Drug Shortages: A Closer Look at a Growing Public Health Concern

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Sponsor:
ABA Health Law Section Public Health & Policy Interest Group
Panelists:
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Health Care
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University of Michigan Healthcare System
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Commissioner, US Food and Drug
Administration

Moderator:
Deirdre Golden, MD, MS, JD, LLM,
University of Michigan School of Public Health
University of Utah Perspective

Erin R. Fox, PharmD, FASHP
Director, Drug Information Service, University of Utah Hospitals & Clinics
Associate Professor (Adjunct), Department of Pharmacotherapy, University of Utah College of Pharmacy
National Shortages and University of Utah

• UU DIS provides drug shortage content to Novation and ASHP

• Public website at www.ashp.org/shortage
  – Partners since 2001
  – Receive voluntary reports submitted via web
  – Collaboration is key - FDA, ASHP, Novation, UU DIS
Website Differences?

• ASHP / Novation
• Drugs impacting clinical practice (includes biologics, devices, etc)
• How to access
• Alternatives
• Contract information (Novation only)

• FDA
• Medically necessary drugs
• Information from manufacturer
## Alternatives

<table>
<thead>
<tr>
<th>Use</th>
<th>Alternative Regimen</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Analgesia in Labor and Delivery</strong></td>
<td><strong>Epidural</strong>&lt;br&gt;Sufentanil: 10-15 mcg with 10 mL bupivacaine (+/- epinephrine).&lt;br&gt;Repeat up to 3 doses no less than 1 hour apart. 6,12,17&lt;br&gt;Intravenous&lt;br&gt;Butorphanol: 1-2 mg every 3-4 hours as needed 12,18,19&lt;br&gt;Nalbuphine: 5-10 mg every 3-6 hours as needed 12,18,20&lt;br&gt;Patient controlled intravenous analgesia&lt;br&gt;Remifentanil: 0.2-0.93 mcg/kg bolus dosing with 1-3 minute lockout intervals. 18,21&lt;br&gt;Spinal Epidural&lt;br&gt;Sufentanil: 10-20 mcg 12</td>
<td>Remifentanil is not given intraspinally because it contains glycine. 13&lt;br&gt;Optimal dosing has not been established for remifentanil in labor analgesia 21</td>
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<td><strong>Sedation for Procedures</strong></td>
<td><strong>Propofol</strong>:&lt;br&gt;Monitored Anesthesia Care (labeled dose): 0.5 mg/kg over 3-5 minutes followed by infusion at 1.5-4.5 mg/kg/hr&lt;br&gt;Procedural sedation (unlabeled): 1 mg/kg followed by supplemental doses of 0.5 mg/kg every 3 minutes as needed in combination with benzodiazepine: 17&lt;br&gt;Fentanyl 25-50 mcg intravenous, repeat every 3-5 minutes as needed. Maximum dose: 500 mcg in 4 hours.&lt;br&gt;Morphine 1-2 mg intravenous, repeat every 3-5 minutes as needed. Maximum dose 20 mg.</td>
<td>Intravenous medications used for procedural sedation include propofol, fospropofol, methohexital, dexmedetomidine, and benzodiazepines (eg, midazolam, lorazepam) in combination with opioids (eg, fentanyl, morphine).&lt;br&gt;Choice of agent may be based on procedure to be performed and pharmacokinetic properties, such as onset and duration of analgesia, of individual opiate agonists. 23</td>
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Prevalence

• Point in time prevalence study
• June 1, 2011 (n = 238 shortages)
  – 11% of all FDA approved agents marketed in the US were short.
  – 23.1% of injectable FDA approved agents were short.
  – 27 / 238 shortages were antineoplastic agents (11.3%)

National Drug Shortages
New Shortages by Year
January 2001 to September 30, 2012

Note: Each column represents the # of new shortages identified during that year
University of Utah Drug Information Service
National Drug Shortages – Active Shortages by Quarter

Note: Each column represents the # of active shortages at the end of each quarter. Q1-10 = Jan-Mar 2010. University of Utah Drug Information Service
Reasons for Shortages: Sterile Injectables

• Few suppliers
  – Majority of the market supplied by 7 manufacturers
  – Contract manufacturers – the company that supplies the product didn’t always manufacture

• Lack of redundancy
  – Multiple products made on existing manufacturing lines
  – No resiliency in process for glitches

• Complex manufacturing process
  – No simple fixes for quality problems
  – Problems typically affect multiple products

• Economics

National Shortages vs. Chemotherapy Shortages
New Shortages by Year
January 2001 to December 31, 2011

University of Utah Drug Information Service
April 2010

- Irvine facility closes.
- Impacts 49 drugs – 18 are chemotherapy.
- Manufacturing problems at the same time at other facilities.
- Manufacturing resumed spring of 2011, but still not up to former capacity for some agents.
Safety

• Clinician survey data show clear harm
• Alternative agents – errors due to different strengths or doses, efficacy differences, lack of data
• No drug available – delays in cancer treatments, no treatment for seizures, long term vitamin deficiency

ISMP Medication Safety Alert! April 19, 2012
http://www.nutritioncare.org/News/Industry_and_Product_News/A_S_P_E_N__Releases_Results_of_Multivitamin_Shortage_Survey/
University of Michigan ASHP Survey

- 32% of responders reallocated existing staff to manage shortages
- Labor costs to manage drug shortages - $216 million for all health systems nationwide

AJHP. 2011; 68:e13-21
Government Action

• Executive Order – 10/31/11
• FDA Interim Final Rule – December 2011
• Senate and House Bills provide basis for language included in FDASIA / PDUFA
• FDASIA signed July 9, 2012

Predictions for 2012

• FDA prevention strategies decrease rate of new shortages
• Manufacturing problems continue (expect increase or same rate of quality related MedWatch reports)
• 3 to 4 years out from improved or expanded facilities
• Continued patient/clinician/facility impact
Thank you!

• ASHP Drug Shortage Resource Center
  www.ashp.org/shortage

• Contact Information
  Erin.Fox@hsc.utah.edu
  801-587-3621
A Practicing Physician’s Perspective

Grant M. Greenberg, MD, MHSA, MA
Assistant Professor, Department of Family Medicine and Medical Director, Chelsea Health Center, University of Michigan Health System
Quick Poll of the Audience

• Have you or someone you know been affected by an UNEXPECTED shortage after receiving a prescription medication?

• If yes, did the alternative create either increased cost, delays in care, or unexpected side effects?
Increased Costs: “Hidden”

• Higher co-pay for branded medication
• Lower compliance coupled with increased cost
• Lower efficacy of alternate rx options
• Uncompensated Health Care Professional Office Administrative Costs
  – Prior authorizations
  – Phone “tag”
Treatment Delay

• When do we find out about a shortage?
• How rapidly does a message from a pharmacy or patient get to the ordering Health Care Professional?
• How often does this message contain all the information needed to make an alternative rx at a glance?
Increase risk for medication errors

• Physicians are creatures of habit.

• We are reluctant to stray from what we know works, and what we are familiar with.

• We keep abreast of what we commonly manage, and practice within the scope of our comfort zone

• Entering into a unexpected, unplanned, potentially unfamiliar situation…
Case Discussions
Thank you!

• Contact Information
  ggreenbe@umich.edu
  734-475-4484
A Review of FDA’s Approach to Medical Product Shortages

Peter Lurie, MD, MPH
Office of Policy and Planning, Food and Drug Administration
Outline

• Summary of FDA report

• Administration actions

• Impact of administration actions
Methods

• Meetings with FDA product centers
  – CDER, CBER, CDRH, CVM

• Other FDA meetings
  – CDER Office of Compliance, Office of Regulatory Affairs

• Meetings with external stakeholders
  – Manufacturers’ associations, manufacturers, wholesalers, group purchasing organizations, professional associations, non-governmental organizations, academics

• Development and analysis of new drug shortages database

• Other data analyses prepared for this report

• Review of published and unpublished data
Number of U.S. Drug Shortages FDA’s Drug Shortage Program Helped Address, 2005-2010

(Source: CDER Drug Shortage Program)
Drug Shortages by Primary Reason for Disruption in Production and Supply, 2010-2011

(Based on 127 drug shortages between January 1, 2010 and August 26, 2011)
Examples of Quality and Manufacturing Issues

• Foreign material
  – Bacterial and mould
  – Glass, metal and fiber

• Crystallization of active ingredient

• Precipitants (reaction between container and ingredients)

• Labeling/packaging errors

• Failure to meet specifications

• Equipment breakdown

• Natural disasters
Drug Shortages by Primary FDA Action Taken, 2010-2011

(Based on 127 drug shortages between January 1, 2010 and August 26, 2011)
Prevented Drug Shortages by Primary FDA Action Taken, 2010-2011

Expedited review 71%

Regulatory flexibility and discretion 20%

Ask other firms to increase production 7%

Communication with DEA 1%

Regulatory discretion regarding importation 1%

(Source: CDER Drug Shortage Program
Based on 137 drug shortages prevented between January 1, 2010 and September 26, 2011)
FDA Authorities

- **Can**
  - Require notification in certain circumstances
    - Life-threatening or life-sustaining
    - 6 months in advance
    - Non reporters listed on FDA website
  - Notification of manufacturing changes

- **Can’t**
  - Make a company make a drug or make more drug
  - Regulate how much and to whom a drug is sold
  - Consider pricing
Manufacturing and Marketing Factors Unique to Sterile Injectables

• Complexity of manufacture
• Dedicated manufacturing lines often required
• “Just in time” manufacturing and inventory management
• Market concentration
Percentage of Generic Injectable Market Held by Top Manufacturers, 2001-2010

(Source: IMS Health, IMS National Sales Perspective™. Extracted August 2011.)
Number of Injectable Molecules by Number of Manufacturers, 2010

(Source: IMS Health, IMS National Sales Perspectives™, Extracted September 2011. Based on 569 sterile injectable molecules.)
Overarching Themes

• The problem is complex and stems from interconnected economic, legal, regulatory and policy factors
• FDA has taken on the task of preventing and mitigating shortages, preventing 344 shortages since the beginning of 2010
• Many of the root causes are beyond FDA’s purview
• Efforts to address the problem will need to be multifaceted, sustained and involve multiple stakeholders
Administration Actions
October 2011

• Presidential Executive Order
  – Broader reporting of manufacturing discontinuances
  – Further expediting regulatory review
  – Reporting stockpiling and exorbitant pricing to Department of Justice

• Letter to manufacturers
• Endorsement of S. 296 and H.R. 2245
• Release of FDA and HHS reports
Administration Actions
Since October 2011

- Drug Shortages Working Group
  - Database
  - Model assessing probability of future shortages
  - Report to Department of Justice
- Discussions with Drug Enforcement Administration
- Doubling of Drug Shortage Program staff
- Interim Final Rule
  - Interprets mandatory reporting requirements
- Draft Guidance
  - Provides guidance on mandatory and voluntary reporting requirements
- Stakeholder meetings
- FDASIA
Notifications of Potential Drug Shortages to FDA, 2011-2012
Number of Drug Shortages Prevented, 2011-2012

- January - September 2011: 44
- January - September 2012: 200
Number of Drug Shortages, 2011-2012
Summary

The Executive Order has been associated with:

• An up to twelve-fold increase in notifications

• A 1.5-fold increase in shortages prevented compared to this time last year

• A 44% decrease in drug shortages compared to this time last year
Thank you!

• Contact Information

peter.lurie@fda.hhs.gov
301-796-7527
Resources

For more information about the ABA Health Law Section, please visit www.abanet.org/health or contact Simeon Carson at 312-988-5824 or carsons@staff.abanet.org