Medication Shortages

Why They Happen and What to Do
Agenda

• Introduction

• Speakers
  – Maryann E. Mazer-Amirshahi, PharmD, MD, MPH
  – Eric Lavonas, MD
  – Michael R. Cohen, RPh, MS, ScD (hon.), DPS (hon.)

• Q & A

WebEx Problems: 1-800-985-9074 and then press 2 to reach technical assistance
Asking Questions

The question and answer period of the webinar will be interactive. We have scheduled approximately 10 minutes for questions at the end of the presentation. To submit a question, simply type your question in the designated area in the right hand column of the screen at any time during the webinar. If your question is not selected to be answered during the webinar, you can re-submit your question via email to info@urgentmatters.org
Dr. Maryann Amirshahi is an emergency medicine physician at MedStar Washington Hospital Center. Dr. Amirshahi completed her PharmD at the University of the Sciences in Philadelphia, followed by medical school at Temple University. She completed her emergency medicine residency at the Hospital of the University of Pennsylvania, medical toxicology fellowship at the George Washington University, and clinical pharmacology fellowship at Children’s National Medical Center. She also received an MPH from the George Washington University focusing on environmental and occupational health. She is board certified in emergency medicine and medical toxicology. She serves as a toxicology consultant for the Mid-Atlantic Center for Children’s Health and the Environment and the National Capital Poison Center. Her research interests include medication safety, medical toxicology, and prescription drug abuse.
Speakers

Dr. Eric Lavonas is Associate Director of the Rocky Mountain Poison and Drug Center in Denver, Colorado. A graduate of the University of Rochester and the SUNY Upstate Medical University, Dr. Lavonas completed emergency medicine residency training at Methodist Hospital of Indiana and medical toxicology fellowship at Carolinas Medical Center. Dr. Lavonas is Program Director of the Medical Toxicology Fellowship at the RMPDC, Chair of the Pharmacy and Therapeutics Committee for the Denver Health and Hospital Authority, Physician Quality Officer for Drug and Device Safety for the DHHA, and Associate Professor of Emergency Medicine at the University of Colorado School of Medicine. His research interests include carbon monoxide poisoning, envenomations, medication safety, and cost/quality relationships in hospital pharmacy operations. When not at work, he can be found chasing his children through the great Colorado outdoors.
Speakers

Michael R. Cohen is president of The Institute for Safe Medication Practices, a non-profit healthcare organization that specializes in understanding the causes of medication errors and providing error-reduction strategies to the healthcare community, policy makers, and the public. He is editor of the textbook, Medication Errors and serves as co-editor of the ISMP Medication Safety Alert! publications that reach over 2 million health professionals and consumers in the US, as well as regulatory authorities and others in over 30 foreign countries. He is editor for the website, consumermedsafety.org and writes a guest column called Check-Up that appears weekly on the Philadelphia Inquirer website. Dr. Cohen previously served as Vice Chair of the Patient Safety Advisory Group for the Joint Commission and currently serves as a consultant to FDA. In 2005 he was recognized as a MacArthur Fellow by the John D. and Catherine T. MacArthur Foundation. In 2008 The Joint Commission and National Quality Forum awarded Dr. Cohen the prestigious John M. Eisenberg Patient Safety and Quality Award in recognition of his life-long professional commitment to promoting safe medication use and a safe medication delivery system.
Objectives

- Understand the scope of the problem
- Describe why shortages occur
- Implications for the emergency department
- Discuss potential mitigation strategies
Definitions

• Total supply of all clinically interchangeable versions of an FDA-regulated drug product is inadequate to meet the projected demand at the user level

• A supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent
Historical Perspective

• Dramatic increase in drug shortages over past decade
• Shortages impact primarily generic injectables
• Increased duration and frequency
• Multiple therapeutic alternatives impacted
• Increased impact on patient care
Why Drug Shortages Occur

• Quality issues
• Manufacturing landscape
• Compliance with good manufacturing practices
• Market factors, pricing structure
Why Drug Shortages Occur

• Increased demand
• Raw materials
• Shipping delays
• FDA review of older medications
## ED Medications Impacted

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Agents Involved</th>
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<tbody>
<tr>
<td>Analgesics</td>
<td>Fentanyl, Hydromorphone, Ketorolac, Morphine</td>
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<td>Antiemetics</td>
<td>Metoclopramide, Ondansetron, Prochlorperazine, Promethazine</td>
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<td>Electrolyte Solutions</td>
<td>Calcium chloride, Calcium gluconate, Magnesium sulfate, Potassium chloride, Sodium bicarbonate</td>
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ED Medications Impacted

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<thead>
<tr>
<th>Medication Class</th>
<th>Agents Involved</th>
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<tbody>
<tr>
<td>Local Anesthetics</td>
<td>Bupivacaine, Lidocaine, Procaine, Tetracaine</td>
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<td>Rapid Sequence Induction</td>
<td>Etomidate, Propofol, Succinylcholine</td>
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<td>Sedatives</td>
<td>Diazepam, Lorazepam, Midazolam, Pentobarbital, Phenobarbital</td>
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Institutional Response to Shortages
Denver Health

- 532-bed academic level one trauma center
  - 121,623 ED/psych ED/urgent care visits
  - 24,077 admissions
  - Medical & surgical specialty clinics
- 8 FQHCs, 16 school-based health clinics: 443K encounters (+ correctional care)
- Paramedic division: 95,244 encounters
- Denver Public Health
- Denver CARES – substance abuse treatment
- Rocky Mountain Poison and Drug Center
Life Cycle of a Shortage

• Discover (“Surprise!”)
• Search for alternate supply
• Assess inventory, burn rate, and alternatives
• Plan and intervene
  – Redistribute, redirect, reformulate, communicate
• Track
• Resolve
### Medication Shortages

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Dosage Form(s)</th>
<th>Concentrations Affected</th>
<th>Anticipated Resolution Date</th>
<th>Reason Shorted</th>
<th>Total Quantity at DH</th>
<th>Estimated Daily Utilization</th>
<th>Contingency Plan / Therapeutic Substitution</th>
<th>Hidden in CPOE</th>
<th>Pharmacy System Alert Activated</th>
<th>Pharmacy Discussion / Comments</th>
<th>Attachments</th>
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<tbody>
<tr>
<td>ACETYL-CYSTEINE 10% VIALS OF ANY VOLUME</td>
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<td>CAFFEINE/SODIUM BENZOATE</td>
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<td>CALCIUM CHLORIDE 10% VIALS</td>
<td>IM/IV</td>
<td>All</td>
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<td>MARKET SHORTAGE ITEM</td>
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<td>0 in pyxis</td>
<td>0 vials IN PHARMACY</td>
<td>NOT AVAILABLE AT ABC</td>
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<td>CEFOTETAN 2GM VIALS</td>
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<td>HYDROXYZINE 50MG/ML VIALS</td>
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<td>METRONIDAZOLE IVPB 500MG BAGS</td>
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<td>NALBUPHINE 10MG/ML AMP. 10X1ML</td>
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<td>SODIUM PHOSPHATE</td>
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<td>VECCORONIUM 10MG VIALS</td>
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ASHP vs FDA

www.ashp.org/drugshortages

• 248 current shortages

www.accessdata.fda.gov/scripts/drugshortages/default.cfm

• 73 current “critical” shortages
Temporizing Measures

- Repackaging bulk → unit of use
- Alternate formulations with POC messaging
- Compounding
- Redistribution of supply
- Measures to decrease utilization
  - Messaging to providers
  - Changes to standard order sets
  - Autosubstitution
Recent Examples: ED High Impact

- Epinephrine 1:10,000 syringes
- Sodium bicarbonate syringes
- Calcium chloride / calcium gluconate
- Antiemetics
  - Metoclopramide, prochlorperazine, ondansetron
- Sedatives
  - Etomidate, propofol
- Mannitol 20%
- Droperidol
- Paralytic agents
Other Recent Examples

- Magnesium sulfate
- Fentanyl amps
- Papaverine
- Injectable phosphates
- Cephalexin
- Chemo agents: vinblastine, etoposide, doxorubicin, 5-FU, paclitaxel, (leucovorin)
Impact

• Cost
  – Personnel: ~ 0.5 FTE, + leadership
  – Drug costs hard to track

• Safety: No known patient harm events
  – Several reported near-misses
  – Complete outages of some drugs

• Some examples where waste was eliminated and care was improved
EMS Faces Greater Challenges

• Difficulty centralizing inventory
  – Controlled substances: Difficulty moving supply
• Less training on alternative therapies
• Multi-agency protocols limit flexibility
• Environment of care
• Nobody to double-check drug/dose
What Keeps Me Up at Night

• Critical medication errors
• Outages of drugs for which there is no good clinical alternative
• Compounding: Errors, breaches in sterility
• Inability to complete cycles of chemotherapy
• Opioid diversion
Organizational Lessons Learned

- Labor-intensive & expensive
- Leadership + communication + Lean
- High risk for error
  - Everywhere, and especially EMS
  - Opioids: Risk of diversion
- Best results in departments with strong clinical leadership
- Can’t fix everything
ISMP National Medication Errors Reporting

Operated by the Institute for Safe Medication Practices
www.ismp.org

ISMP is a federally certified patient safety organization (PSO)
Drug Shortages-Serious and Widespread Problem

When vital drugs run out, patients pay the price

Drug shortages affect local hospitals

Drug Shortages Distress Hospitals

USMP/MG1/14-0122 4/14
What we hear from the field

• Clinical effects
  – Less than optimal treatment options
  – Compromised or delayed medical treatment
  – Medication errors and adverse patient outcomes
  – Rationing, restrictions on use

• Financial effects
  – Higher alternative acquisition costs
  – Reallocation and/or addition of staff
  – Management of adverse events

• Emotional effects
  – Strained professional relationships
Additional fall out

• Delay in updating computer systems/bar-coding systems with alternative products and strengths
• Stock management, education and communication requirements
  – Possible dispensing and administration errors
• Using opened medications past safe period of time
• Using expired medications
• Reliance on outsourcing to compounding pharmacies
• Purchasing unapproved injectable medications from unlicensed sources
Factors leading to shortages

• Manufacturing remediation due to quality issues
  – Particulate matter is a prominent cause
  – Manufacturing failures increase demand for supply from another company
  – Other company not able to keep up with demand. Multiple products on single line; working at capacity

• Active pharmaceutical ingredient may be available from a sole source
Factors leading to shortages

• Generic injectable medications produced by few companies (often 2 at most)
  – Teva, Hospira and Bedford Labs produced 71% of sterile injectables between 2001 and February 2012 (Tufts research).
  – American Regent shut down – Trace elements, selenium, zinc sulfate, potassium and sodium phosphate, calcium gluconate and calcium chloride
• Hoarding (company will allocate supplies for known shortages)
• FDA actions
New Shortages by Year
January 2001 to March 31, 2014

Note: Each column represents the number of new shortages identified during that year.
University of Utah Drug Information Service
Erin.Fox@hsc.utah.edu, Twitter: @foxerinr
Active Drug Shortages by Quarter

Note: Each column represents the number of active shortages at the end of each quarter.

University of Utah Drug Information Service

Erin.Fox@hsc.utah.edu  Twitter: @foxerinr
Active Shortages
Top 5 Drug Classes

Active Shortages 3/14

- Antimicrobials: 36
- Chemotherapy: 33
- Cardiovascular: 24
- CNS: 43
- E-Lytes: 33

University of Utah Drug Information Service
Common Drug Classes in Short Supply – 2010 - 2014

University of Utah Drug Information Service
Shortages of Basics

• Frequent fliers - 10 medications short > 50 times between 2001 and 2013
  – Dextrose, diazepam, epinephrine, fentanyl, lorazepam, morphine, ondansetron, nalbuphine, naloxone, promethazine

• July 7, 2014 - FDA Drug Shortages: New and Updated
  – Atropine Sulfate Injection (Currently in Shortage)
  – Bumetanide Injection (Currently in Shortage)
  – Fentanyl Citrate (Sublimaze) Injection (Currently in Shortage)
  – Lorazepam (Ativan) Injection (Currently in Shortage)
  – Morphine Sulfate (Astramorph PF, Duramorph, Infumorph) Injection (Preservative Free) (Currently in Shortage)
  – Ondansetron (Zofran) Injection (Currently in Shortage)
  – Potassium Acetate Injection, USP 2mEq/mL (Resolved)
  – Procainamide HCL Injection (Resolved)
  – Sufentanil Citrate (Sufenta) Injection (Currently in Shortage)
What’s New - The Food and Drug Administration Safety and Innovation Act (FDASIA) - July 2012

- Companies must notify FDA of planned meaningful production disruptions or discontinuations (6 months required)
  - Prior, notification applied only to companies that were the sole manufacturer of a critical FDA-approved drug product
  - Now includes temporary/intermittent breaks in manufacturing

- Now includes biologic products
- FDA may expedite new application review
- FDA required to establish drug shortages task force to develop, publish, and implement a strategic plan for enhancing FDA’s response to preventing and mitigating drug shortages
What’s New

– FDA - Drug Shortage Task Force

– Strategic plan
  • Enhanced coordination, communication, decision-making (internal)
  • Enhanced communication with field (external)
  • Evaluation of effect on research/clinical trials
  • Evaluation of “qualified manufacturing partner program”

– Staffing in FDA’s Drug Shortages section up to 11 FTE from 4 FTE

– Increased interest from new manufacturing firms
Improvements Seen

• FDA can work more closely with manufacturers to restore production
• Early notification from manufacturers about possible shortages, as requested in the Since Executive Order - a 6-fold increase in notifications to FDA
• Increased notifications and allocation of additional FDA resources have resulted in real progress in addressing shortages
• FDA helped prevent 195 drug shortages in 2011 and 282 drug shortages in 2012
FDA actions to address drug shortages

- Focus and prioritize efforts based on medical necessity
- Expedited review of regulatory submissions
- Expedited inspections
- Expedited importation
- Exercising enforcement discretion
- Request increased production
- Identifying alternative manufacturing sources and overseas suppliers
- Extending expiration dates based on stability data (working with manufacturer)
- Working with the manufacturer to resolve the underlying cause of the shortage
Drug Quality and Security Act of 2013

• Source of drugs in short supply?
• New section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
  – Specifies requirements for registration as an outsourcer
• Outsourcers exempt from FDA approval requirements (NDA or ANDA) and certain labeling requirements required of traditional manufacturers
• Must comply with 503b labeling requirements
  – Must comply with CGMP requirements
  – To compound something in short supply, must be on FDA list of approved ingredients
Drug Quality and Security Act of 2013

- Inspected by FDA according to a risk-based schedule (defined in Act)
- Must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound
- FDA Commissioner: “If compounders register with the FDA as outsourcing facilities, hospitals and other health care providers can provide their patients with drugs that were compounded in outsourcing facilities that are subject to CGMP requirements and federal oversight”
The goals of the summit were to:

• Discuss the scope and causes of drug shortages
• Shed light on the harm to patients that is occurring due to drug shortages
• Discuss the potential need for changes in public policy and stakeholder practices to prevent patient harm from shortages
• Develop an assertive action plan that reflects the recommendations and intent of stakeholders to work together to stop patient harm and disruptions in patient care caused by drug shortages
Summit – April 2013

• April 2013- Reconvened with manufacturers on April 18, 2013 to address why more change has not been realized

ISMP: Institute for Safe Medication Practices
ASHP: American Society of Health-System Pharmacists
ASCO: American Society of Clinical Oncology
ASA: American Society of Anesthesiologists
AHA: American Hospital Association
A.S.P.E.N.: American Society Parenteral and Enteral Nutrition
Topics from the Joint Meeting

• “Essential drug” list – drugs no one should ever run out of essential nutritionals – e.g., phosphate injection, trace elements, calcium, etc.

• BARDA (Biomedical Advanced Research and Development Authority) system for stockpiling
  – Stockpiling manufacturing capacity, not drugs

• Explore corporate tax credits for firms that invest in quality

• Greater use of extending expiration dates by FDA and company. Manufacturer must notify FDA and show data for unreleased product but FDA will step up requests for companies to extend dating of product already in the field. Difficult to extend when out of company control
• The 2014 Drug Shortages Summit will bring together provider organizations, pharmaceutical manufacturers, regulators, and other experts to discuss the drivers of ongoing drug shortages and examine solutions. Specific objectives of the meeting are to:
  • Identify ongoing manufacturing and production factors that affect drug shortages, and discuss strategies to address these factors;
  • Examine incentive programs that might address underlying economic factors in drug shortages, and discuss their merits
  • Identify additional strategies to address drug shortages, including contracting strategies and unit-of-use packaging.
  • Proceedings will be issued following the meeting.
GAO Reports

• 2011 - Strengthen FDA’s ability to respond
  – Congress should require manufacturers to report to FDA
  – FDA should enhance ability to respond

• 2014 – Public health threat continues
  – FDA is working to prevent shortages
  – FDA should enhance data analysis to focus on early identification of risk factors

www.gao.gov/products/GAO-12-315T

www.gao.gov/products/GAO-14-194
AHA wants FDA to address IV fluids shortage

By Virgil Dickson
Posted: March 21, 2014 - 2:30 pm ET

Nationwide IV Fluid Shortage Threatens Care

ONLINE FIRST

Bridget M. Kuehn, MSJ

JAMA. Published online April 23, 2014. doi:10.1001/jama.2014.3647

Rationing Salt Water — Disaster Planning and Daily Care Delivery

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

Journal Watch

Saline from Spain and Norway to Help Alleviate Shortage

To Ease IV Fluid Shortage, FDA Allows Baxter to Import from Spain

BY BRIDGET M. KUEHN on MAY 5, 2014
IV Fluids Shortage

- 3 suppliers
- All suppliers state “increased demand”
- Real reason behind the increased demand is unclear
- Rolling shortages, unclear allocations (expect problems through summer?)
  - Available fluid type, volume will vary
  - Imported saline available, access difficult, costs prohibitive
Unique Shortage

• Past shortages of IV fluids, but not all suppliers, all products at once!
• IV fluids are both a supply and a treatment
• Impacts large numbers of patients whether they are hospitalized, receiving dialysis or an infusion, or undergoing a procedure
Example of Errors/Adverse Outcomes

- **Sodium Phosphate**
  1) **Hypophosphatemia**
     - Substituted oral product, causing delay of correction of low serum phosphate
     - Patient vomited oral product and required transfer due to severe hypophosphatemia
     - Adult deficiencies because only providing sodium phosphate in infant PN
     - Infants developed bone fractures
  2) **Hyperkalemia**
     - Had to use potassium phosphate in patients with already high serum potassium levels, renal patients, infants (also contains more aluminum which is neurotoxic, especially to preterm infants)
     - Too rapid infusion rate of potassium component of potassium phosphate
  3) **Hypercalcemia**
     - In neonates due to inadequate phosphorous to balance calcium in PN
  4) **Dosing errors**
     - Calculation errors glycerophosphate conversion, concentration differences)
     - Mix-ups between potassium and sodium phosphate
Pros and Cons of Importation

**Pros**
- Very helpful for specific drugs
- Much needed as a back-up plan
- Helpful despite unanswered questions in terms of safety
- Would not have been able to treat critically ill patients without imported drugs

**Cons**
- Presents issues with drug files, interaction checking, barcode scanning
- Need stability information for products to be useful for home use
- Cost prohibitive
- Not timely enough to meet patient needs; shortage improved before products available
- Would need more similar products to be most helpful (trace elements)
- Package type and labeling precludes use in an accustomed manner
- Shorter stability, waste issues with imported drugs
Making a Difference?

+ FDA prevents hundreds of shortages
+ More suppliers choose to work with FDA early
+ Decreased rate of new shortages

– Ongoing shortages not resolving
– Manufacturing problems
– Continued patient impact
It may get worse before it gets better....

- FDA increasing inspectors in India, China
  - Many generic houses moving production
  - Import bans
  - Falsified data, shoddy product
- No new large suppliers to replace permanent closures
- Focus on biosimilars
- Who will make the basics that we need?
But there is some hope

- Trend of decreasing new shortages is real
- Some manufacturers are stepping up, new production models for quality
- Action is moving towards prevention, early identification of manufacturing issues
ISMP National Medication Errors Reporting

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