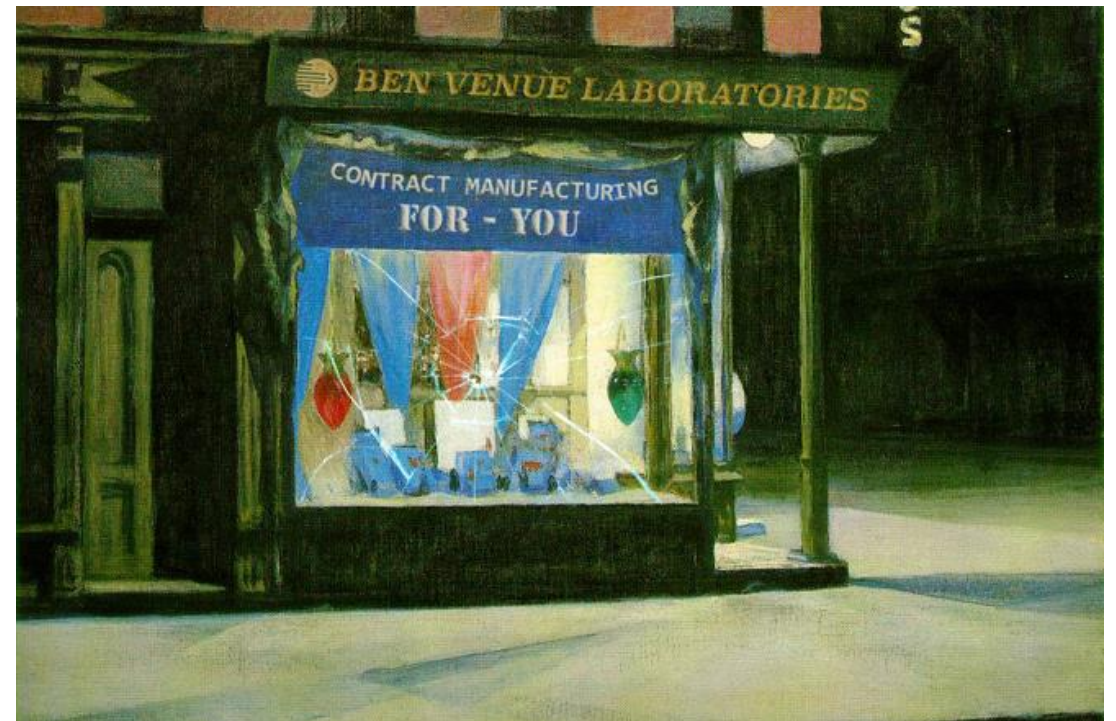
On demand:

- Many of these drugs are ‘medically necessary’.
- Demand for generics has increased:
 - As baby boomers retire, there’s been growth in Medicare insured population
 - Growth in population served by Medicaid, in ACA plans, in high deductible commercial plans
- Demand for lower prices from manufacturers has also increased:
 - Shift of care to and acquisition of community practices by hospitals – now eligible for discounted GPO and 340B prices
- Economics terminology: “Demand curve has shifted downward and to the right – demand more elastic”



What is a drug 'manufacturer'?

- When shortages are threatened or occur, stakeholders need to know which drugs and which manufacturers are impacted.
- Complicated manufacturer definitions and opacity constrain prudent planning.
- Makes researching supply in this area challenging.



Who makes this drug?

Some regulatory basics

- Manufacturing consists of making two products: Active pharmaceutical ingredients (API) and Finished dosage form (FDF).
- Drug developers make their own API/FDF, or outsource to contract manufacturing organizations (CMOs).
- When submitting an NDA/BLA/ANDA, the sponsor files its own Drug Master File (DMF) specifying its own manufacturing method and site details, or refers to the approved DMF of the CMO on file at FDA.
- NDA/BLA/ANDA sponsor can list their own facilities and CMO facilities as “backup”.

CMOs, repackagers complicate manufacturer definition

- **‘Manufacturer’ may map to**
 - **Application holder** – firm holding an NDA, BLA, ANDA
 - Manufacturer ≠ sponsor if drug is made by CMO.
 - **(NDC) Labeler** – company assigned NDC code (21 Code of Federal Regulations (CFR) 207.25)
 - Commonly found in claims data
 - If product is made by CMO or repackager, manufacturer ≠ labeler.

Manufacturer identity and location are restricted

- FDA collects information on CMOs and API/FDF manufacturing sites when collecting annual PDUFA and GDUFA user fees.
- However actual CMO and API/FDF manufacturer is not public information – Drugs@FDA.gov, NDC, FOIA.

- To implement GDUFA I, FDA began collecting self-reported information on generic drug manufacturing locations including domestic and foreign active pharmaceutical ingredients (API) and finished dosage form (FDF) facilities.
- This data was made public and provides an unprecedented window into the current structure of generic drug manufacturing.

J Law Biosci. 2018 May; 5(1): 103–141.

Published online 2018 Apr 11. doi: [10.1093/jlb/lsy002](https://doi.org/10.1093/jlb/lsy002)

PMCID: PMC5912081

PMID: [29707218](https://pubmed.ncbi.nlm.nih.gov/29707218/)

The generic drug user fee amendments: an economic perspective

[Ernst R Berndt](#),¹ [Rena M Conti](#),² and [Stephen J Murphy](#)³

Large multi-product firms dominate generic drug manufacturing

Table 6.

Size Distribution of Claimed ANDA Portfolio Sponsors and Ownership Distribution as of April 30, 2017.

ANDA Portfolio Size	Number of Sponsors	Cumulative Share of Sponsors (%)	Number of ANDAs	Share of ANDAs Held (%)	Cumulative Number of ANDAs
1	18	18	17	0.2	17
2	7	25	16	0.2	33
3	6	31	18	0.2	51
4	7	38	28	0.4	79
5	3	41	10	0.1	89
6–10	10	51	82	1.0	171
11–19	8	59	119	1.5	290
20–50	16	75	444	5.6	734
51–150	11	86	1051	13.2	1785
151–300	7	93	1478	18.6	3263
>300	7	100	4703	59.0	7966

Notes: ANDA is Abbreviated New Drug Application.

Source: Authors' calculations from 'Program Fee List—Excel file'. Available at <https://www.fda.gov/forindustry/userfees/genericdruguserfees/UCM531828.xlsx> (accessed July 22, 2017).

- 80% of ANDAs held by 7% of ANDA sponsors.

Manufacturing generic drugs occurs at foreign facilities

Table 2.

Generic Manufacture Facility Counts and Location from Annual Self Identification Responses.

Fiscal Year	Finished Dosage Form (FDF) Facilities			Active Pharmaceutical Ingredient (API) Facilities			Total Number of Facilities			
	Domestic	Foreign	% Foreign	Domestic	Foreign	% Foreign	All	Domestic	Foreign	% Foreign
2013	325	433	57.1	122	763	86.2	1643	447	1196	72.8
2014	315	433	57.9	128	775	85.8	1651	443	1208	73.2
2015	271	410	60.2	103	692	87	1476	374	1102	74.7
2016	283	422	59.9	115	721	87.3	1541	398	1143	74.2
2017	255	420	62.2	101	688	87.3	1464	356	1108	75.7
MEAN	290	424	59.5	114	728	86.7	1555	404	1151	74

Source: Authors' calculations from the following data files: For FY 2013, see <https://www.gpo.gov/fdsys/pkg/FR-2012-10-25/pdf/2012-26256.pdf>; for FY 2014, see <https://www.gpo.gov/fdsys/pkg/FR-2013-08-02/pdf/2013-18625.pdf>; for FY 2015, see <https://www.gpo.gov/fdsys/pkg/FR-2014-08-01/pdf/2014-18108.pdf>; for FY 2016, see <https://www.gpo.gov/fdsys/pkg/FR-2015-08-03/pdf/2015-18915.pdf>; and for FY 2017, see <https://www.gpo.gov/fdsys/pkg/FR-2016-07-27/pdf/2016-17801.pdf> (accessed Apr. 18, 2017).

- 60% of finished drugs made at foreign facilities; 90% of base ingredients made at foreign facilities.

How competitive is the generic drug manufacturer market?

- Stylized facts suggests strong competition:
 - Generics commonly capture 80-90 percent of molecule sales within 2 years post-loss of exclusivity (LOE).
- However little is known about actual patterns of generic manufacturer supply:
 - Entry, sustained supply, exit.
 - In specific product types and over time.
 - How this may relate to shortages, other performance outcomes.



THE LANDSCAPE OF US GENERIC PRESCRIPTION DRUG MARKETS, 2004-2016

Ernst R. Berndt
Rena M. Conti
Stephen J. Murphy

Working Paper 23640
<http://www.nber.org/papers/w23640>

- Study examined longitudinal trends in manufacturer supply in a ‘prevalent’ generic drug cohort.
- Quarterly data from IQVIA National Sales Perspective 2004-2016.
- Manufacturer=‘labeler’.
- Drug market defined as combination of molecule-formulation.

We found generic drug markets are highly concentrated

- Supply:
 - The median number of manufacturers in each drug market is 2, the mean 5.
 - 40 percent of markets are supplied by 1 manufacturer & the share supplied by 1 or 2 has been increasing.
 - Concentration has increased due to more exits & less entrants, related to timing of ACA, GDUFA I.
 - Fewer entrants & more exits among non-oral drugs over time.
- Performance outcomes:
 - Revenues: Quarterly sales revenue per quarter for a manufacturer-product are surprisingly small (median= less than \$10 million).
 - Prices:
 - Prices of generic drugs are falling over time.
 - Increased prices of generic drugs are positively correlated with reduced manufacturer counts.

Our new study asks same questions about generic entry and performance outcomes in an 'incident' drug cohort

- Quarterly data from IQVIA National Sales Perspective.
- Manufacturer='labeler' (n=164).
- Drug market defined as combination of molecule-formulation.
- **Cohort: All products** experiencing LOE between 2009-2012 (n=160), follow through 2016 (Quarter 15 of data).
- **LOE** defined by data, double checked by search of public records.

We found stylized facts don't fit drugs undergoing LOE in recent years

- 75% sample experienced entry 15 quarters post-LOE.
- Mean #entrants=6, #exits=1.4; much fewer entrants among non-oral drugs.
- Entrants are multiproduct generic firms, low mean revenue/drug (\$558M).
- Drugs with no entry non-oral, low quarterly revenue pre-LOE (\$28M vs. \$168M).
- Incumbents of no entry drugs are multiproduct branded & generic firms, high mean revenue/drug (\$1505M).
- Exiting firms are multiproduct generic firms, mean revenue/drug pre-exit (\$333M); surprisingly high mean volume share (72%).

In terms of performance, incident drug cohort also exhibits some surprising trends

- Mean sales volume appears to be stable post-LOE for oral drugs; non-oral drugs sales volume increases (sometimes substantially).
- Generics gain substantial market share post-LOE (>90%) among orals; much less generic market share (80%) among non-orals post-LOE.
 - Brands may even gain market gain over time among non-orals.
- While prices decline post-LOE among orals; prices do not decline as much and may even increase among non-orals post-LOE.

This empirical work raises other key unanswered questions

- What product, firm characteristics determine entry and exit post-LOE?
 - Legal rationales? Manufacturing problems? Gaming tactics?
- Are there more 'potential suppliers' than actual suppliers?
 - What are their characteristics?
 - What is their availability over a drug's lifecycle?

We welcome the discussion.

Thank you.

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Session 2: The Economics of Drug Shortages

 #DrugShortagesMtg | @dukemargolis

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Session 3: The Health Impacts and Economic Consequences of Drug Shortages

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Session 4: Manufacturing & Supply Challenges

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AMERICAN REGENT™

Reliable. Responsive. Respected.

Injectable Drug **Shortages**

Harsher Singh

Chief commercial officer

Who is American Regent?



50 years serving the injectable market



3 US sterile manufacturing sites with a \$200M CAPEX investment underway in the US



99% of our products are manufactured in the USA



Deep back catalog of ANDA and DESI products that could help ease current shortages



Speed counts. Flexibility matters. Quality and reliability are paramount. Because **patients should never have to wait** for the medications they need.



The United States system for Gx injectable purchasing strives for the highest possible quality at the lowest possible cost



- No redundant capacities and systematic underinvestment
- Long, over-stretched supply chains
- Increased rents by intermediaries who control market share and therefore scale economies

Cost of a cup of coffee: \$1.90 – \$5.25 or more

Cost of Ondansetron vial (current drug shortage): <\$1 for 42mg/ 2 ML

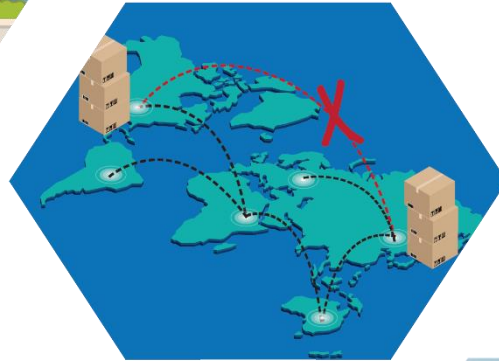


Causes of shortages

There are 3 causes of shortages in the sterile injectable market



Manufacturing site interruptions



Supply chain breakdowns



Cyclical shortages

Longer, more complex and sensitive supply chains



Longer, more complex,
and sensitive supply chains



In search of cost advantages manufacturers were forced to
evolve their supply chains



Less flexible and more
regulated supply chain

Complexity of DESI pathway

Time to rejuvenate shortage ANDA

Inventory holding pattern

Unforeseen changes in
product economics

New supply chains are spread across multiple countries,
companies, and technologies



These supply chains are much more likely to 'break' and
take much longer to react to inconsistent demand



1. Shorter supply chains with increased API and fill finish capabilities in the US to quickly respond to market changes
2. Investment in more flexible filling lines that can pivot quickly to new products or presentations



Less flexible and more regulated supply chain



Longer, more complex,
and sensitive supply chains

Less flexible and more
regulated supply chain



Complexity of DESI pathway

Time to rejuvenate shortage ANDA

Inventory holding pattern

Unforeseen changes in
product economics



Greater complexity in manufacturing and regulatory environment has come at the cost of both throughput and flexibility, particularly for older facilities



New isolator technologies together with product specific formulation requirements make it difficult to ramp up production quickly



Make to release times for injectables are higher due to sterility testing requirements



Increased, early transparency on potential shortages so that manufactures can choose whether or not to scale up production e.g.; rapidly post redacted 483s to FDA website, include remediation status on 483s

Complexity of DESI pathway



Longer, more complex,
and sensitive supply chains

Less flexible and more
regulated supply chain

Complexity of DESI pathway



Time to rejuvenate shortage ANDA

Inventory holding pattern

Unforeseen changes in
product economics

>30%¹ Proportion of FDA reported injectable shortages
comprised of previously/ currently marketed
unapproved products

\$2M Cost to file NDA creates an incentive to file only
where a barrier to competitive entry is created

**Manufacturers can only afford this if they can differentiate
through a new presentation, titrated specifications, or exclusivity**



1. Reduced filing costs for DESI products
2. Consistent guidance and implementation of Guidance on Unapproved Marketed Drugs

1. The products include: Magnesium Sulfate Injection, Calcium Gluconate Injection, Potassium Chloride Injection, Potassium Phosphate Injection, Sodium Chloride 0.9% Injection Bags, Sodium Chloride Injection USP, 0.9% Vials and Syringes, Sodium Chloride 23.4% Injection, Aminophylline Injection, USP, Atropine Sulfate Injection, Calcium Chloride Injection, USP, Dextrose 5% Injection Bags, Dextrose 50% Injection, Diphenhydramine Injection, Epinephrine Injection, 0.1 mg/mL, Erythromycin Lactobionate for Injection, USP, Lidocaine Hydrochloride (Xylocaine) and Dextrose Injection Solution-Premix Bags, Lidocaine Hydrochloride (Xylocaine) Injection, Lidocaine Hydrochloride (Xylocaine) Injection with Epinephrine, Morphine Sulfate Injection, USP, Penicillin G Procaine Injection, Phosphate Injection Products, Sodium Acetate Injection, USP, Sodium Bicarbonate Injection, USP, Sodium Phosphate Injection, Ethiodized Oil (Lipiodol) Injection



Time to rejuvenate shortage ANDA



Longer, more complex,
and sensitive supply chains

Less flexible and more
regulated supply chain

Complexity of DESI pathway

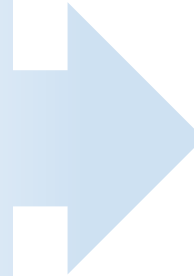
Time to rejuvenate shortage ANDA

Inventory holding pattern

Unforeseen changes in
product economics



It often takes a
long time to bring
back a product
even if a
manufacturer has
an intact ANDA/
prior experience
with a product



If the API supplier has changed, a
new PAS must be filed and new
batches placed on stability

If the filling line has had any
changes, the product requires a
PAS

If the container has changed in
any way, new studies are needed



1. Accelerated review/ CBE-30s for shortage products
2. When there is a history on file, allowing justifications through lab data, with the appropriate commitments, until cGMP data is available



Inventory holding pattern

Longer, more complex,
and sensitive supply chains

Less flexible and more
regulated supply chain

Complexity of DESI pathway

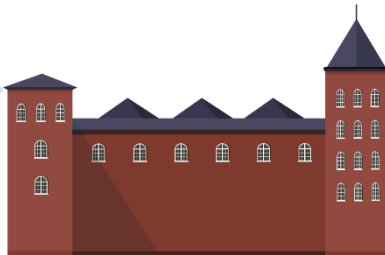
Time to rejuvenate shortage ANDA

Inventory holding pattern

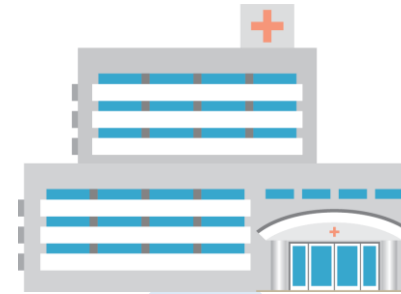
Unforeseen changes in
product economics



Sometimes have
small disruptions
due to release
testing, weather, or
other factors



Low Stock
Levels



Desire to hold stock when
markets are susceptible
to shortages

“Whiplash”
shortages
where a
significant
increase in
demand drives
a sensitive
market into
shortage



1. Incentiving minimum stock levels with requirements that:
 - Distributors must maintain
 - Manufacturers must alert the FDA if they fall below
2. Consolidating and reporting national stock levels publicly across the supply chain to prevent speculation

Unforeseen changes in product economics



Longer, more complex,
and sensitive supply chains

Less flexible and more
regulated supply chain

Complexity of DESI pathway

Time to rejuvenate shortage ANDA

Inventory holding pattern

Unforeseen changes in
product economics

Medicaid
rebate
penalty

31cents Reference price - based on very different
regulatory and COGS structures

COGS today are significantly higher

<10% Current margin

240K Medicaid pricing penalty annually

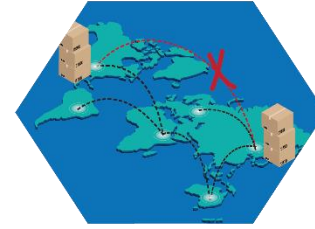


1. Increased reimbursement for sterile injectables¹
2. Revise Medicaid rebate penalty approach

1. <https://news.bloomberglaw.com/pharma-and-life-sciences/higher-prices-could-cure-some-drug-shortages-fda-chief-says>



API supply reliability



API supply reliability

FDA audits & restrictions
on API suppliers

Manufacturer exclusivity
with multiple API suppliers



Global
demand
variations



API raw
material
changes

**High regulatory/
quality yardstick**

**Gx is the lowest cost
buyer and therefore
first casualty**

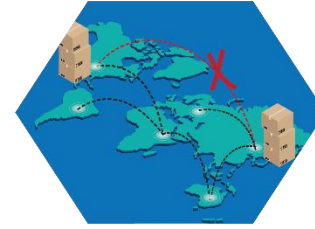
**Sensitive to
geo-politics**



More/ incentives for on-shore API manufacturing



FDA audits & restrictions on API suppliers



API supply reliability

FDA audits & restrictions on API suppliers

Manufacturer exclusivity with multiple API suppliers



Many offshore API suppliers are getting acclimatized with GMP regulations



This sometimes creates delays in manufacturing and documentation

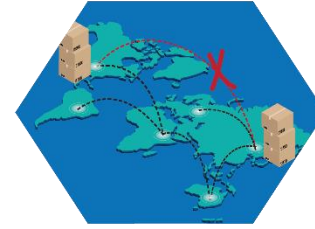


In extreme situations API suppliers are not able to produce for the US market



1. Immediate notice of audits
2. Modified barrier for secondary suppliers (e.g., require only 1 batch to be made for stability for the second supplier – we may still test 3 lots of API)
3. Evolved DMF listings to be more detailed and accurate

Manufacturer exclusivity with multiple API suppliers



API supply reliability

FDA audits & restrictions
on API suppliers

Manufacturer exclusivity
with multiple API suppliers



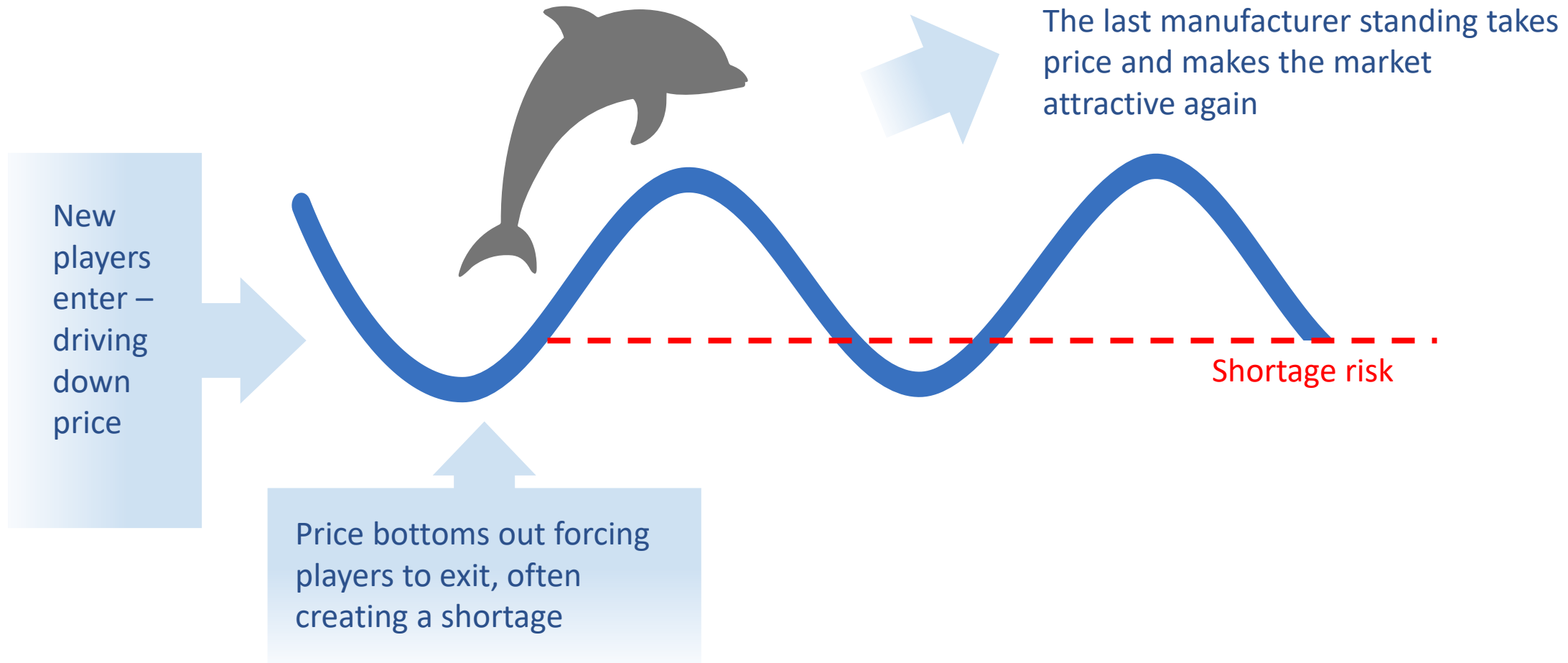
Manufacturing companies
sometimes contract exclusively
with multiple API suppliers to
create a barrier to entry



Increased FTC antitrust oversight in the industry



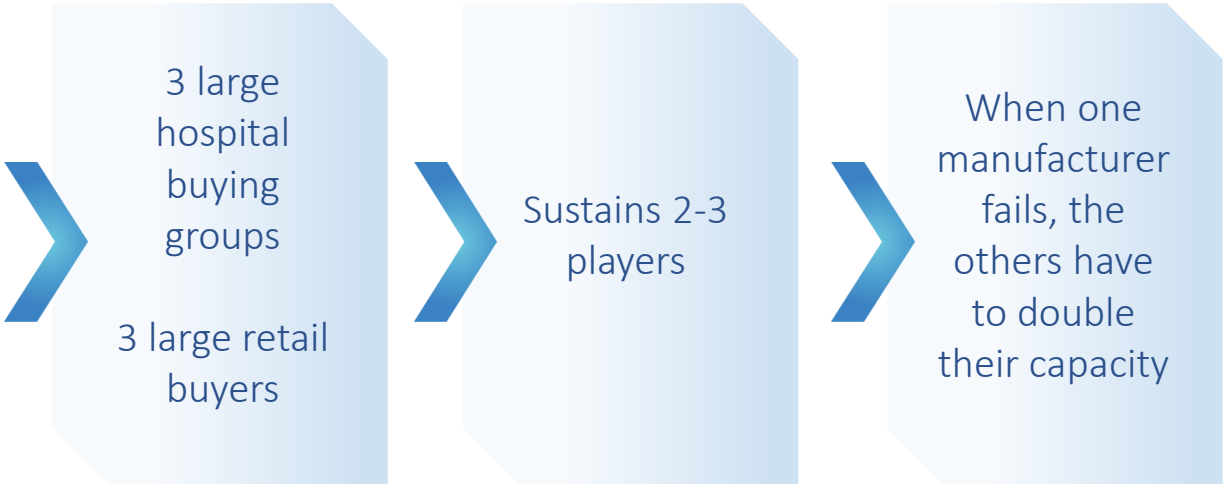
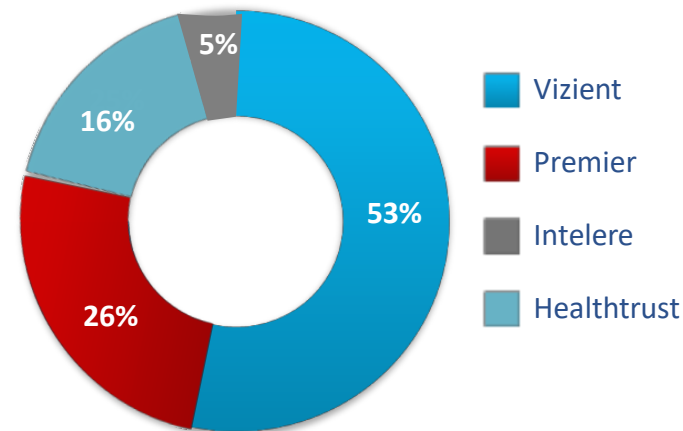
Cyclical shortages



Consolidation & concentration in the Industry



GPO segmentation ¹
Estimated US Hx market mix



Increased FTC antitrust oversight in the industry

1. IMS Health, MAT October 2017 and internal analysis. Non-retail includes hospitals, clinics, long term care, home healthcare and federal facilities



Disincentive to enter outside bid roll



- Large GPOs operate on 5 – 7 year cycles for most high volume products
- There is a disincentive to enter during these cycles since incumbents have the right of first refusal
- This means that competitors only launch products around the end of bid cycles – increasing the likelihood of shortages during the 5 – 7 year period where 2 – 3 players ‘own’ a market



Shorten bid cycles



Session 4: Manufacturing & Supply Challenges

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Drug Shortages – How to Prevent

Martin VanTrieste

Civica Rx President and CEO

Duke - Margolis – FDA

Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions

November 27, 2018

We Must Deliver Quality Medicines in a Reliable Manner at Fair and Sustainable Prices



Serving Patients is a Privilege that Comes with Significant Responsibilities



Drug Shortages Harm Patients



“All drug shortages are the result of economics, financial and management decisions”

Martin VanTrieste

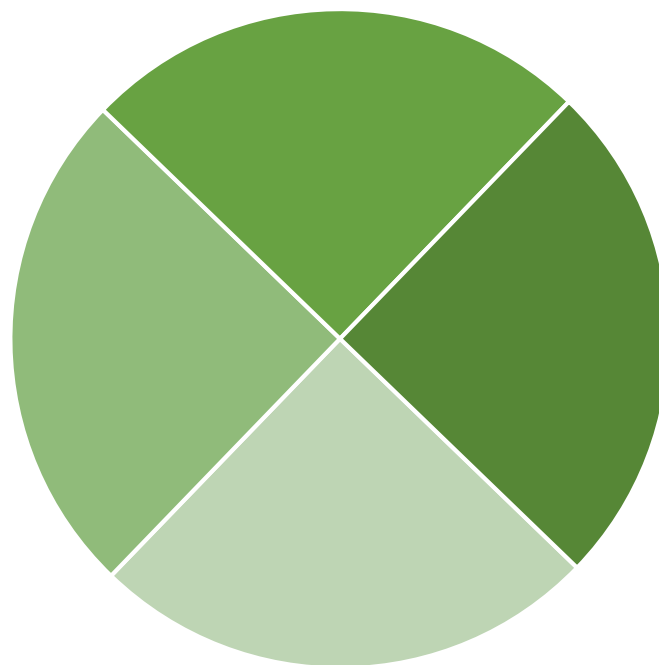


What Has Changed Since The Year 2000?



All participants in the generic drug ecosystem have played a part, and to solve drug shortages must implement changes

Economic Reasons for Drug Shortages



Low Prices & Predatory Pricing

Long & Complex Supply Chains

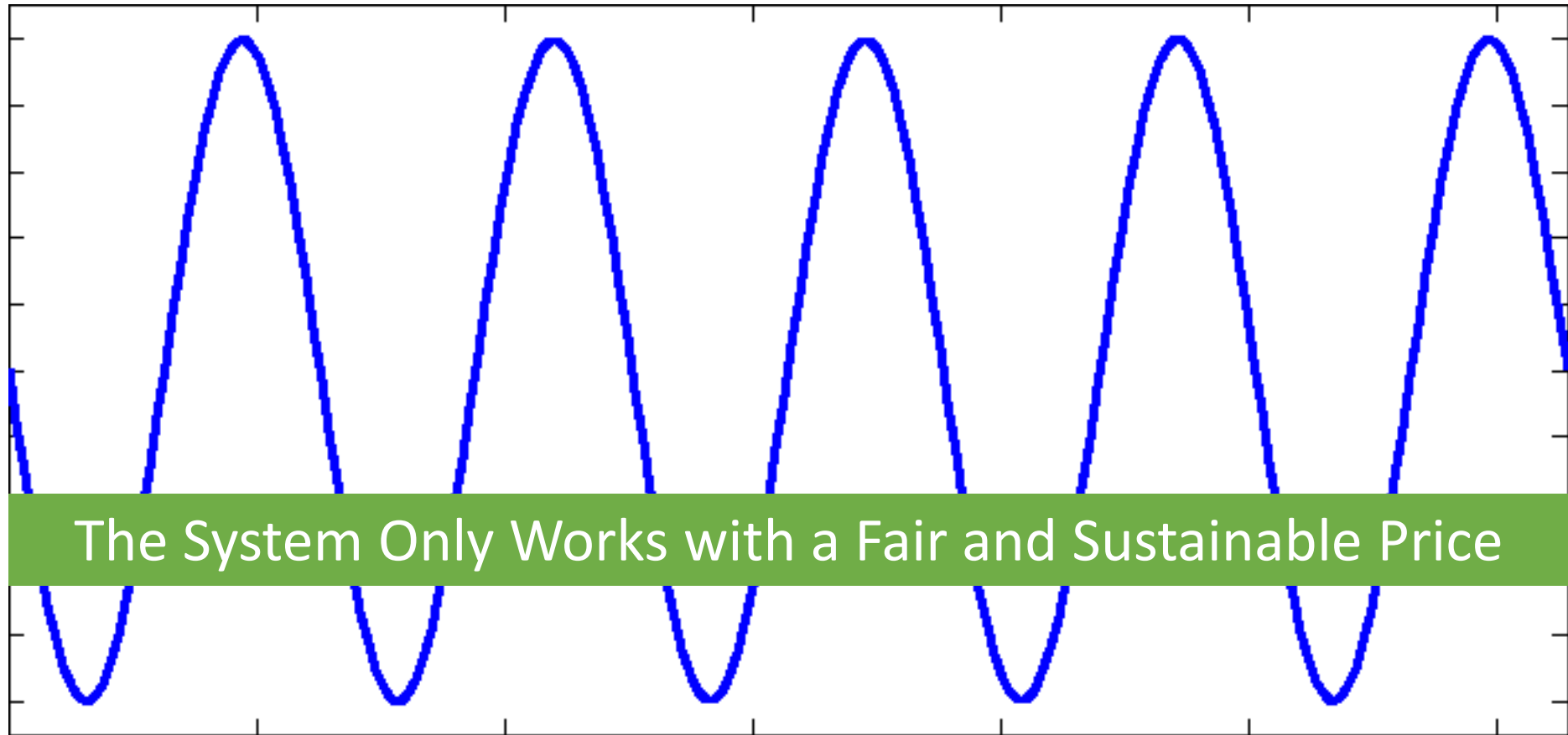
Sole Source Contracts

Inventory Levels

Cyclical Shortages – Best Prediction – Eliminating Uncertainty



\$2,000 per vial is not a **Fair Price** eventually leading to excess capacity and price starts to drop



\$2.00 per vial is not a **Sustainable Price**, eventually leading to drug shortages

Civica Rx's Approach to Prevent Drug Shortages



Not-For-Profit

**Establish Fair
And Sustainable
Prices**

**Long-Term
Guaranteed
Contracts**

**Promote
Competition**

**Redundant
Manufacturing**

**No Fees or Rebates
And
Price Transparency**

Safety Stocks

**Country Of
Origin
Transparency**

Committed to eliminating uncertainty within the supply chain and creating a robust and reliable supply chain

Membership and Governance



Governing Members (10+)

Hospital Systems including: Catholic Health Initiatives, HCA Healthcare, Intermountain Healthcare, Providence St. Joseph Health, the Mayo Clinic, SSM Health, and Trinity Health

Philanthropies: John & Laura Arnold Foundation, Peterson Center on Healthcare, West Health

Founding Members (15)

Partnering Members (Unlimited)

Governance

- ✓ **Board of Directors** consisting of 7 governing members, 3 philanthropic organizations, the CEO and three independent directors
- ✓ **Drug Selection Committee** consists of Pharmacy executives from the 7 governing, 3 philanthropies and 15 founding members
- ✓ **Medical Trends Committee** consists of clinicians from 7 governing, 3 philanthropies and 15 founding members

More than 150 Health Systems Have Expressed Interest

No One Company or Organization Can Fix the Problem



How can the government help?

- ✓ Provide incentives to establish and maintain high-quality manufacturing practices, to develop redundancy in manufacturing operations, to expand capacity, and /or to create other conditions to prevent or mitigate shortages.
- ✓ Waive fees for essential medicines that have been routinely in shortage
- ✓ Create a process to monitor inventory of essential drugs
- ✓ Enhance sharing information about drug shortages

Contact Information

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Session 4: Manufacturing & Supply Challenges

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Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions

Washington Marriott Metro Center

November 27, 2018

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Session 5: Drug Purchasing & Demand Challenges

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Premier and Our Role in Stopping or Mitigating Drug Shortages

Leading a provider-led transformation of healthcare that consistently delivers high quality, high value care

Scale

- 4,000+ hospital/health systems
- Hundreds of thousands clinicians
- 165,000 other providers
- Clinical, financial, operational data on ~45% hospital discharges
- Aggregate \$60+ billion in supply chain spend

Alignment

- ~60% owned by health systems
- 10 health system board members

Co-innovation

- Co-develop solutions with members
- ~140 health systems participating in committees
- ~1,450 hospitals in performance improvement collaboratives



Premier believes that a holistic, multi-stakeholder, and inter-agency approach is necessary to truly address drug shortages.

Sustainable solutions to address drug shortages must decrease barriers to entry, namely the time and cost to enter the marketplace, while maintaining the quality and safety of the product.

Our goal is to eliminate drug shortages.

Contributing Factors to Drug Shortages

*There is no single cause of drug shortages.
Multiple contributing factors result in drug shortages.*



Entry of Low Cost Competitor



Issue

- The entry of a low cost competitor can create a ripple effect on the market that ultimately results in a drug shortage.



Examples

- Scenario A – Entry of a low cost competitor results in others exiting the market.





Solutions

- Improve regulatory efficiency and predictability during drug shortages:
 - Expedite review of newly submitted ANDAs by beginning review of the application while awaiting submission of the 6-month stability data. A parallel review process can decrease the amount of time needed to review an ANDA and therefore help bring a competitor to market sooner.
 - Expedite facility inspections and review of manufacturing changes that would help mitigate or prevent a drug shortage.
 - Appoint a senior-level drug shortage navigator to coordinate with each manufacturer who submits an ANDA for a drug shortage product. This position should reside within the OGD and responsibilities would include shepherding drug applications through the internal review and approval processes at FDA and maintaining communication with the manufacturer.
 - Expedite NDAs for shortage drugs in situations where a NDA is preferred over an ANDA to help improve the formulation, dosage form, or delivery system of a shortage drug.



Solutions

- Create incentives for manufacturers to enter the market for low revenue products:
 - Develop a mechanism for reimbursing GDUFA fees to manufacturers who submitted an ANDA for a shortage drug after a specified period of time of successfully entering the market. The increased GDUFA fees, and newly created program fees for generic manufacturers, are often a barrier to entry as the potential revenue on a shortage drug does not outweigh the cost of filing fees. A reimbursement mechanism, in lieu of waiving or reducing fees upfront, will help ensure market entry and provide incentive for manufacturers to ensure a quality manufacturing process.
 - Address the loophole in the Competitive Generics Therapy (CGT) pathway so that the first approved manufacturer is guaranteed exclusivity. Currently, the first manufacturer is only granted exclusivity if they begin marketing the product before the FDA approves a second manufacturer, something that can occur days after the first approval. A manufacturer needs affirmation that as the first manufacturer they will have a period of exclusivity and also sufficient time to bring their product to market upon approval.



Solutions

- Create pathways for interim solutions to help address drug shortages:
 - Expand the FDA drug shortage list to include regional shortages and shortages based upon dosage or administration form, similar to the criteria used for the ASHP drug shortage list. A more comprehensive list will allow the temporary use of 503B outsourcing facilities to mitigate shortages while a longer-term and more permanent strategy is being developed.

Quality and Manufacturing Issues



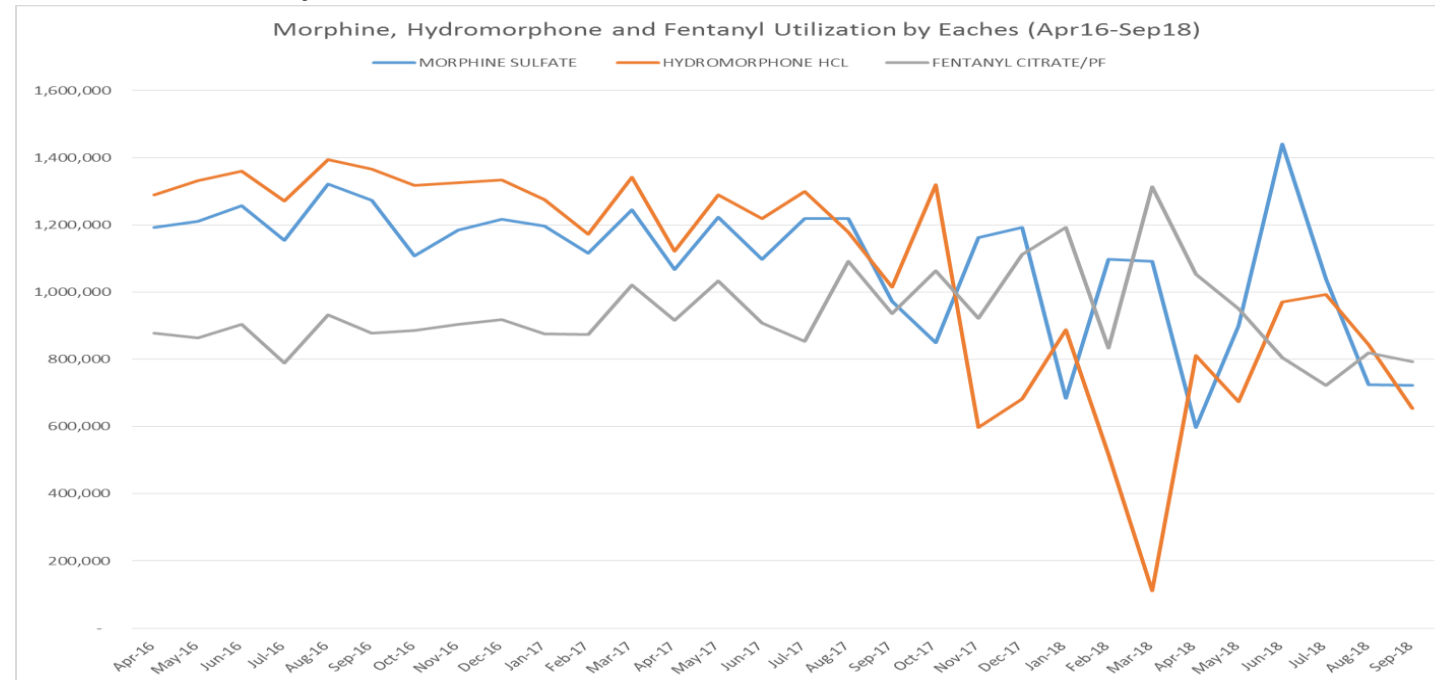
Issue

- In a market with few manufacturers, when one manufacturer encounters quality or manufacturing issues and exits the market for an extended period of time, downstream pressure is placed on the remaining manufacturers to ramp up supply and fill the market void.
- In certain scenarios, external factors prevent other manufacturers from ramping up such as capacity restrictions and DEA quota allocations, resulting in drug shortages.



Examples

- The ongoing shortage of injectable narcotics has been a major patient safety concern for health systems.





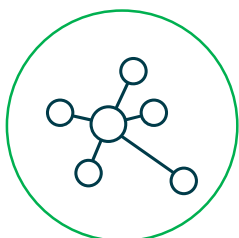
Solutions

- Improve the regulatory violation process for cGMP by shortening turnaround times and improving and standardizing processes for FDA reviews to identify problems prior to shutting down facilities. More rapid review of corrective actions taken by manufacturers would help moderate fluctuations.
- Improve coordination within various FDA offices - such as ORA, ODS, OGD – to understand downstream impact of cGMP violations or manufacturer shutdowns on drug shortages and proactively develop mitigation strategies.
- Develop a list of critical medications that are needed for patient care in case of an emergency, natural disaster, or other urgent situation. Require manufacturers of critical medications to report where such medications are manufactured so the FDA can use mapping technology to account for potential impact of natural disasters, facility shutdowns, and other situations on drug shortages and appropriately mitigate.
- Creation of an inter-agency, White House-level ‘Drug Shortage Point Person’ to improve cross-agency coordination on issues related to drug shortages, such as the ongoing shortage of generic injectable opioids. A Drug Shortage Point Person will streamline needed communication and cooperation among stakeholders such as the HHS, DEA, FEMA, VA, CMS, FDA, DOD and other stakeholders.



Issue

- Over 80% of API and raw materials required for drug manufacturing are manufactured overseas.⁵ The heavy reliance on foreign manufacturing of API and raw materials results in downstream drug shortages when a foreign manufacturer fails to meet cGMP or exits the market.
- The extent and duration of API or raw material shortages is unknown and results in downstream impact on hoarding and the gray market.
- The Chinese Blue Sky Initiative is resulting in API and raw material manufacturers being required to either halt production or shut down. Manufacturers are concerned that this may further exacerbate shortages, and may result in increased shortages for oral solid dosage forms.
- New tariffs are also putting pressure on foreign manufacturers of raw materials and may lead to entities exiting the market resulting in downstream drug shortages.



Examples

- The recent valsartan recall was due to an impurity with the API. Almost all manufacturers relied on a single API manufacturer, resulting in a major shortage.
- The recent injectable opioid shortages were exacerbated by an inability of the manufacturer to acquire the raw materials necessary for the injector.



Solutions

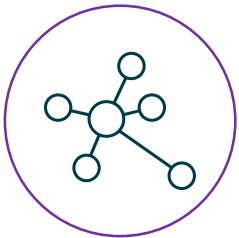
- Create incentives to encourage on-shore manufacturing of API and raw materials.
- Extend FDASIA Title X reporting requirements to API and raw material manufacturers, including strengthening the reporting requirements to include disclosure of the problem resulting in the shortage, the extent of the shortage, and the expected duration of the shortage to help understand the downstream impact on drug shortages.
- Prioritize FDA reinspection of facilities that are sole manufacturers of API or raw materials when cGMP or other quality issues are identified. Develop action plans and work closely with manufacturers to prevent facility shutdown and downstream drug shortages.
- Maintain directory of API sources used by manufacturers to expedite downstream notification if there is an issue with an API manufacturer and implementation of drug shortage mitigation strategies.

Change in API Requirements



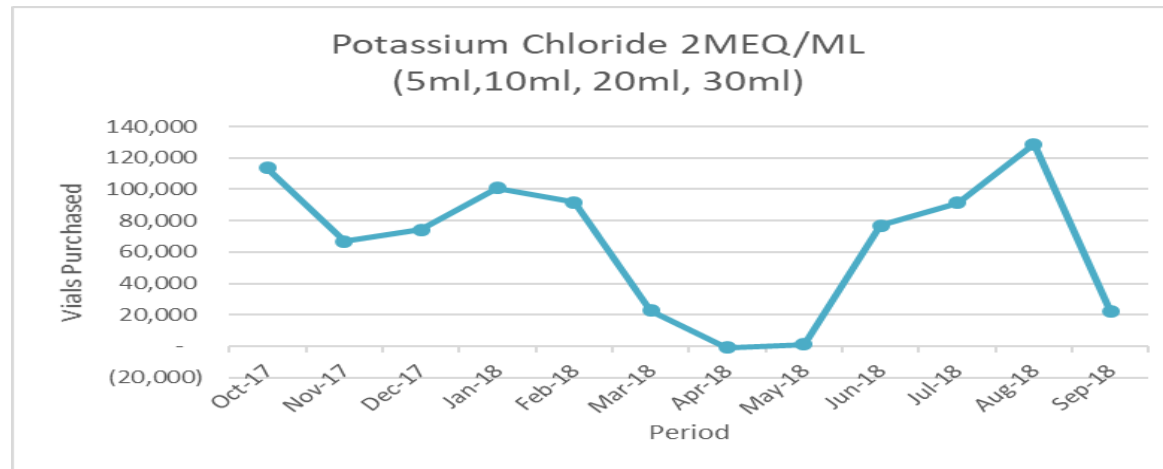
Issue

- Updates to USP monographs will often result in changes to API requirements.
- The changes to API requirements are typically effective immediately, resulting in shortages as manufacturers must suspend manufacturing using the old API and await new API, which can take several months, to resume manufacturing.



Examples

- Changes to API requirements for potassium chloride resulted in a shortage.



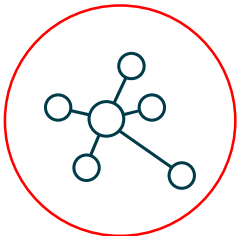
Solutions

- Permit a phase-in period of at least 6-12 months for changes in API requirements where old API can continue to be used until new API is available. An exception should exist if the prior API was associated with harm or adverse events necessitating the need for a change in API requirements.



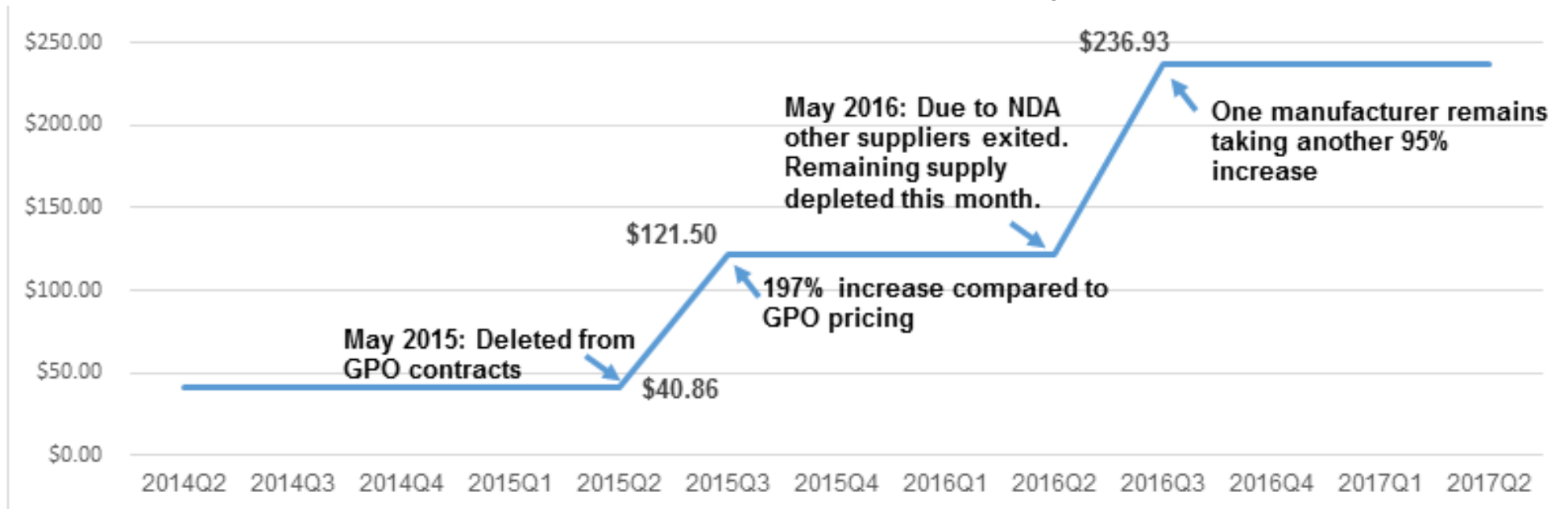
Issue

- DESI drugs are often at-risk for shortages as legacy manufacturers are required to exit the marketplace abruptly and typically only 1 or 2 manufacturers reenter the marketplace under the new requirements.
- During a DESI drug shortage, it is difficult for new manufacturers to enter the marketplace given the need to prove efficacy, an expensive and timely process for manufacturers.
- DESI drugs are also subject to significant price increases.



Examples

Potassium Chloride 20MEQ/15ML liquid





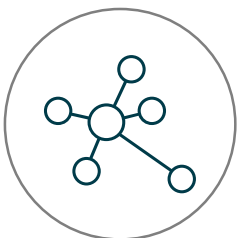
Solutions

- Refine the “unapproved drugs” compliance policy initiative to permit the use of real-world evidence to demonstrate efficacy.
- Announce in the *Federal Register* the first NDA submission for a DESI drug and solicit additional NDA submissions.
 - Allow for 18 to 24 months after the *Federal Register* notice before requiring current manufactures to exit the market. This would help provide stability in the market, mitigate threats of a shortage, and allow sufficient time for other manufacturers to consider submitting a competing NDA.
- Lower, or remove altogether, NDA filing fees for DESI drugs to encourage manufacturers to enter the market as high NDA fees are often a deterrent, or not feasible, for generic manufacturers.
- Streamline and simplify filing requirements for DESI drugs, making the application more akin to an ANDA, or at most a 505(b)(2) paper NDA. Generic manufacturers are often not familiar with the NDA process and would be more inclined to submit applications if they resembled a traditional ANDA.
- Expedite review of competing NDAs to encourage competition in the marketplace and mitigate potential shortages due to reliance on a single manufacturer.



Issue

- During drug shortages, shortage drugs are often sold at exorbitant prices by unauthorized vendors.
- The gray market creates patient safety concerns as the products may not have been stored properly and therefore the integrity of the product cannot be confirmed.



Examples

- Recently, several Premier private label products have been found in the gray market:
 - Ondansetron - 1642% price increase
 - Naropin – 291% price increase
 - Rocuronium – 691% price increase



Solutions

- Timely implementation of the DQSA track and trace requirements.
- Require distributors to implement checks and balances systems for shortage drugs, similar to suspicious order monitoring requirements for controlled substances, to identify potential diversion of shortage drugs to the gray market.
- Promote the reporting of gray market offers to the FDA Office of Criminal Investigations. Share reported incidents with the FTC.
- Implementation of CMPs for entities selling products to the gray market.

**Issue**

- During drug shortages, hoarding often occurs as providers are concerned about having adequate supply of products and do not know the duration and severity of the shortage.
- This further exacerbates shortages as product is not available in the supply chain for other entities.
- Hoarding often results in product being returned as unused or expired in lieu of being used for patient care.

**Solutions**

- Strengthen FDASIA Title X reporting requirements to include disclosure of the problem resulting in the shortage, the extent of the shortage, and the expected duration of the shortage to help alleviate provider concerns and discourage hoarding.
- Collate and make publicly available information about the severity of the shortage, expected duration, and mitigation strategies (e.g. remediation efforts by manufacturer, entry of additional manufacturers, potential importation, etc). This information should be provided in a uniform manner, be easily found on the FDA website, and updated in a timely and consistent manner (e.g. monthly).

- 1. Reducing time and financial barriers to market entry for manufacturers of shortage drugs.***
- 2. Empowering FDA with greater information insight and authority so as to avoid unforeseen problems that inadvertently create shortages.***
- 3. Addressing supply chain issues that increase or perpetuate a shortage.***

Session 5: Drug Purchasing & Demand Challenges

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FDA Meeting: Product Availability Update

Understanding product shortages

Product Shortages

Explanation of industry changes



Supplier manufacturing issues

- Issues getting Active Pharmaceutical Ingredient (API).
- Issues at the production facilities.
- The Drug Supply Chain Security Act (DSCSA)
- FDA regulatory findings.



Manufacturer pricing pressures

- Inability to take price increases due to negative press coverage.
- Approval of additional ANDAs result in more competition on pricing and SKU rationalization.



Industry consolidation activity

- Fewer competitors in the retail market and more aggressive formulary bid processes mean more margin pressure for the suppliers and SKU rationalization.
- Some manufacturers have stopped production on many unprofitable items.



DEA and regulatory pressures

- Manufacturing issues resulting in warning letters and/or regulatory actions.

Product Shortages

Issues beyond AmerisourceBergen's control



Fill rates for injectable items remain at all time lows due to manufacturing complexity, regulatory hurdles, profitability and scale of the market.



DEA regulations around yearly allotment of controlled substances dictating that we cannot order any additional quantities.



Generic Cliff – With fewer generic launches -- these manufacturers are examining their product portfolios and looking to eliminate less profitable or negative margin items.

Market Shortage Overview

What we are seeing

Generic Rx dollars on back-order have increased month over month worsening by 432% from April 2017 to September 2018.



Approximately 1/3 of our total Generics Rx inventory is on backorder.



The count of items on back-order has only doubled, indicating that less product is available on allocated and shortage products.



Injectable service levels have worsened dramatically since July 2018 from the high 60% range (very bad) to the low 50% (terrible).



While all AmerisourceBergen customers are feeling the effects of these shortages, health systems are the most adversely affected.

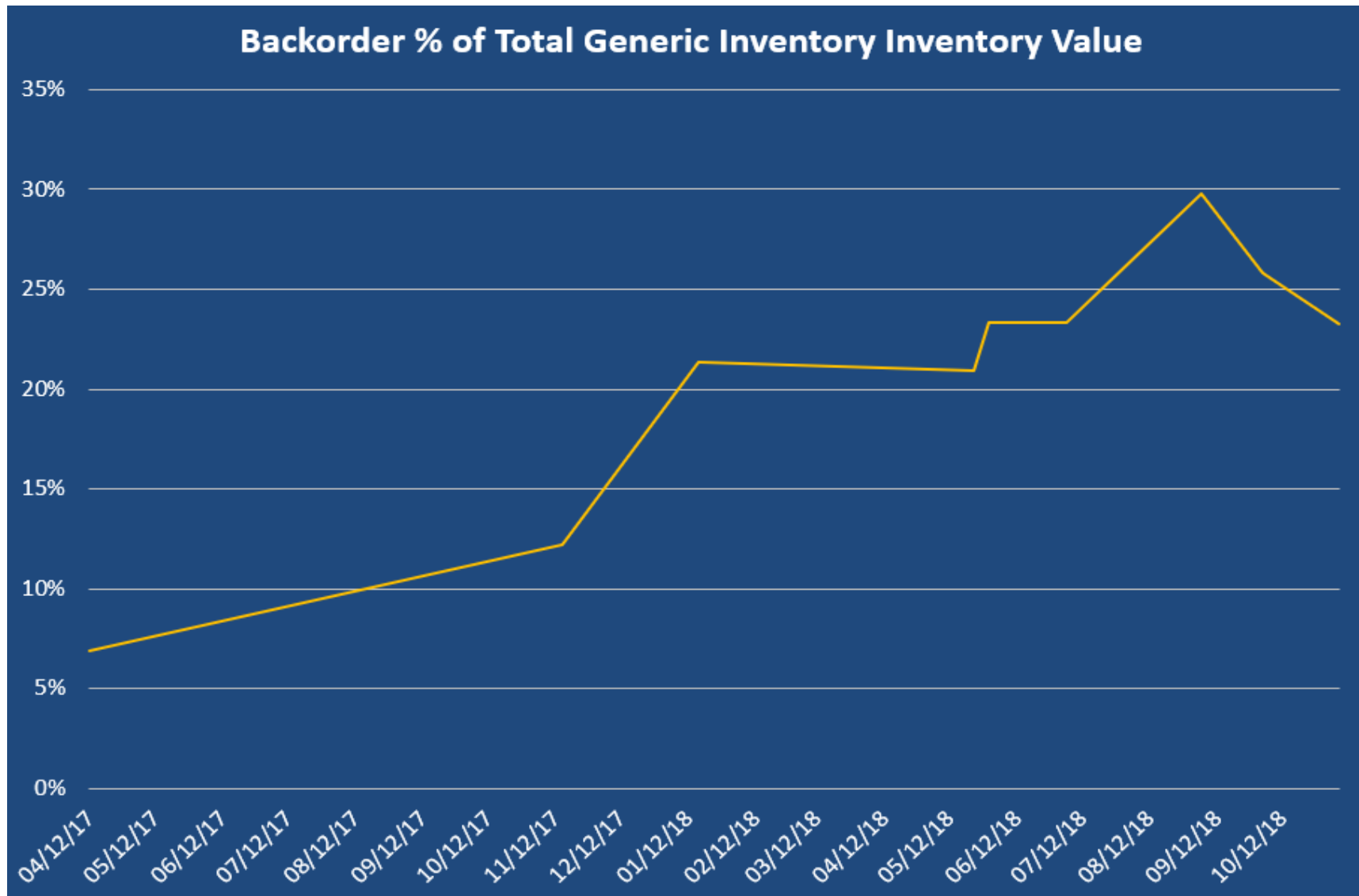


Due to market conditions, very irregular buying patterns have emerged.



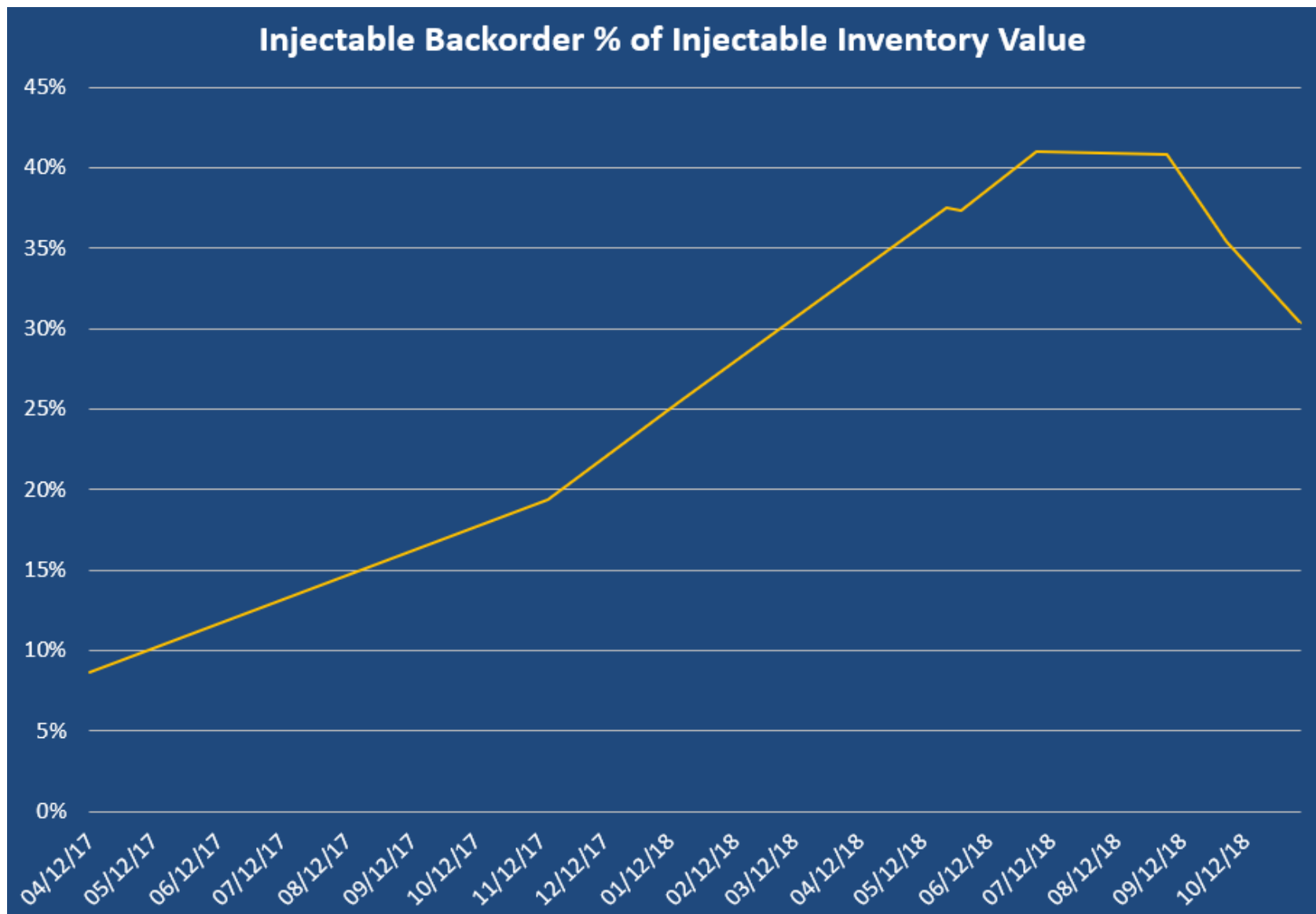
Value of Generic Back Orders Over Time

Generic Rx products – full-line distribution



Value of Generic Injectable Back Order Over Time

Generic Rx products – full-line distribution



5 Things We are Doing to Manage the Market Shortages

What you need to know

#1

Daily review of omits related to market shortage items for potential allocation.

#2

Systematically add days of inventory to items related to market-shortage items.

#3

Injectable supplier meetings to discuss strategies for recovery – the market shows little sign of improvement in the near term.

#4

Review of supplier allocation practices to ensure ABC gets its fair share at the right time.

#5

Internal transfer of market-shortage items to balance the DCs based on item recovery dates. Very limited opportunities due to severity of shortages.

AmerisourceBergen Market Shortage Allocations

Fair share program

- Intend to prevent hoarding behavior and provide access to products in short supply.
- Allocations may be limited to one item/supplier or the allocation may be applied to similar items across multiple vendors if the shortage is severe.
- Parameters are set to provide customers a minimum amount of product.
- Allocation settings are reviewed daily based on inventory levels and market intelligence.
- Historical allocation quantities may be adjusted to accommodate new or changing business.



Where knowledge,
reach and partnership
shape healthcare delivery.

Session 5: Drug Purchasing & Demand Challenges

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Manufacturers' Take: Economic Contributors to Drug Shortages

Marcie McClintic Coates, Head of Global Policy, Mylan

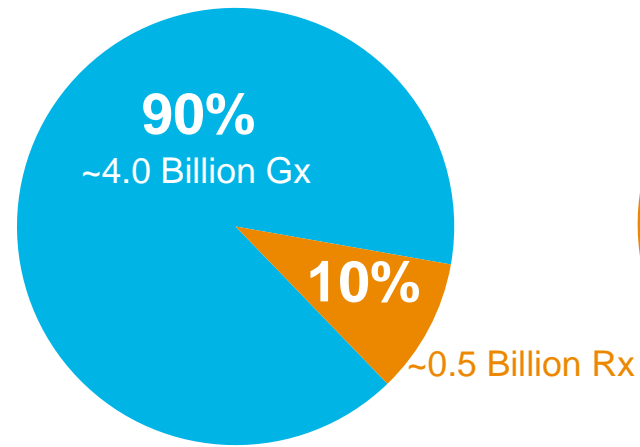
The following comments are made on behalf of the broader generic industry based on public information and are not specific to Mylan or a specific company.

Generics Drive Access and Savings for the U.S. System

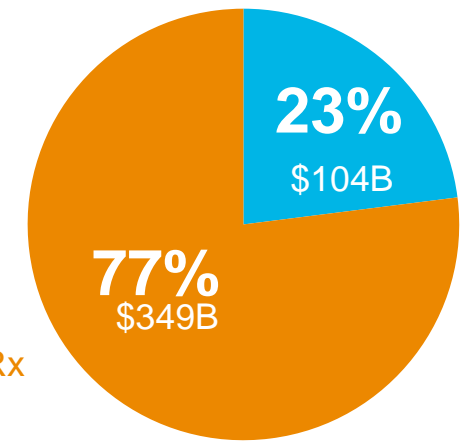
- Generics fill 90% of prescriptions yet only account for 23% of prescription spend²
- Top 100 Medicare generics by volume were sold by manufacturers for average of 10 cents/unit¹

Prescription Spend = \$453B²

Prescription Volume



Prescription Spend



● Generics

● Brand

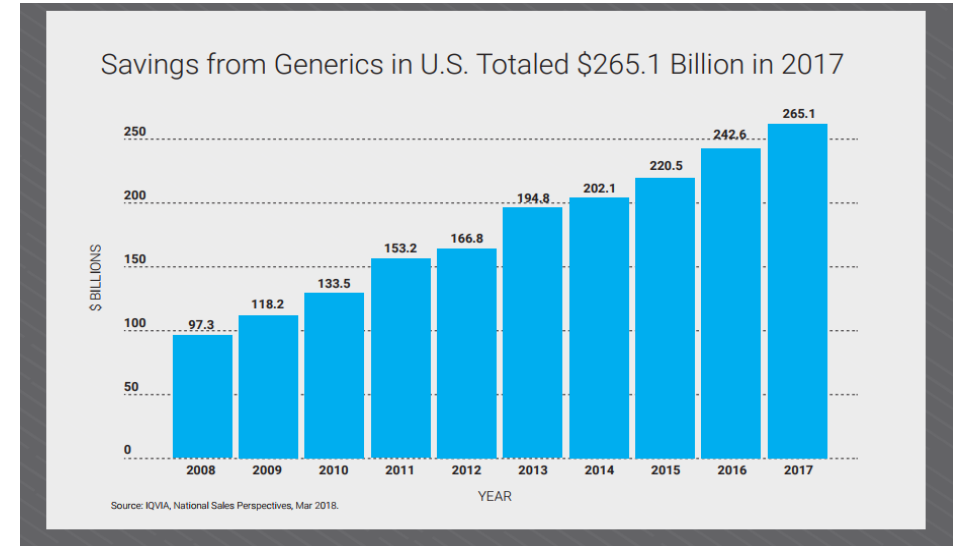
¹AAM white paper: "Ensuring the future of accessible medicines in the US" from February 2018:

²Total Prescription spend of \$453B for 2017 from IQVIA report (Medicine Use and Spending in the U.S.: A Review of 2017 and Outlook to 2022) from April 2018; Total number of prescriptions for 2017 from IQVIA prescription data; Breakdown of prescription and spend based on percentages from the AAM Annual Savings Report for 2017 (<https://accessiblemeds.org/resources/blog/2018-generic-drug-access-and-savings-report>).

Multiple pressures across generic industry...

Despite all of the value generics offer patients and payors...

Multiple pressures across industry are threatening future generic access and patient savings



Significant deflationary pressure on generics



Downward pricing pressure from buyer consolidation

FDA approvals up for 4th, 5th, 6th + generics

Medicaid CPI penalty for generics

State laws target generics

Less uptake for first/complex launches

200+ generic manufacturers
provide 90% of generic RXs to
3 buying groups

Generic drug prices
overall have decreased
15% each year for the
last 7 years, per IQVIA

Various factors drive up costs to operate



Increasing costs to manufacture, develop, comply and take on legal challenges

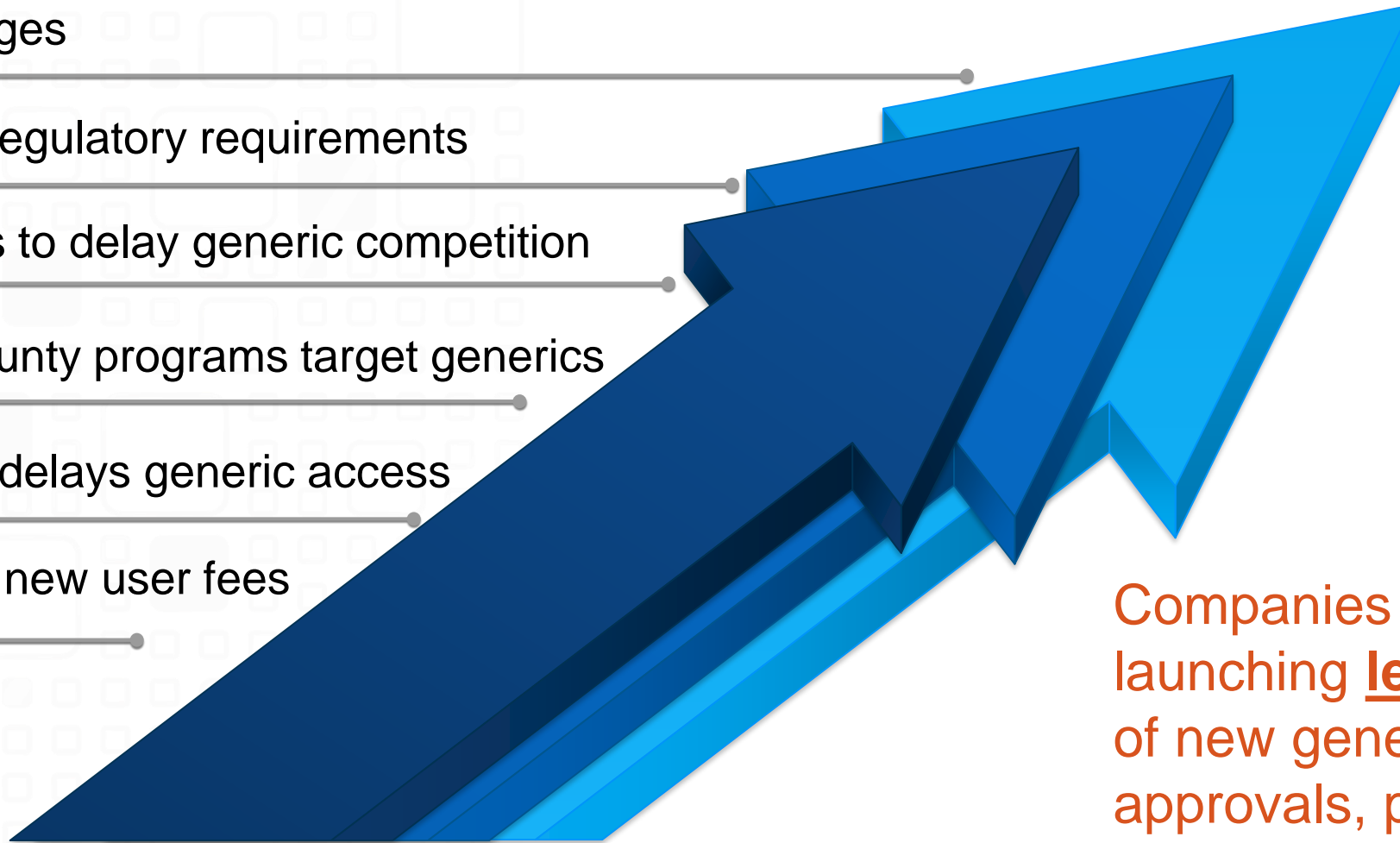
Heightened regulatory requirements

Brand tactics to delay generic competition

State and county programs target generics

Trade policy delays generic access

\$2 billion+ in new user fees



Companies are now launching less than 50% of new generic drug approvals, per AAM

Multiple pressures across generic industry...



“Right now our energy is focused primarily on **the U.S. oral solids business...It’s a unique situation. There are significant pricing declines.** At least in the medium term, we don’t see a shift to that situation, so we’re **assessing how best to optimize** that, given that dynamic.” (Comments made during Q4, 2017 earnings call before announcing proposed sale of core U.S. generics business in Sept. 2018) - *Novartis (Sandoz) Q4, 2017*

“In 2016 and 2017, we made very tough decisions that impacted our generics manufacturing network. **These manufacturing rationalizations over the past two years** have resulted in the sale of our Charlotte, North Carolina, facility and the closure later this year of our Huntsville, Alabama, location. In addition, **we discontinued a total of approximately 85 generic products that were not significant contributors**” - *Endo Q4 2017*

“[T]he overall situation on U.S. generics and pricing ...we had a consolidation on the buyers side and you’ve had a situation where suppliers may be accepting of lower prices because they used to have a healthy margin...**and if you take a race to the bottom on price...the only way out of that negative spiral is of course to stop it** ...without harming any patients...we’ve met with our major customers and supplied a list of products we specifically wanted to address. **About 80% of the product we will get out of** and they will move to other suppliers and about 20% of the product we will see an increase in price” - *Teva Q1 2018*

“On a year-over-year basis, generic revenue declined .. due largely...our **decision to proactively discontinue low-value products**..The pruning of our portfolio of low-value products accounted for approximately \$8 million of year-over-year decline in sales.” - *Amneal Q2, 2018*

“While rationalizing...**we have packed up the products where there are more than six, seven, eight, 10 competitors** so they’re not very likely from the drug shortage point of view...We have kept products if we are one of the two or one of the three suppliers we continue to supply.” - *Mylan Q2, 2018*



Finding a sustainable public policy solution ...

1. **Encourage access to more affordable medicine.** Generics should be encouraged through formulary and payment policy that drive maximum access. (Ie, Rescind 2016 CMS guidance that encourages generic and brands on mixed formulary tiers for Medicare Part D)
2. **Market dynamics.** Ensure buying approaches do not hinder sustainable competition and discourage future investment in complex products. Patients should get the benefit of price reductions and benefits from their insurance from first \$ spent particularly when patients have direct responsibility at pharmacy counter.
3. **Reduce regulatory burden and minimize costs.** Reduce manufacturer costs to operate by revisiting current policies (ie, generic taxes, CPI penalty etc). Scrutinize new proposed costs and legislation at federal and state levels to ensure these do not accelerate market exits
4. **Stop brand abuses that delay generic access.** Accelerate entry of first generics and prevent additional generic barriers like REMS abuse, IP abuse, etc

Session 5: Drug Purchasing & Demand Challenges

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DRUG PURCHASING & DEMAND CHALLENGES

Estay Greene, PharmD, MBA

Vice President of Pharmacy Services

Blue Cross and Blue Shield of North Carolina

PROPRIETARY & CONFIDENTIAL

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**BlueCross BlueShield
of North Carolina**

- Wholesale Acquisition Cost (WAC)
- Average Wholesale Price (AWP)
- Rebate
- Maximum Allowable Cost (MAC)
- Single-Source Generic
- Generic Effective Rate

- Education around safety and efficacy
- Two tier design
- Free samples and plan designs
- Dispense as Written penalties

Results of these programs and loss of patents have lead to generics accounting for the vast majority of prescriptions but a fraction of the cost.

MARKET CHANGES DUE TO SUCCESS



- Mitigation of prescription drug inflation
 - Low costs leading to access issues
- Less manufacturers for certain products
 - Topical example
- High single source generic costs
 - “Patent-Cliff” Strategies

- Monitoring of the supply chain which leads to reimbursement changes
 - MAC fluctuation
 - Member confusion
 - Pharmacy complaints
- Tamiflu shortage
 - Suspension impacted
 - Increased costs by up to 66%
- ADHD shortage
 - Generic manufacturers on backorder
 - Rebate available on brand and coverage has remained

- Less manufacturers for creams and ointments
 - Generic topical steroids to be similar to a branded product
 - Solutions:
 - Place on higher tier
 - Step Therapy
- Patent-Cliff
 - High cost for a single source generic so promote rebateable brand
 - Place the high cost generic in higher tier with step therapy
 - Place brand in a lower tier and link to generic price

ESOMEPRAZOLE LOCKOUT/NEXIUM PREFERRED

During Initial Coverage Phase						
	Gross Cost	Member Cost Share	Plan Liability	Pharma Gap Coverage Gap	Rebates	Net Plan Liability
Nexium	\$ 200.00	\$ 40.00	\$ 160.00	N/A	\$ 100.00	\$ 60.00
Single Source Esomeprazole	\$ 160.00	\$ 60.00	\$ 100.00	N/A	\$ 0.00	\$ 100.00
				Net Plan Savings		\$ 40.00
During Coverage Gap						
	Gross Cost	Member Cost Share	Plan Liability	Pharma Gap Coverage Gap	Rebates	Net Plan Liability
Nexium	\$ 200.00	\$ 95.00 (47.5%)	\$ 5.00 (2.5%)	\$ 100.00 (50%)	\$ 100.00	(\$ 95.00)
Single Source Esomeprazole	\$ 160.00	\$ 115.20 (72%)	\$ 44.80 (28%)	N/A	\$ 0.00	\$ 44.80
	Member Savings	\$20.20		Net Plan Savings		\$ 139.80

- Limited impact for RX benefit
- Inflation
- Biosimilars

Session 5: Drug Purchasing & Demand Challenges

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Session 6: Strategies & Next Steps to Reduce Adverse Clinical and Economic Consequences and Safeguard Public Health

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Healthcare Group Purchasing Organizations (GPOs):

Helping America's Hospitals, Long-Term Care Facilities, and Other Healthcare Providers Prevent and Mitigate Drug Shortages

Healthcare Supply Chain Association (HSCA)

Todd Ebert, R.Ph., President & CEO

November 27, 2018



Overview: GPOs are Critical Sourcing and Cost-Savings Partners to Hospitals, Long-Term Care, Other Providers

Healthcare group purchasing organizations (GPOs) leverage purchasing volume to **lower prices on healthcare products and services**, which lowers costs for patients, hospitals, payers, Medicare and Medicaid, and taxpayers. GPOs are on the front lines of healthcare, working alongside their healthcare provider partners **to help patients and combat difficult challenges** such as drug shortages, generic drug price spikes, natural disaster response, cybersecurity threats and more.

- The GPO mission is focused on **reducing healthcare costs, increasing competition and innovation, supporting transparency, and improving healthcare processes and outcomes.**
- Virtually **every hospital** and the vast majority of **non-acute care facilities** in the U.S. use one or more GPOs.
- The average GPO contract administrative fee is **1.22% to 2.25%**. *(Source: US Government Accountability Office)*
- GPOs are **competitive** and GPO membership is **completely voluntary** – providers can and do purchase off-contract, and GPO use is **driven by value provided.**
- In 2017, former FTC Chair Jon Leibowitz examined GPOs and found that **GPOs save money, operate in a competitive environment**, and that the **current GPO funding model supports lower costs and increased competition.**
- GPOs are **industry leaders in preventing and mitigating drug shortages** by working collaboratively with hospitals, manufacturers, distributors, Congress, FDA, HHS, and other stakeholders to ensure that providers and patients have access to the life-saving drugs they need.

GPOs are Taking Critical Steps to Help Healthcare Providers Mitigate Drug Shortages

Ongoing prescription drug shortages continue to jeopardize patient access to care. **GPOs are working vigorously with regulators, providers, manufacturers and distributors** to ensure a safe and reliable supply of product, and are **taking a number of innovative steps to help avoid generic drug price spikes** and mitigate or **eliminate prescription drug shortages**, including:

- **Tracking data on shortages** and strategize with member hospitals when there is potential for supply chain disruption;
- Helping hospitals **source and safely migrate to alternate products** when shortages arise;
- Helping hospitals lessen their exposure to shortages by **evaluating manufacturer quality and reliability when sourcing or awarding contracts**, and helping providers **establish best practice purchasing procedures**;
- Identifying **additional manufacturers for products in shortage** and helping bring them to market;
- Coordinating supply chain operations during **natural disasters and emergencies**;
- Engaging in policy advocacy to increase competition and supply, including **expedited FDA review, closing REMS loophole, swift uptake of biosimilars; annual production limits for injectable narcotics; and approved bulk substances for 503B compounding**.

GPOs Use Innovative Contract Provisions to Provide Predictability and Flexibility to Hospitals and Suppliers

GPOs utilize their unique line of sight to help prevent and mitigate shortages throughout the entire supply chain. **GPOs utilize a dynamic contracting process with hospitals and suppliers to ensure a sufficient supply of product**, helping to protect patient access to essential medications through a number of ways, such as:

- Including **failure-to-supply clauses in their supplier contracts** to incentivize suppliers to produce a sufficient amount of product;
- Working with suppliers **to identify anticipated provider purchase volume**, which **helps suppliers establish fair, volume-based price points** to continue producing supply;
- **Communicating provider needs in advance** so that manufacturers can plan their production capacity and avoid shortage situations;
- **Securing purchase volume and fair pricing for suppliers** in potential shortage situations to ensure **they have incentive to continuing producing** an adequate supply;
- Safeguarding the ability of **hospitals to contract with additional suppliers** for products in shortage;
- Ensuring contracts establish dynamic and open lines of communication with suppliers, as well as freedom to purchase from alternative sources, **to allow good faith collaboration and secondary suppliers to ensure adequate supply.**

GPOs Participate in Multi-Stakeholder, Provider-led Effort to Prevent and Address Critical Drug Shortages

HSCA participates in a **drug shortage working group** composed of leading healthcare provider organizations – including hospitals, health-system pharmacists, physicians, GPOs, and other supply chain stakeholders – to develop recommended policy proposals to help prevent and address drug shortages. **The group recently met with senior U.S. Food and Drug Administration (FDA) officials** to share information and assess potential solutions.

- The following are **policy recommendations to comprehensively address drug shortages** by expanding on the important work that FDA is already doing and providing FDA with the necessary authority, resources, and flexibility:
 - **Encourage early drug shortage alerts, ongoing multi-stakeholder communications, and inter-agency coordination** to mitigate risk and reduce the likelihood of shortage situations;
 - **Enhance transparency requirements for drug shortage information** to ensure that all stakeholders take the most effective steps toward addressing drug shortages;
 - Integrate **FDA drug shortage list** with ASHP’s national industry list;
 - **Strengthen Title X of FDASIA to require notifications** to include disclosure of the source of the disruption, extent of the shortage, and expected duration of the shortage;
 - Improve the regulatory violation process for current good manufacturing practices by **shortening turnaround times and improving and standardizing processes of FDA reviews to identify problems prior to shutting down facilities**;
 - Require manufacturers to **develop current drug shortage action plans** that help prevent, identify, and actively respond to drug shortage situations.

The Drug Shortage Working Group participants include:

*American College of Emergency Physicians
America’s Essential Hospitals
American Hospital Association
American Medical Association
American Society of Anesthesiologists
American Society of Clinical Oncology
American Society of Health-System Pharmacists
American Society for Parenteral and Enteral Nutrition
Children’s Hospital Association
Federation of American Hospitals
Healthcare Supply Chain Association*

Session 6: Strategies & Next Steps to Reduce Adverse Clinical and Economic Consequences and Safeguard Public Health

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The Management of Drug Shortages

Health Canada

November 27, 2018

YOUR HEALTH AND SAFETY... OUR PRIORITY.



Objectives

- Provide an overview of steps Health Canada has taken to facilitate a coordinated rigorous approach to drug shortages in Canada
- Provide details related to the Multi-Stakeholder Steering Committee on Drug Shortages
- Share information on the mandatory public reporting of drug shortages in Canada
- Highlight successes and current challenges

Background

In 2012, several drivers caused Health Canada to look at its role in the management of drug shortages...

- Drug shortages had become a complex, national and global problem and a serious, ongoing issue for Canada's health care system.
- In early 2012, a business decision by one of Canada's generic drug manufacturers instigated some of the largest drug shortages known in Canada's history sparking significant concern, and resulting in an Emergency Debate in the House of Commons and a Standing Committee on Health (HESA) report.

As a result, Health Canada worked with other key players to clearly define roles and responsibilities.

The Governance

- Health Canada, together with the Province of Alberta, launched a **Multi-Stakeholder Steering Committee on Drug Shortages (MSSC)** made up of government, industry and health care representatives, to work towards a more rigorous and coordinate approach to drug shortages.
- The MSSC is supported by the work of several groups
 - **Health Canada's Drug Shortages Unit** is responsible for: drug shortage case management; compliance verification and promotion in relation to mandatory reporting; and stakeholder engagement.
 - **The Provincial and Territorial Task Team on Drug Shortages** coordinates with the health system to confirm and assess shortages, notifies Health Canada when facilitation is needed and confirms and assesses shortage specifics with stakeholders.
 - **Federal/Provincial/Territorial Working Group** clarifies roles & responsibilities and develops process and tools.

MSSC Drug Shortage Tools

The MSSC has developed a number of key tools for stakeholders.

- **Protocol for the Notification and Communication of Drug Shortages:** Sets clear expectations in anticipation of, or in response to drug shortages.
- **Multi-Stakeholder Toolkit:** Describes the Canadian drug supply chain, clarifies roles and responsibilities of key players, and identifies the tools and strategies to address drug shortages.
- **Guidance Document to Mitigate Drug Shortages through Contracting and Procurement:** Outlines best practice contracting guidelines, procurement strategies and tools to address drug supply chain shortage vulnerabilities.
- **Preventing Drug Shortages: Identifying Risks and Strategies to Address Manufacturing-Related Drug Shortages in Canada:** Proposes strategies to reduce and prevent the manufacturing-related causes of drug shortages in Canada.

Public Notification of Drug Shortages

- On March 14, 2017 amendments to the *Food and Drug Regulations* came into force that make it mandatory for drug authorization holders to publicly report drug shortages and discontinuations to a third-party website.
- drugshortagescanada.ca was launched on March 14, 2017 and a mobile application is available for download.
- Under mandatory reporting, priorities include:
 - **Compliance Verification:** Verifying compliance with the regulations in response to signals and continued compliance promotion.
 - **Website Enhancements:** Identification, development and release of enhancements to the website.
 - **Data Visualization and Monitoring:** Increase transparency and monitoring through regular reporting of drug shortage and discontinuations stats.

Successes and Challenges

- Through the work of the MSSC, progress has been made in several key areas.
 - Multi-stakeholder collaboration on the identification of strategies to mitigate / prevent shortages
 - Clear roles, responsibilities and process
- Notification on drugshortagescanada.ca enables the drug supply chain and the healthcare system to respond appropriately to minimize impact.
- It is often difficult for Health Canada to acquire timely and accurate information on supply within the supply chain and healthcare system.
 - Collaboration on tools and process to assist with information gathering is ongoing.
- It is sometimes a challenge to encourage stakeholders to collaborate in managing a supply situation.
 - Stronger partnerships and engagement on issues through MSSC.

Thank you

Canada.ca

drugshortagescanada.ca

hc.drug.shortages-penurie.de.medicament.sc@canada.ca

Session 6: Strategies & Next Steps to Reduce Adverse Clinical and Economic Consequences and Safeguard Public Health

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Identifying “Essential” Drugs at Risk for Shortage

Ashley B. Boam, MSBE
Director

Office of Policy for Pharmaceutical Quality
CDER/Office of Pharmaceutical Quality

Points to Consider

- Goals
 - Develop a set of criteria that would readily allow a manufacturer to determine if a product is considered at risk
 - Consider using to identify eligibility for targeted FDA and other stakeholder actions to prevent or mitigate shortage
- Consider a variety of risk factors/vulnerabilities
 - National security
 - Product-related
 - Manufacturing facility-related
- Consider how application of this criteria could be integrated into current FDA processes and inform future FDA actions

Impact on National Security

- Vulnerability might be defined as drug products necessary under emergency conditions to mitigate an adverse impact on the U.S. public health, such that a shortage of these drug products could impact national security
- Drugs used in:
 - emergency response (i.e., supportive care)
 - response to specific chemical, biological and radiological/nuclear (CBRN) threats

Identifying Drugs Critical for National Security

Leverage existing resources:

- Products critical in emergency response – examples include:
 - [The Critical Commodities List](#) (2011)
 - [50 Drugs Every Emergency Physician Should Know” – American Academy of Emergency Medicine Resident and Student Association](#) (2015)
 - [Advanced Cardiac Life Support \(ACLS\) Crash Cart Supply Checklist](#) (2016)
 - [Emergency Drug Index – Mosby’s Paramedic Textbook, 4th Edition](#) (2013)
- Products critical in response to specific targeted threat agents – examples include:
 - [FDA Website: Emergency Preparedness](#) (Drugs) (2018)
 - [Strategic National Stockpile Formulary List](#) [non-public] (2018)
 - [HHS Chemical Hazards Emergency Medical Management \(CHEMM\) Antidotes for chemical threats](#) (2017)
 - [HHS Radiation Emergency Medical Management \(REMM\) Antidotes for radiation threats](#) (2018)

Product-Related Risk Factors

- Identifying “medically necessary,” “essential,” “important” drugs
 - Many organizations have a definition (WHO, FDA/CDER, etc.)
 - For this purpose, consider criteria from section 506C of the FD&C Act associated with shortage notification requirements:
 - Life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery
- Known risk factors for shortage
 - History on the FDA drug shortage list (see FDA’s [drug shortage database](#))

Lookback Period	Number and Percent of Drugs* on the FDA DS List	1-Year Shortage Rate for Drugs on the FDA DS List	1-Year Shortage Rate for Drugs Not on the FDA DS List
5 Years	157 (7.8%)	15.3%	1.6%
4 Years	118 (5.8%)	17.8%	1.7%
3 Years	81 (4.0%)	19.8%	1.9%
2 Years	51 (2.5%)	19.6%	2.2%
1 Year	23 (1.1%)	8.7%	2.6%

*As of August 3, 2018 for drug products that were on the market as of July 2017, limiting to those products that were not initially in shortage at the time of the assessment.

Manufacturing Facility-Related Vulnerabilities

- Component supply chain with limited capacity
 - Single Active Pharmaceutical Ingredient facility
 - Single Finished Dosage Form facility
- Significant quality issues at a manufacturing facility (e.g., violative inspection history), especially where that facility is the only one approved or qualified to perform an essential operation

Other Factors Considered

- Market share
 - Analysis of currently marketed products indicates not discriminatory (many marketed products are sole source)
- Volume
 - Hard to determine given variation in unit dose (bottle of liquid, single vial, tablets, etc.) and administration (one-time, chronic)
 - Low volume drugs can still be critical to have available for the patients that need them
- Environmental factors (e.g., fire, weather, conflict)
 - Difficult to define sufficiently for self-identification
 - Can be challenging to predict

Issues for Ongoing Work

- Fit for Purpose
 - Further analysis of predictive value of parameters needed
- Process
 - Refining criteria includes a discussion of how the criteria will be used and maintained
 - If adopted would need to be integrated into FDA processes

Session 6: Strategies & Next Steps to Reduce Adverse Clinical and Economic Consequences and Safeguard Public Health

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Session 7: Public Comment Period

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Identifying the Root Causes of Drug Shortages and Finding Enduring Solutions

Washington Marriott Metro Center

November 27, 2018

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