Drug Shortages
University of Utah Perspective

September, 2012

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

UNIVERSITY OF UTAH HEALTH CARE

Disclosure

- University of Utah Drug Information Service provides drug shortage information to Novation and the American Society of Health-System Pharmacists (ASHP) with support from Novation LLC.

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

Shortage Report Process

Report

- UUDIS
- FDA
- ASHP
- Novation

Verify

UUDIS

- Research
- Suppliers
- Evaluate
- Share

Post

ASHP

Novation

- Follow-up
- Updates
- Alternatives

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

Example Fields
www.ashp.org/shortage

Safety

Remifentanil, alfentanil, fentanyl and sufentanil may sound alike/look alike. However, dosage recommendations vary significantly between the agents.[5-8] Patient harm can occur if these agents are used erroneously. Use extra caution not to confuse these agents.

Alternative Agents & Management

- Alternative opiate agonists vary in onset time and duration of action, see Table 1.[5-15]
- No single agent can be substituted for fentanyl. The choice of an alternative agent must be patient-specific and based on the clinical situation, venous access, renal and hepatic function, and other comorbid conditions. Utilize stakeholder clinicians to help make specific plans for individual patient populations. Table 2 provides some alternatives to fentanyl for specific clinical situations.
- Some presentations of alternative agents including sufentanil and butorphanol are in short supply.[16]
- Drawing up individual doses in syringes may help conserve product. Ensure USP 797 requirements are met.
- Consider reserving fentanyl for high risk populations such as newborn and obstetrics.

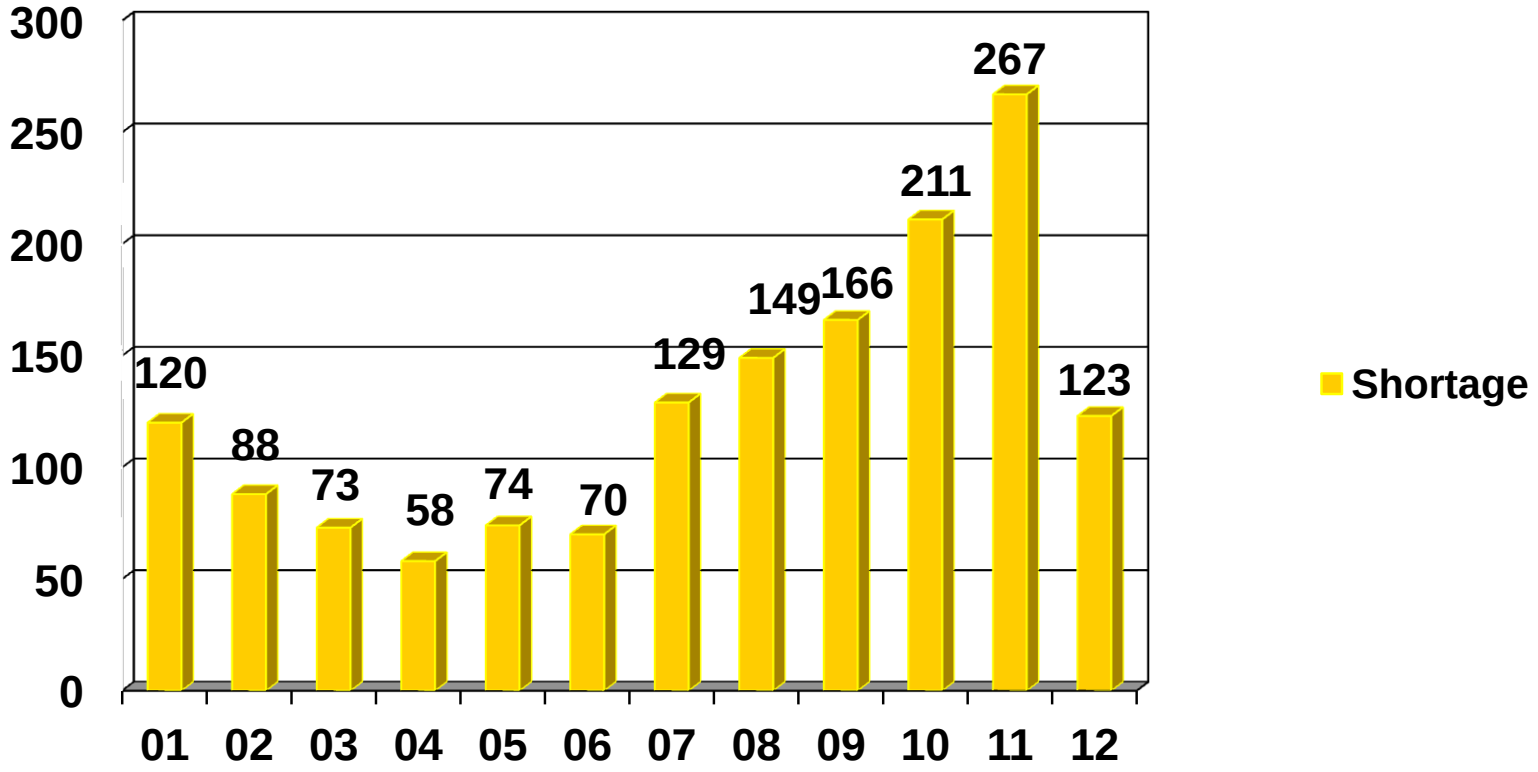
Alternatives

Table 2. Selected Alternatives to Fentanyl for Specific Clinical Situations

Use	Alternative Regimen	Comments
Analgesia in Labor and Delivery	*Epidural* Sufentanil: 10-15 mcg with 10 mL bupivacaine (+/- epinephrine). Repeat up to 3 doses no less than 1 hour apart. [6,12,17] *Intravenous* Butorphanol: 1-2 mg every 3-4 hours as needed[12,18,19] Nalbuphine: 5-10 mg every 3-6 hours as needed[12,18,20] *Patient controlled intravenous analgesia* Remifentanil: 0.2-0.93 mcg/kg bolus dosing with 1-3 minute lockout intervals. [18,21] *Spinal Epidural* Sufentanil: 10-20 mcg [12]	Remifentanil is not given intraspinally because it contains glycine.[13] Optimal dosing has not been established for remifentanil in labor analgesia[21]
Sedation for Procedures	Propofol: [22] Monitored Anesthesia Care (labeled dose): 0.5 mg/kg over 3-5 minutes followed by infusion at 1.5-4.5 mg/kg/hr 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] Fentanyl 25-50 mcg intravenous, repeat every 3-5 minutes as needed. Maximum dose: 500 mcg in 4 hours. Morphine 1-2 mg intravenous, repeat every 3-5 minutes as needed. Maximum dose 20 mg.	Intravenous medications used for procedural sedation include propofol, fospropofol, methohexital, dexmedetomidine, and benzodiazepines (eg, midazolam, lorazepam) in combination with opioids (eg, fentanyl, morphine). 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]

Problem Magnitude

National Drug Shortages
New Shortages by Year
January 2001 to August 31, 2012

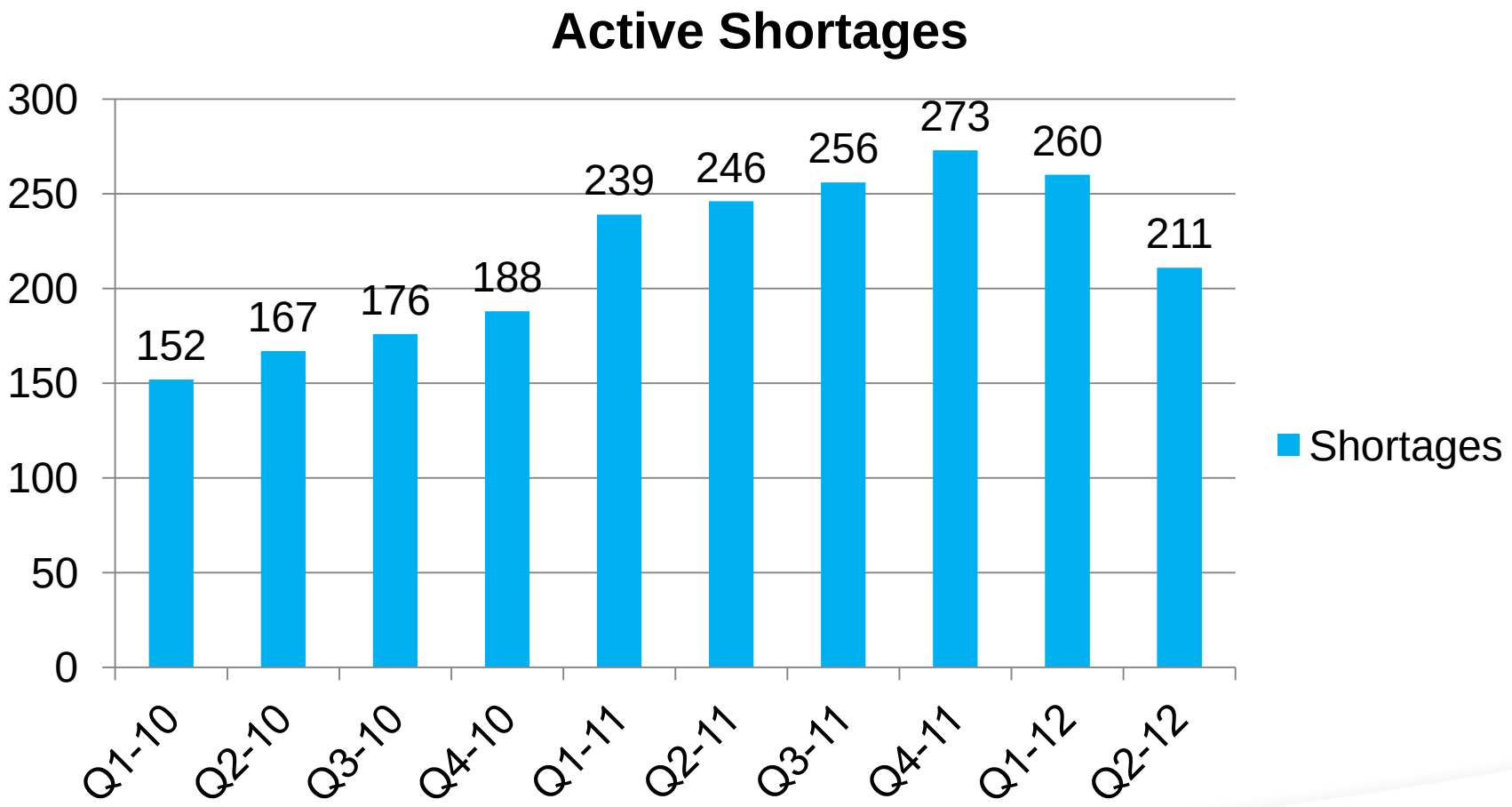


Note: Each column represents the # of new shortages identified during that year

University of Utah Drug Information Service

UNIVERSITY OF UTAH HEALTH CARE

National Drug Shortages – Active Shortages by Quarter

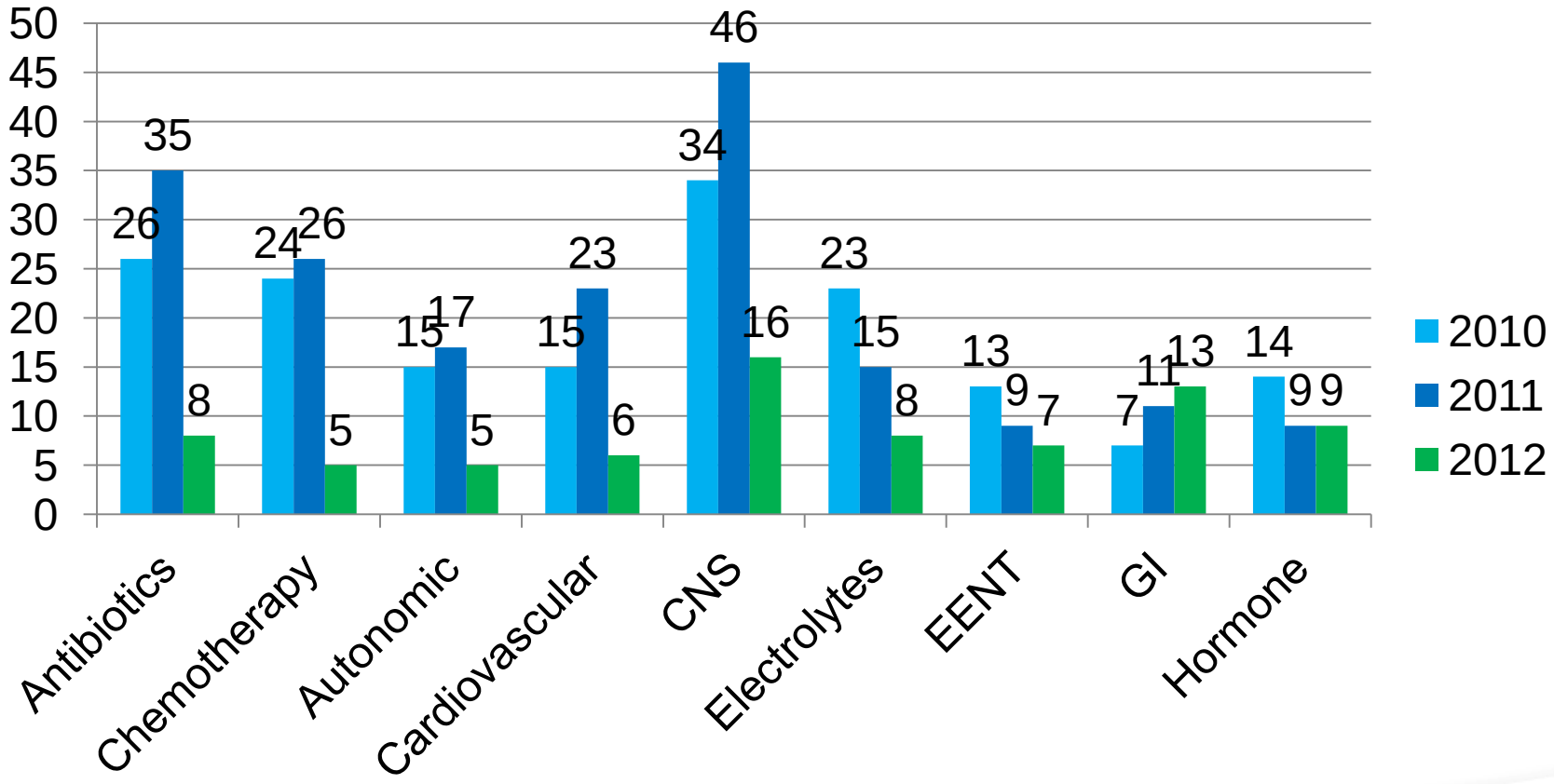


Note: Each column represents the # of active shortages at the end of each quarter. Q1-10 = Jan-Mar 10.

University of Utah Drug Information Service

UNIVERSITY OF UTAH HEALTH CARE

Common Drug Classes in Short Supply – 2010, 2011, 2012*



***Through June 30, 2012**

University of Utah Drug Information Service

UNIVERSITY OF UTAH HEALTH CARE

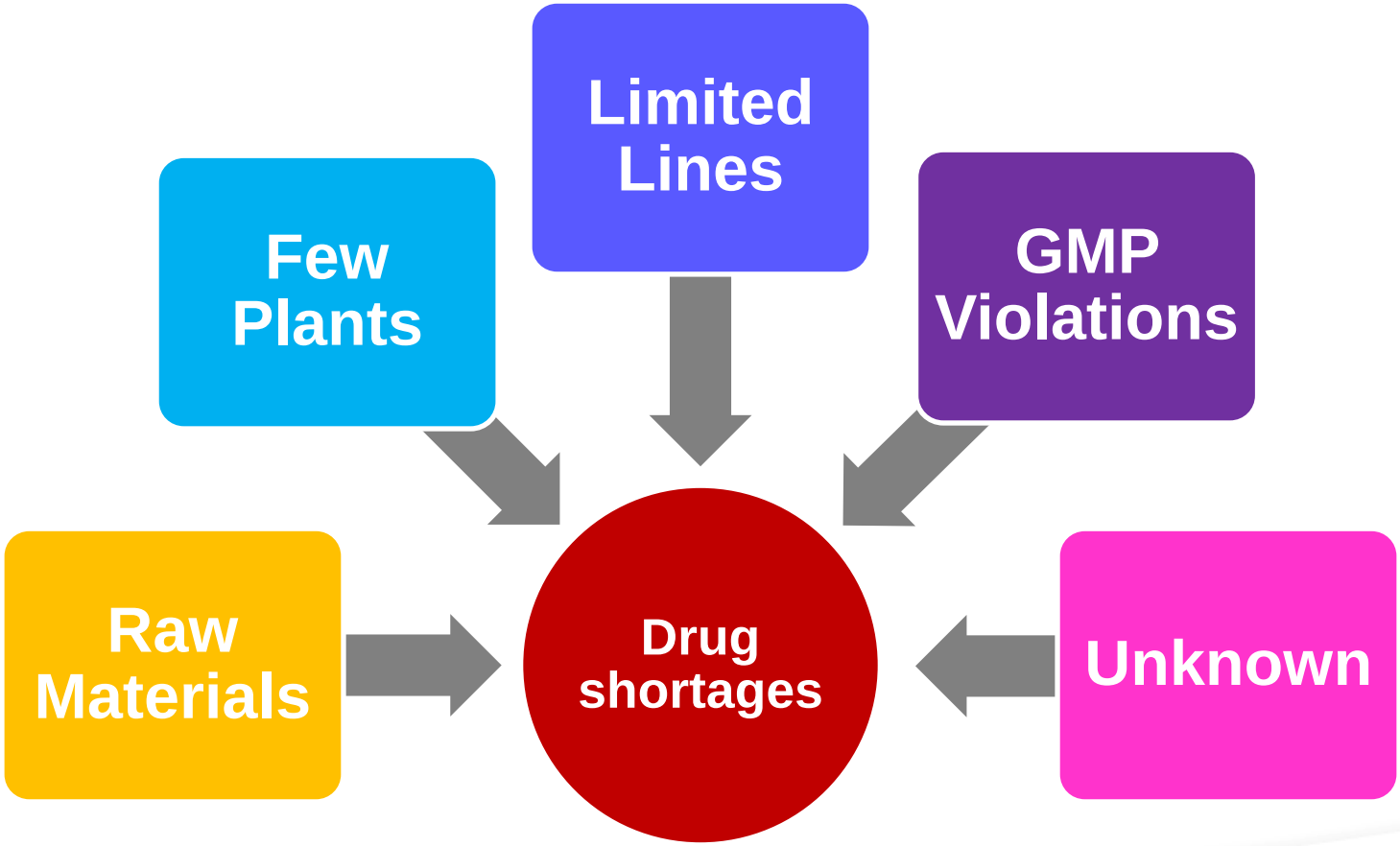
Reasons

Reasons for Shortages: Sterile Injectables

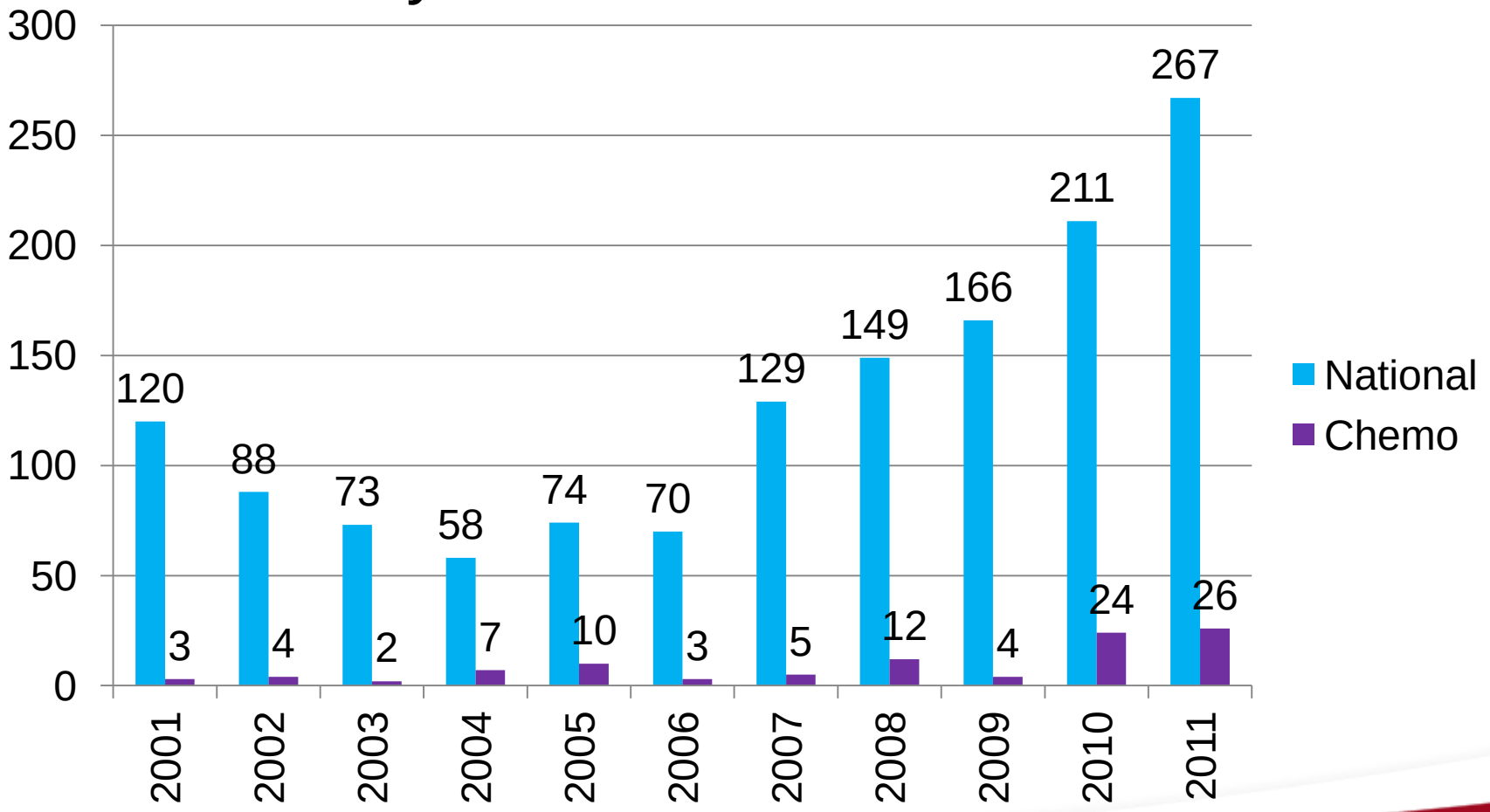
- Few suppliers
  - Majority of the market supplied by 7 manufacturers
  - Contract manufacturers – the company that supplies the product didn't always manufacture
- Lack of redundancy
  - Multiple products made on existing manufacturing lines
  - No resiliency in process for glitches
- Complex manufacturing process
  - No simple fixes for quality problems
  - Problems typically affect multiple products
- Economics

http://aspe.hhs.gov/sp/reports/2011/DrugShortages/ib.shtml

Manufacturing Problems



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



University of Utah Drug Information Service

UNIVERSITY OF UTAH HEALTH CARE

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.

Root Cause?

- Why are the manufacturing facilities in such bad shape?
- Quality issues are serious.
  - Mold, insects, contaminants
- Quality issues take a long time to fix!

FDA Can …

- Allow importation (11 agents 2010-2012, manufacturer dependent)
- Encourage increased production / speed approvals
- Use regulatory discretion (low risk / measures to ensure safety)
- Extend expiration date if data available
- Require notification under FDASIA
  - Any supply disruption, delay, or manufacturing problem 6 months prior or ASAP.
  - No penalties for not reporting.
  - Voluntary reports increased 6 x after Obama Exec Order

FDA is not able to **require**...

- Continued manufacturing
- Increased production
- Disclosure of a reason for the shortage
- Disclosure of sales (to whom and quantity)

FDA's Focus

- Medically Necessary Drugs
- Safety first
- Preventing Drug Shortages
  - 2011 = 195 prevented
  - 2012 (July) = 93 prevented

Minimize Impact

Regional Issues

- Supply chain
- Wholesaler
- Region of country
- Local competition
- Patient mix

Day to Day Logistics

- Be flexible, tenacious, detail oriented
  - Use different brands (even brand name!)
  - Can you order product differently or access other supply?
  - Can you use an alternative?
  - Establish an RSS feed for ASHP shortage updates, subscribe to FDA updates

Food for thought on expired meds

- Long-term expiration dating – studies done under ideal storage conditions
- Dept of Defense study – did not include any liquid, injectable products
- Joint Commission does not allow use of expired products
- Most state laws prohibit pharmacists from dispensing expired drugs

Safety

ISMP Survey - 2010

- Morphine Sulfate – 2 deaths related to shortage
- Heparin pre-mix bags – compounding errors due to shortage (5-fold errors)
- Epinephrine pre-filled syringes – overdoses (10-fold errors)

ISMP Medication Safety Alert! Sept 23, 2010.

ISMP Survey - 2011

- Detailed survey sent out November 2011
- Most frequent events occurred with chemotherapy (27%), opioids (17%), electrolytes (7%), and antibiotics (5%)
- Most frequent harm events: inadequate alternative (35%), error related to form/strength (27%), no treatment (27%), compounding error (6%)

ISMP Medication Safety Alert! April 19, 2012

ASPEN Parenteral Multivitamin Shortage Survey

- Survey 4/24/12 to 5/2/12 - 800 responses
- Adult multivitamins – 70% short
- Pediatric multivitamins – 26% short
- No vitamins for patients on TPN - 27%
  - Concerns – cardiac failure due to thiamine deficiency (after 3 – 4 weeks w/o vits)
  - Megaloblastic anemia (after 4 – 5 weeks w/o folate)

http://www.nutritioncare.org/News/Industry_and_Product_News/A_S_P_E_N__Releases_Results_of_Multivitamin_Shortage_Survey/

National Attention

Summits

- ASA, ASCO, ASHP, ISMP – Invitation Shortage Summit – November 2010
- FDA Public Workshop on Drug Shortages – September 2011

GAO Report - 2011

- 1190 shortages between 1/1/01 – 6/20/11
- Average duration 286 days
- 64% of shortages were frequent fliers
- Strengthen FDA's ability to respond
  - Congress should require manufacturers to report to FDA
  - FDA should enhance ability to respond

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

ASPE Economic Analysis 2011

- Limited capacity will take years to resolve
- Pricing
  - For 44 oncology products short since 2008, prices decreased by a mean of 26.5% between 2006 and 2008. Oncology products not impacted by shortages showed no price decreases.
- http://aspe.hhs.gov/sp/reports/2011/DrugShortages/ib.shtml

IMS Institute Report - 2011

- Half of all generic injectables are in short supply
- Few Suppliers
  - 50% of shortages = 1 – 2 suppliers
  - 2/3 of shortages = 3 or fewer suppliers
- Volume vs. Suppliers
  - Stable volumes but not suppliers

http://www.imshealth.com/portal/site/ims/menuitem.edb2b81823f67dab41d84b903208c22a/?vgnextoid=a6fbcc0f68f73310VgnVCM100000ed152ca2RCRD

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

http://www.ashp.org/menu/Advocacy/FederalIssues/DrugShortages.aspx

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

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%)

Journal of Generic Medicines. 2011;8(4):210-218

University of Michigan ASHP Survey

- Autumn 2010 – survey of 1322 directors of pharmacy – ASHP members.
- 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

American Hospital Association Survey (June 2011)

- Survey sent to hospital CEOs 6/1/11
- 820 hospital responses received by 6/22/11
- Key Findings:
  - 99.5% of hospitals had at least 1 shortage
  - 82% of hospitals had delayed treatment
  - 75% of hospitals rationed or restricted
  - Majority reported increased costs

Quality-Related MedWatch Alerts

- http://pharmacyservices.utah.edu/alerts/
- 2012 (July) – 30 quality related alerts
- 2011 – 21 quality related alerts
- Most quality related alerts aren't related to shortages, but demonstrate overall pattern.