Drug Shortages Summit

November 5, 2010

Summary Report

The Drug Shortages Summit was co-convened by the American Society of Health-System Pharmacists (ASHP), the American Society of Anesthesiologists (ASA), the American Society of Clinical Oncology (ASCO), and the Institute for Safe Medication Practices (ISMP) on November 5, 2010 in Bethesda, Maryland. 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; and
- 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 participants included representatives from health professional organizations, pharmaceutical manufacturers, and supply chain entities. Representatives of the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention also attended portions of the meeting as observers. A complete list of attendees is found in Appendix A.

This summary report reflects discussion at the Drug Shortages Summit, including recommended actions that will be further evaluated and implemented, if appropriate, based on an assessment of feasibility, impact, and resources required for implementation. Compliance with legal requirements (e.g., Federal Trade Commission regulations) and avoidance of unintended consequences (e.g., hoarding,

manufacturing disincentives) will also be factored into this evaluation. Next steps will focus on establishing workgroups to explore, prioritize, and develop detailed action plans to achieve summit recommendations that are selected for implementation based on these criteria. Additional information will be available from the co-conveners and at www.ashp.org/drugshortages as these plans are developed.

Introductory comments by Henri R. Manasse, Jr., Ph.D., Sc.D., Executive Vice President and Chief Executive Officer, ASHP; Mark A. Warner, M.D., President, ASA; and Michael P. Link, M.D., President-elect, ASCO illustrated the negative effect of drug shortages on patient care, including delayed care, inferior clinical outcomes, and patient injury or death. Participants were encouraged to collaborate to address what was described as a public health crisis. Presentations by Erin R. Fox, Pharm.D., Manager, Drug Information Service, University of Utah Hospitals & Clinics; Burgunda (Gundy) V. Sweet, Pharm.D., Director, Drug Information and Medication Use Policy, University of Michigan Health System; and Michael R. Cohen, R.Ph., M.S., Sc.D., President, ISMP described causes and current trends for drug shortages, resource utilization for managing drug shortages, and safety concerns associated with drug shortages), respectively. Details of these presentations are provided in appendices B and C; data from a survey on resource utilization are not provided due to pre-publication embargo. FDA staff, including CAPT Valerie Jensen, R.Ph., Associate Director, CDER Drug Shortage Program and CDR Jouhayna Saliba, Pharm.D., Senior Program Manager, Center for Drug Evaluation and Research (CDER) Drug Shortage Program, provided an overview (Appendix D) of Agency activities in this area, described current regulatory authority related to drug shortages, and responded to participant questions. Additional information on causes, impact, and proposed solutions for drug shortages and an antitrust statement are contained in the background documents provided to participants prior to the summit (Appendices E through H).

Outcomes of the Drug Shortages Summit included development of initial recommendations and participant agreement to continue collaborating to address issues associated with drug shortages. Broad areas of work will include exploring strategies to:

- Improve communication among stakeholders in the pharmaceutical supply chain and health care providers, and
- Remove barriers faced by the FDA and drug manufacturers to minimize the impact of drug shortages.

Regulatory and Legislative Factors

Summary of Causes: Regulatory barriers and ambiguities, including the lack of FDA authority to require notification and other actions, were considered significant contributors to drug shortages. Examples include the absence of a requirement for manufacturers to notify FDA of anticipated market withdrawal and no statutory authority for enforcing notification requirements for medically necessary drugs. Several drug shortages (e.g., concentrated morphine sulfate solution, levothyroxine injection) have been precipitated by actual or anticipated action by the FDA as part of the Unapproved Drugs Initiative, which is designed to increase enforcement against drugs that lack FDA approval to be marketed in the United States. (These drugs are commonly called pre-1938 drugs, referring to their availability prior to passage of the Food, Drug, and Cosmetic Act of that year.) Some participants noted that the cost and complexity of completing a New Drug Application (NDA) for those unapproved drugs is a disincentive for entering or maintaining a market presence. Other regulatory barriers include the time for FDA review of Abbreviated New Drug Applications (ANDA) and supplemental applications, which are required for changes to FDA-approved drug products (e.g., change in source for active pharmaceutical ingredients (API), change in manufacturer). Manufacturers described this approval process as lengthy and unpredictable, which limits their ability to develop reliable production schedules. Participants noted that some FDA activities are based on internal policies, not regulation. While this was perceived as allowing for flexibility and discretion, it may also result in unpredictable or delayed responses. Some participants believed that a perceived backlog of applications awaiting approval may be related to insufficient FDA resources. Another contributing cause to drug shortages may be the availability of improved assays and other technologies that have resulted in issuance of new product specifications (e.g., revised United States Pharmacopeia [USP] standards for assessing heparin potency). In addition, when one manufacturer submits revised standards that are accepted by USP, other companies are required to meet the new specifications. Shortages may be caused when companies are delayed in complying with these new requirements. For controlled substances, pre-established Drug Enforcement Agency (DEA) quotas can delay or prohibit manufacturers from obtaining API to increase production of these products when another manufacturer experiences a shortage or production issue. Other potential causes that were discussed, but considered less or not causative of drug shortages included evolving regulatory requirements for packaging (e.g., barcodes), Risk Evaluation and Mitigation Strategies, and inconsistencies in international drug approval processes that prevent use of foreign products when shortages occur.

Recommendations:

- Explore expanding FDA authority to require manufacturer notification of market withdrawals (e.g., notification required 9 to 12 months prior to planned market exit).
- Evaluate the current FDA definition of medically necessary, including the established criteria and responsible party for making this determination, to assess the need for increased FDA statutory authority in this area.

- Define and implement evidence-based and other criteria for identifying critical drug therapies that are vulnerable to drug shortages. Criteria might include factors such as availability of therapeutic alternatives, supply chain characteristics, and other elements that determine products' vulnerability for shortages.
- Explore providing incentives (e.g., tax credits) to manufacturers that produce critical drug products or upgrade manufacturing plants to meet or exceed Good Manufacturing Practices (GMP) in exchange for guarantee of continued production of these therapies.
- **Require** confidential notification of FDA when there is a single API or manufacturing source. Notification would also apply to informing FDA of an interruption in the supply of raw materials, API, or manufacturing processes. *(This recommendation also listed under Raw Materials Sourcing and Manufacturing Factors as a voluntary action).*
- Explore reauthorization of Prescription Drug User Fee Act (PDUFA) as a mechanism to establish a modified/reduced user fee program for generic drugs, which would provide FDA additional resources to support prioritization and expedited review of supplemental applications and ANDA. Intent of user fee program would be to provide more timely approval of applications and incentivize manufacturers to enter market based on increased ability to plan production schedules.
- Establish an expedited approval pathway for those unapproved drugs (i.e., pre-1938 therapies) that are deemed critical therapies. In addition, reduce or eliminate the current NDA user fee that is required for these products. Incentives could also be considered.
- Assess the need to establish or enhance use of existing processes to expedite approval of ANDA, supplemental applications (e.g., alternate source API), and new or altered production lines for drugs in short supply. In addition, advocate for additional FDA resources to minimize wait time for approval of these applications.
- Evaluate processes for new product specifications (e.g., USP standards), including appropriateness of timeline for implementation. (Note: Invite USP to participate in these discussions).
- Increase collaboration with industry, DEA, and FDA to establish a process that would more readily modify API quotas in response to drug shortages of controlled substances.
- Establish improved processes to extend product stability for products in short supply.
- **Require** manufacturing redundancies (e.g., multiple manufacturing sites for a sole product or multiple API sources, when available) as part of the FDA approval process. *(This recommendation also listed under Raw Materials Sourcing and Manufacturing Factors as a voluntary action).*

Other proposed solutions discussed briefly by summit participants included harmonizing international drug approval processes in order to minimize barriers to importation (when desirable) and clarifying the definition of public health emergency to determine if this mechanism could facilitate allocation and other activities that avoid or minimize the effect of drug shortages.

Raw Materials Sourcing and Manufacturing Factors

Summary of Causes: Manufacturing-related causes that contribute to drug shortages are multifactorial. Inability to fully comply with GMP, which results in production stoppages or recalls, was considered a major cause. It was noted that FDA has increased inspections of injectable drug manufacturing processes based on the higher likelihood of harm should these processes be inconsistent with GMP. Manufacturers have also voluntarily increased their quality standards, which on occasion, has resulted in companies being temporarily unable to meet their own standards. Participants recognized that there is limited understanding of the complexity and inter-relatedness of drug production activities. For example, increased product demand in response to another drug product shortage may result in a secondary shortage. Manufacturers generally run production lines at full capacity and may be unable to quickly accommodate increased market demand or FDA requests to produce additional quantities of these alternative therapies. Unpredictable timelines for FDA approval of supplemental applications and ANDA for new-to-market generics also contribute to uncertainty in production planning processes. In addition, there are limited sources of API. Some API are sole source products, which increases a product's vulnerability to drug shortages. Other causes that were discussed, but considered less or not causative of drug shortages included natural disasters and changes in product formulation.

Recommendations:

- **Encourage** confidential notification of FDA when there is a single API or manufacturing source. Notification would also apply to informing FDA of an interruption in the supply of raw materials, API, or manufacturing processes. *(This recommendation also listed under Regulatory/Legislative Factors as a proposed required action.)*
- **Encourage** manufacturing redundancies (e.g., multiple manufacturing sites for a sole product or multiple API sources, when available). *(This recommendation also listed under Regulatory/Legislative Factors as a proposed required action.)*
- Establish or improve mechanisms to communicate anticipated or actual manufacturing and inventory problems (e.g., standardize terminology for causes of shortages, eliminate causes being described as "reason unknown " or "not provided"). Some information may require privileged communication between FDA and manufacturers to avoid unintended consequences (e.g., hoarding, releasing business information that supports fair business competition). Other mechanisms should focus on improving communication and transparency among supply chain entities and health care providers. Ensuring that information on the reason for and anticipated duration of the shortage reaches frontline clinicians was considered key.
- Maintain/improve adherence to GMP to avoid quality issues and recalls.

Business and Market Factors

Summary of Causes: Several market factors were noted as contributing to drug shortages, including consolidation of firms that leads to fewer manufacturers for a given product, reassignment or

reallocation of production lines, lack of transparency or communication about actual or possible product shortages, and lack of business incentives to enter a specific product market. Some participants believed that insufficient profit margins and product liability concerns are factors that lead to market withdrawals. However, manufacturers stated that these factors do not contribute to the decision to discontinue a product, which was described as being multifactorial (e.g., complexity of manufacturing newer drugs can necessitate shifting of manufacturing resources away from other products). Other causes that were discussed, but considered less or not causative of drug shortages were unpredictable fluctuations in product demand (i.e., changes in clinical practice) and patent challenges.

Recommendations:

- Improve communication to, among, and from product manufacturers and FDA, including detailed information on reason and anticipated duration of shortage. Also enhance communication to supply chain entities and health care providers (e.g., Dear Provider letters).
- Decrease barriers/disincentives to market entry *(See recommendations under Regulatory/Legislative Factors).*

Distribution Factors

Summary of Causes: Inventory practices by health care facilities (e.g., just-in-time inventory) and supply chain entities (e.g., sole source and bundled purchasing) were identified as a significant factor that contributes to the impact of drug shortages on patient care. This practice results in little or no inventory cushion to address short-term shortages. In addition, regional and local differences in product availability were described as resulting from contractual agreements with wholesalers and group purchasing organizations (GPOs). Current systems for product allocation are intended to address this, but are often imperfect based on a lack of reliable information on resumed product availability. Another system limitation is the inability of GPOs to determine competitive pricing that would facilitate establishing multiple contracts for a specific product. Drug procurement is especially challenging for ambulatory infusion centers and small and rural facilities, which generally lack the business relationships that can facilitate product availability for larger facilities or health systems. The grey market (i.e., distribution channels other than those authorized by the manufacturer) and price escalations for products in short supply were also discussed. The potential for hoarding and price gouging were described as a significant concerns related to drug shortages.

Recommendations:

- Enhance communication among manufacturers, health professional associations, and FDA to support product distribution.

- Consider distribution options for products in short supply (with increased information exchange among supply chain members).

Another proposed solution discussed briefly by summit participants was creation of a national "stockpile" for critical therapies. However, it was noted that this approach would require an initial expanded supply of products that already had limited availability. Direct manufacturer distribution of products in short supply was discussed, but not preferred, because of limitations in the current model. For all recommendations, participants were especially cautious of avoiding unintended consequences (e.g., hoarding) related to distribution practices.

Drug Shortages Summit

Summary Report:

Appendix A

Drug Shortages Summit
November 5, 2010

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Drug Shortages Summit
November 5, 2010

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Drug Shortages Summit

Summary Report:

Appendix B

Drug Shortages Overview & Trends November 5, 2010

Erin R. Fox, PharmD
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Shortages and University of Utah Drug Information Service

- UU DIS provides drug shortage content to Novation and ASHP
  - Partners since 2001
  - Receive reports submitted to ASHP and Novation
  - Collaboration is key - FDA, ASHP, Novation, UU DIS

Drug Shortage Resource Center

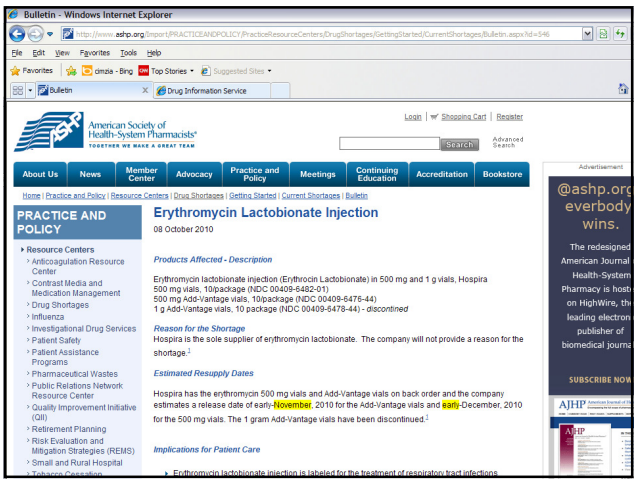
- www.ashp.org/shortage
- Current, Resolved, No Longer Available
- Report a shortage
- ASHP Guidelines
- Other content
  - Safety Alerts and Warnings (MedWatch summaries)
  - Unapproved Drugs
  - Articles, news stories,
  - Sample policies for drug shortages, IVIG

Shortage Report Process

- "Report a shortage" button generates an email to UU DIS, Novation, ASHP, FDA
- UU DIS works to verify the shortage
- UU DIS reports back and Novation / FDA share any additional information
- Notices updated daily
- Alternatives included for severe shortages and when applicable.

Tracking

- UU DIS following 177 shortages (11/3/10)
- 140 current shortages listed at ASHP
  - Weekly updates for 40 – 60 shortages
  - Updated based on new ETAs, reports of worsening availability



Web Posting Content

- Affected products
- Reason for the shortage
- Estimated resolution
- Implications for patient care
- Management strategies
- Safety recommendations

Example – Erythromycin Lactobionate Injection

Situation	Recommendation	Comments
Gastroparesis[3,4,6,7]	Metoclopramide 10 mg orally or IV QID administered 30 minutes before meals. Erythromycin 250 mg orally TID	Side effects such as drowsiness and tardive dyskinesia may limit the utility of metoclopramide.[6]
Gastroparesis following partial large or small bowel resection surgery with primary anastomosis[8]	Alvimopan 12 mg orally 30 minutes to 5 hours before surgery, then 12 mg orally twice daily for up to a maximum of 15 doses	May only be used in hospitals. Hospitals must be enrolled in the Entereg Access Support and Education (EASE) program.
Premature Rupture of Membranes (PROM)	Ampicillin 2 gram IV Q6H and erythromycin 250 mg IV Q6H for 48 hours then give oral doses of amoxicillin and erythromycin for 5 days.[9-11]	Limited information available for azithromycin.[11,12]
Prevention of perinatal Group B Streptococcal disease in penicillin-allergic patients[5]	Low-risk for anaphylaxis: Cefazolin 2 g IV initially, then 1 g IV Q8H until delivery High-risk for anaphylaxis: Clindamycin 900 mg IV Q8H until delivery	Current MMWR guidelines recommend either cefazolin, clindamycin, or erythromycin for penicillin-allergic patients

Clinical Detail – Erythromycin Shortage

- Premature Rupture of Membranes (PROM)
  - What is recommended?
  - Ampicillin 2 grams IV every 6 hours plus erythromycin 250 mg IV every 6 hours followed by oral therapy
  - Limited information regarding azithromycin

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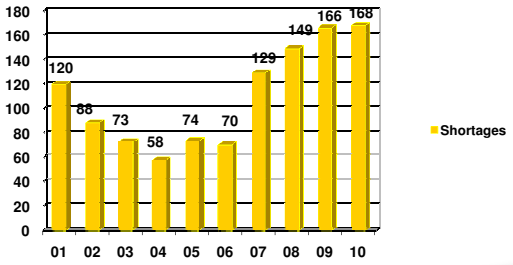
National Drug Shortages
January 2001 to October 31, 2010



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

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Reasons for Shortages

- Consolidation in the industry
- Raw materials
- Supply chain issues
- Manufacturing / Regulatory issues
- Changes in clinical practice
- Business decisions
- **Unknown (most frequent reason!)**

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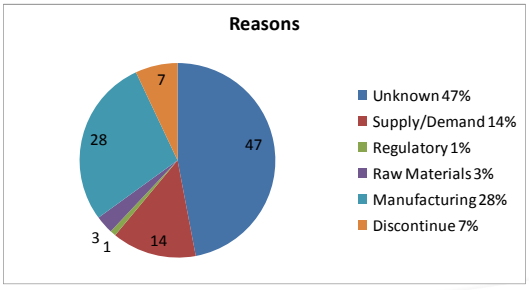
Reasons for Shortages 2010



Data from University of Utah DIS

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Fragile Supply Chain

- Consolidation = fewer suppliers
- Tighter inventories = less resiliency
- Increasing production to make up a 20% market share virtually impossible.
- Foreign sites
  - ~1200 NDA's for 2007
  - 13% US, 39% India, 43% China

Harris G. Drug Making's Move Abroad Stirs Concerns. NY Times, January 20, 2009

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Business Decisions

- Consolidation
- Free enterprise system – single source items
- Business decisions
  - Profitability
  - Costs - GMP improvement / violation
  - Annual quotas (production halts)
  - Vacations

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Manufacturing Problems

- Sole source / time to source new raw materials (companies don't have to disclose)
- Few manufacturers of sterile injections
- Same production lines for multiple items

Provisional observations on drug product shortages: effects, causes, and potential solutions. *AJHP*. 2002;59:2173-2182

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Example – Manufacturing & Consolidation

- Factory shutdown for quality fixes
- Over 45 individual products impacted
- 27 current, active shortages listed on ASHP/Novation website
  - Amikacin
  - TMP/SMZ
  - No specific timeline for recovery

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Recalls

- Challenging on their own
- May precipitate a shortage
- Can create immediate emergencies, wiping out all stock (phosphenytoin, TMP/SMZ)

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Unapproved Drugs

- New regulatory issue
- Many agents used daily are unapproved
  - DESI (drug efficacy study implementation) drugs
  - Wrap-up drugs
  - Drugs marketed after 1962 (never approved)
- Creates uncertainty in the market
  - Examples: phenylephrine injection, levothyroxine injection, thiopental injection

Fox ER, Tyler LS. *AJHP.* 2009;66:798-800

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Regional Issues

- Shortages vary widely depending on:
  - Wholesaler
  - GPO
  - Region of country
  - Local competition
  - Patient mix

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Gray market

- In face of shortage, this company has product – faxes, phone calls
- Specialize in shortages
- Expensive (10 – 1000 x usual cost)
  - No guarantee of proper storage, pedigree
  - Possible counterfeit / compounded agent
  - Not enough for usual use

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Compounders

- Potential resource
- Balance potential safety risks
- Know your compounder
  - Concern for sterility, GMP
  - Deaths due to poorly compounded product during the 2001 betamethasone shortage

Trends - 2010

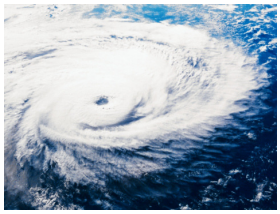
- Unprecedented numbers
- Shortages of critical drugs
- Safety impact (ISMP to address)

Unprecedented Numbers

- Each year the total number of new shortages identified increases
  - 2006 = 70
  - 2007 = 129
  - 2008 = 149
  - 2009 = 166
  - 2010 (10/31/10) = 168
  - 2010 Total Estimate = 202

Perfect Storm

- Manufacturing difficulties at the same time
- Global outsourcing
  - Survey of execs, 50% state outsourced raw materials greatest vulnerability to supply chain (fiercepharma.com, 10/28/10)



2010 Shortages of Critical Drugs

- No simple alternative –may not be optimal, may require treatment delays
- Antineoplastics – 20 shortages (epirubicin, daunorubicin, cisplatin, doxorubicin, leucovorin)
- Antimicrobials – 19 shortages (colistimethate, TMP/SMZ, foscarnet, amikacin)

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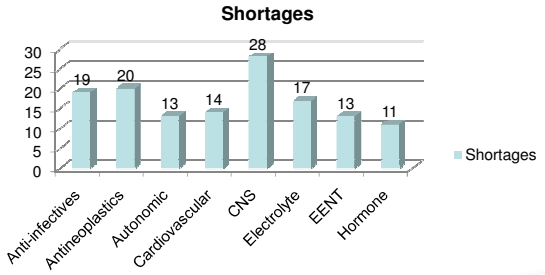
Shortages by Drug Class > 10 Shortages in 2010



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Common Frustrations

- No advance warning
- Constant disaster mindset
- Medication supply must become part of daily therapeutic planning
- "How can I take care of my patients if I don't have the drugs I need?"

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Summary

- Major increase in drug shortages
- University of Utah DIS works to provide shortage information and clinical information to minimize patient impact
- ASHP Drug Shortage Resource Center
  - www.ashp.org/shortage

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Drug Shortages Summit

Summary Report:

Appendix C

Drug Shortages Threaten Patient Safety

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1

Disclosure Information

Michael R. Cohen, RPh, MS, ScD
has no financial relationships to disclose
and will not discuss off label use
and/or investigational use in this presentation.

2

Objectives

- Provide findings from an ISMP survey about the impact of drug shortages in hospitals
- Describe errors associated with the drug shortage during the past year

3

Drug Shortages

- Clinical effects of shortages
  - Adversely affect drug therapy
  - Compromise or delay medical treatment/procedures
  - Result in failure to treat and progression of disease
  - Result in medication errors and adverse patient outcomes

Drug shortages

- Financial effects of shortages
  - Expends tremendous resources
    - Costly alternative medications for provider and patient
    - Significant time spent on addressing shortages
    - Additional costs associated with treatment of adverse outcomes
- Emotional effects of shortages
  - Frustration, anger, mistrust
  - Strain professional relationships

Types and Frequency of Drug Shortage Difficulties

(% of respondents who **frequently** or **always** encountered these problems in past year)

No information about duration of shortage	85%
No advanced warning and suggested alternatives	84%
No information about cause of shortage	83%
Substantial resources developing plan of action	82%
Difficulty obtaining suitable alternative	80%
Experience significant financial impact	78%
Lack of suitable alternative product	70%
Substantial resources preparing alternative	69%
Risk of adverse patient outcomes	64%
Internal hoarding of products	58%
Physician anger towards staff/hospital	55%

6

Additional Difficulties

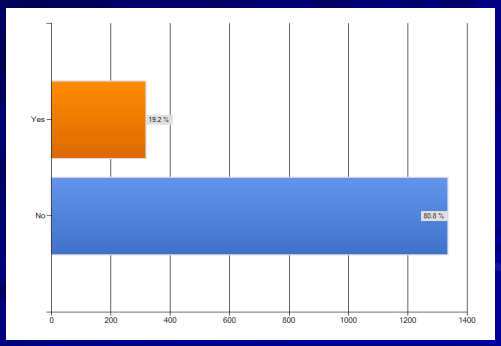
- Inability to keep up with important safety initiatives
  - LASA efforts
  - Double checks
  - Medication reconciliation
- Sterility and stability issues with nursing/ pharmacy compounded products vs. manufacturers' products

Additional Difficulties

- Delay in updating computer systems/bar-coding systems with alternative products/strengths
  - Possible dispensing and administration errors
- Using expired medications
- Using single-dose/unit-of-use containers for multiple patients

Near Misses and Errors

Adverse Patient Outcomes



Examples of Errors and Adverse Outcomes: Morphine

- Dosing errors with alternative drug
  - IV **HYDRO**morphone prescribed at the intended dose of morphine, resulted in death of two patients
  - Switched from 6 mg morphine to **HYDRO**morphone without changing the dose; patient received two doses; over-sedation reversed with naloxone
- Dosing errors with morphine
  - Administered 8 mg of morphine instead of 2 mg; only 8 mg syringes available from manufacturer
  - Administered 10 mg of morphine instead of 2 mg when 10 mg vials were required to replace 2 mg vials
- Product mix-ups
  - Mix-up between pharmacy prepared syringes of morphine and **HYDRO**morphone
  - Morphine 10 mg vial (dispensed to unit after 2 mg vials no longer available) mixed up with vial of heparin 5,000 units; morphine administered IV instead of heparin

Examples of Errors and Adverse Outcomes: Epinephrine

- Delayed/omitted treatment during code
  - Difficulty determining how to extract correct dose from 1:1,000 ampul
  - Epinephrine with intra-cardiac needle in crash cart; cardiac needle jammed through needleless system port and punctured tubing; required tubing change during code
  - Needed intra-cardiac needle but code cart stocked with pharmacy-prepared syringes (no needles) only
- Dosing errors
  - 10-fold overdose when nurse administered contents of 1:1,000 ampul, thinking it held a 1:10,000 concentration
  - Administered entire contents of 1:1,000 (1 mg) ampul IV to patient who was supposed to receive 0.3 mg IM
  - Administered a pediatric emergency syringe of epinephrine to an adult, leading to treatment failure

Examples of Errors and Adverse Outcomes: Propofol

- Dosing errors
  - Miscalculated rate of infusion for Precedex or entered wrong concentration in smart pump
  - Infused alternative drug (Ativan) at typical rate for propofol
- Therapy omissions
  - Cancellation of procedures/anesthesia/ Unnecessary use of general
- Suboptimal outcomes
  - Inadequate sedation and self-extubations
  - Difficulty weaning patients from ventilators
  - Anesthesia awareness
- Adverse side effects of alternative drugs
  - PONV
  - Phlebitis (etomidate)

Other drugs involved in Errors and Adverse Outcomes:

- Chemotherapy
- Neuromuscular blockers
- Antibiotics
- 50% dextrose injection
- Fosphenytoin
- Heparin

Lack of Alternative Product

- Drugs with no viable alternatives
  - Antabuse
  - Pancreatic enzymes
  - Amikacin
  - Acyclovir
- Investigational drug studies
  - Put on hold because can't ensure supply of adjunct therapy
- Postponed procedures, surgery
  - Stem cell transplantations
  - OR procedures, colonoscopies

Issues with Alternative Medications

- Alternatives to drugs with superior efficacy and/or lower risk profile
  - Propofol
- Alternative medications vulnerable to shortage when supply and demand picks up suddenly
  - **HYDRO**morphone
  - Bumetanide
- Enhanced risk of errors and/or adverse outcomes
  - Can't remember all drugs and alternatives, how to safety prescribe, dispense, administer
- Ethical dilemma with rationing
  - Who gets the optimal drug? Who gets the less optimal drug?
  - "You had a curable disease but *not anymore*."

Drug Shortages Summit

Summary Report:

Appendix D

FDA's Role in Addressing Drug Shortages

Agenda

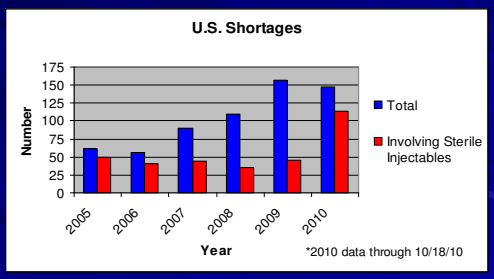
- Shortages – Trends and Causes
- FDA's Role
- Key Issues

General Causes of Shortages

- Manufacturing difficulties/Compliance Issues
- Corporate decisions/discontinuations
- Market Concentration/Limited Capacity
- Raw material/API shortage
- Changes in Clinical Practice
- Emergency Situations
- Hospital/Pharmacy based issues

Shortage Trends – Past 6 years

CDER Drug Shortage Data
(does not include vaccines)



Shortage Trends - 2010

- 2010 – significantly increased numbers of shortages compared to this time last year.
  148 shortages in 2010 as of 10/18/10
  (157 in all of 2009)
- Sterile injectables – greater numbers than past years
  77% of 2010 shortages involve sterile injectables
- Critical drugs involved - succinylcholine, naloxone, furosemide, emergency syringes, etc…

Reasons for Sterile Injectable Shortages - Jan through Oct 2010

- 42% - Due to Product Quality issues (includes particulate, microbial contamination, newly identified impurities, stability changes)
- 18% - Due to Discontinuations
- 18% - Due to Delays/Capacity issues (not due to any other reason)
- 9% - Due to raw material (API) issues
- 5% - Due to loss of manufacturing site
- 4% - Due to component problems/shortage
- 4% - Increase in demand due to another drug shortage

Trends, Continued

- Older Sterile Injectables
  - Not enough capacity
  - Fewer firms making these products
  - Complex manufacturing process
  - Generally not economically attractive

When one firm has problems or discontinues, a shortage almost always occurs.

FDA's Role

- Steps FDA takes when there is a shortage:
  - For manufacturing/quality problems – work with the firm to address the issues. Problems may involve very low risk (e.g. wrong expiration date on package) to high risk (particulate in product or sterility issues). Regulatory discretion may be employed to address shortages to mitigate any significant risk to patients.
  - Encourage remaining firms to ramp up.
  - FDA can expedite issues related to addressing shortages (e.g. new manufacturers, increased expiry, increased capacity, new raw material source, changes in specifications).
  - In rare cases, temporary importation (propofol, foscarnet, ethiodol)

What FDA Can't Do

- FDA cannot force a manufacturer to produce a product Manufacturers are not required to report plans to discontinue producing a product unless they are the sole manufacturer of a drug that is life-supporting; life-sustaining; or intended for use in the prevention of a debilitating disease or condition.. (21 CFR 314.81 FR published 10/07)
- No penalty for not notifying FDA of a discontinuation.

Key Issues

- Notification from firms is important for all shortage issues (not just sole source and not just those firm determines to be medically necessary).
- Early notification leads to better chance of timely resolution - 24 product shortages prevented in 2010 so far due to firms notifying FDA in advance.

Ways to foster shortage prevention:

1) commitment to quality –requires investment of resources by firms

2) redundancy of manufacturing/supplies and increased inventory/stockpiling

- Timely website postings with helpful information for healthcare professionals and patients regarding reasons for shortages and timelines for resolution

Shortage Information

- FDA drug shortage website is:

  http://www.fda.gov/Drugs/DrugSafety/default.htm

- To report shortages our e-mail account is Drugshortages@fda.hhs.gov

Drug Shortages Summit

Summary Report:

Appendix E

ASHP Guidelines on Managing Drug Product Shortages in Hospitals and Health Systems

DEVELOPED BY AN ASHP EXPERT PANEL ON DRUG PRODUCT SHORTAGES: ERIN R. FOX, ANNETTE BIRT, KEN B. JAMES, HEATHER KOKKO, SANDRA SALVERSON, AND DONNA L. SOFLIN

Am J Health-Syst Pharm. 2009; 66:1399-406

Purpose

Drug product shortages can adversely affect drug therapy, compromise or delay medical procedures, and result in medication errors.[1,2] Health care professionals are increasingly concerned about the clinical effect that shortages have on patients and the tremendous resources required to address shortages.[3-5] Adverse patient outcomes related to drug product shortages[1,2,6-9] have prompted aggressive management strategies by health care providers and gained the attention of the Joint Commission,[10] the government,[11,12] and the media.[13,14] Drug product shortages adversely affect health-system finances by increasing the cost of delivering patient care, largely through higher drug acquisition and personnel costs.[6] In addition, shortages create a high level of frustration for everyone involved, including purchasing agents, pharmacists, nurses, physicians, and patients.[7]

Managing drug product shortages is particularly complex for practitioners in hospitals and health systems (hereinafter, "health systems"), because these facilities routinely treat patients with acute or emergent conditions, use a significant number of medically necessary or single-source products, and use high-cost new drug technologies. These health care providers are challenged during drug product shortages to ensure the provision of seamless, safe, and therapeutically equivalent drug therapy, preferably at comparable costs. The pharmacy department must take a leadership role in efforts to develop and implement appropriate strategies and processes for inform-

Developed through the ASHP Council on Pharmacy Management and approved by the ASHP Board of Directors on January 15, 2009. These guidelines supersede the ASHP Guidelines on Managing Drug Product Shortages dated March 28, 2001.

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ing practitioners of shortages and ensuring the safe and effective use of therapeutic alternatives. Strategic planning is required for managing drug product shortages, just as it is for disasters such as major weather events and mass-casualty incidents.

Because a thorough understanding of why drug product shortages occur is essential for their successful management, these guidelines begin with a description of factors that contribute to or exacerbate shortages. The guidelines then describe a three-phase approach to contingency planning for management of drug product shortages and include strategies for prevention. Given the differences and complexities in health-system organizational arrangements and practice settings, some aspects of these guidelines may not be applicable in all settings. Pharmacy managers should use their professional judgment in assessing and adapting these guidelines to meet their needs.

Contributing factors

For the purpose of these guidelines, a drug product shortage is defined as 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. Shortages can be the result of one or a combination of factors throughout the supply chain. The supply chain includes sources of raw materials, manufacturers, regulators, wholesalers or distributors, prime vendors, group purchasing organizations, and end-user health care systems. The factors that follow contribute to disruptions in the availability of drug products.

Raw and bulk material unavailability. Disruptions in the supply of raw or bulk materials are especially problematic when the primary or sole source experiences production difficulties or discontinues production, affecting multiple manufacturers. An estimated 80% of the raw materials used in pharmaceuticals comes from outside the United States.[4] Availability problems can arise when armed conflict or political upheaval disrupts trade, animal diseases contaminate tissue from which raw materials are extracted, climatic and other environmental conditions depress the growth of plants used to produce raw materials, or raw materials are degraded or contaminated during harvesting, storage, or transport.

Manufacturing difficulties and regulatory issues. Drug product shortages can also occur when the primary or sole manufacturer of a drug product halts or delays production in response to a Food and Drug Administration (FDA) enforcement action concerning noncompliance with current good manufacturing practices (cGMPs). Contributing factors may include antiquated manufacturing equipment, a shift of resources from maintenance of equipment and facilities to research and development, loss of manufacturer personnel experienced in production and compliance issues as a result of company mergers or retirements, cGMP-related problems with subcontractors who supply products to multiple pharmaceutical manufacturers, and limited FDA resources for timely inspections of manufacturing sites.[4] Resolution of these issues is often a lengthy process and may include inspections to ascertain cGMP compliance, issuance of an injunction against the manufacturer, or seizure of products. In some instances, a manufacturer's decision to close a specific manufacturing facility results in unintended drug product shortages. Such was the case when the sole source for hyaluronidase production closed, leaving no supplier.[5]

FDA enforcement actions are intended to protect the public from potentially unsafe drug products. These actions are evaluated by FDA's Center for Drug Evaluation and Research (CDER) drug shortage coordinator to determine if the action might create a shortage of a medically necessary drug product.[12] (FDA's definition of a medically necessary product is discussed in the "Government intervention" section below.) In the event that a significant corrective action involves a medically necessary product, FDA will help the manufacturer return to compliance, consider qualifying additional manufacturing sites, or, in extreme circumstances, permit importation of the product from a foreign manufacturing source once the required quality controls are met.

Voluntary recalls. Voluntary recalls, generally related to manufacturing problems, can cause shortages, especially when a sole manufacturer's drug product dominates the market supply. Voluntary recalls are generally temporary and occur as a result of a minor lapse in manufacturing procedures that would not be subject to FDA legal action. Recalls usually affect specific lots and are conducted either because of a lack of assurance that the recalled product is safe or for reasons not related to safety, such as technical deficiencies in the drug's labeling. An ethical dilemma could arise when it is predictable that complying with the voluntary recall may cause a drug product shortage in a given health system.

Change in product formulation or manufacturer. Changes in a product's formulation or manufacturer may also delay product availability. One example is the transition from albuterol metered-dose inhalers (MDIs) containing chlorofluorocarbons to MDIs containing hydrofluoroalkanes in 2006.

Manufacturers' production decisions and economics. Manufacturers' business decisions are based on a variety of factors, including availability of generic products, market size, patent expiration, drug-approval status, regulatory compliance requirements, and anticipated clinical demand. Occasionally, manufacturers temporarily or permanently reduce production

quantities of certain drug products as they shift production efforts or reallocate resources to other products. A manufacturer's reasoned, sound business decision to discontinue production of a drug product because of insufficient financial return or a high cost to correct manufacturing issues can cause an unanticipated, serious shortage, especially in the instance of a sole-source or medically necessary product.[15] For example, a shortage of diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed was precipitated when one of the manufacturers, claiming low revenues, discontinued its product in 2000.[5] Manufacturers are not required to notify FDA of a drug discontinuation unless the product is a sole-source or medically necessary product.[16] For medically necessary drugs, FDA can encourage other manufacturers to produce the product or request that the manufacturer not suspend production until an alternative source is available. However, FDA does not have the authority to require a company to make any product, even if it is medically necessary. Even with advance notice, some agents, such as vaccines or antibiotics, are complex to manufacture, and shortages may result even if other manufacturers are willing and able to produce the product. Similarly, business decisions on the part of wholesale distributors and end-user health systems may contribute to drug product shortages.

Industry consolidations. Manufacturer mergers often result in decisions to narrow the focus of product lines or move a production line to a new facility, resulting in the discontinuation or delayed availability of drug products. Mergers between two companies that manufacture similar product lines typically result in single-source products. As the number of manufacturers of a product decreases, resiliency in the supply chain also decreases, making product supplies more vulnerable. Many vaccines in the United States are single-source products, in part because of discontinuations and consolidations.

Restricted drug product distribution and allocation. Most hospitals and health systems obtain the majority of their drug products through wholesale distributors. Restricted distribution methods that bypass the normal supply chain can also create shortages. As the result of either market approval requirements or postmarketing surveillance, manufacturers limit the availability of specific drug products. Only selected suppliers and end users who comply with manufacturer agreements can obtain the product. A manufacturer can also place restrictions on available limited supplies, requiring health systems to order directly from the manufacturer or through a specialty distributor to receive an allocation.

Inventory practices. Communication and transportation efficiencies throughout the supply chain have allowed inventory reductions at all levels. Most manufacturers, distribution centers, and health systems use "just-in-time" inventory management to reduce the cost of inventory on hand and optimize cash flow. This strategy is recognized as sound business management for all stakeholders, but an unexpected shortage at any point in the supply chain can significantly affect the end user and patient. Some manufacturers and distributors use inventory management strategies that minimize end-of-quarter or end-of-year product inventories or limit shipments based on yearly quotas.

Poor ordering practices, stockpiling before price increases, hoarding caused by rumors of an impending shortage, and unexpected delivery delays may affect inventory levels in individual health systems. Hospitals in rural areas face additional inventory challenges caused by distant distribution centers and the inability to easily borrow an item from a nearby hospital. Drug product shortages may also occur when all hospitals in an area disproportionately use the same wholesaler. Some shortages are wholesaler dependent, as shortages of drugs can occur when contracts with suppliers are delayed.

Unexpected increases in demand and shifts in clinical practice. Occasionally, the demand for a drug product unexpectedly increases or exceeds production capacity. This may occur when a new indication is approved for an existing drug product, when usage patterns change in response to new therapeutic guidelines, when a substantial disease outbreak occurs, or when unpredictable factors influence demand. Shortages may be prolonged when the raw materials are limited or manufacturing processes are complex or dependent on a long lead time. For example, when the Centers for Disease Control and Prevention (CDC) recommended annual influenza vaccination for children age 6–59 months in 2006, only one product had FDA-approved labeling for use in children 6–23 months old.[17,18]

Nontraditional distributors. The increased frequency of drug product shortages has precipitated the development of nontraditional distributors, also known as open-market, gray-market, or alternative distributors. These specialty, licensed distributors or brokers obtain products in short supply for the purpose of reselling them to end users who are unable to obtain them through their normal suppliers. These distributors aggressively market the availability of these products to hospitals, specialty health systems, home care agencies, and physician practices, generally at substantially higher prices. Typically, these distributors have a limited quantity of product, often only enough for one or two patients. Many do not offer a return or refund on a product if it expires or is not used. Especially worrisome is the inability to ascertain the product's

pedigree or ensure the reliability of the product's source, which could be outside the United States, and proper handling and storage throughout the chain of custody. The extent to which the activities of such nontraditional distributors contribute to drug product shortages is unknown.

Compounding pharmacies have also pursued the production of drugs that are in short supply. Caution is warranted because preparations from these pharmacies may not meet applicable state or federal standards (e.g., *United States Pharmacopeia* chapter 797 or FDA labeling requirements). The sources of raw materials used by compounding pharmacies have been questioned, and apparent lapses in quality control have resulted in serious patient injury, including death.[13]

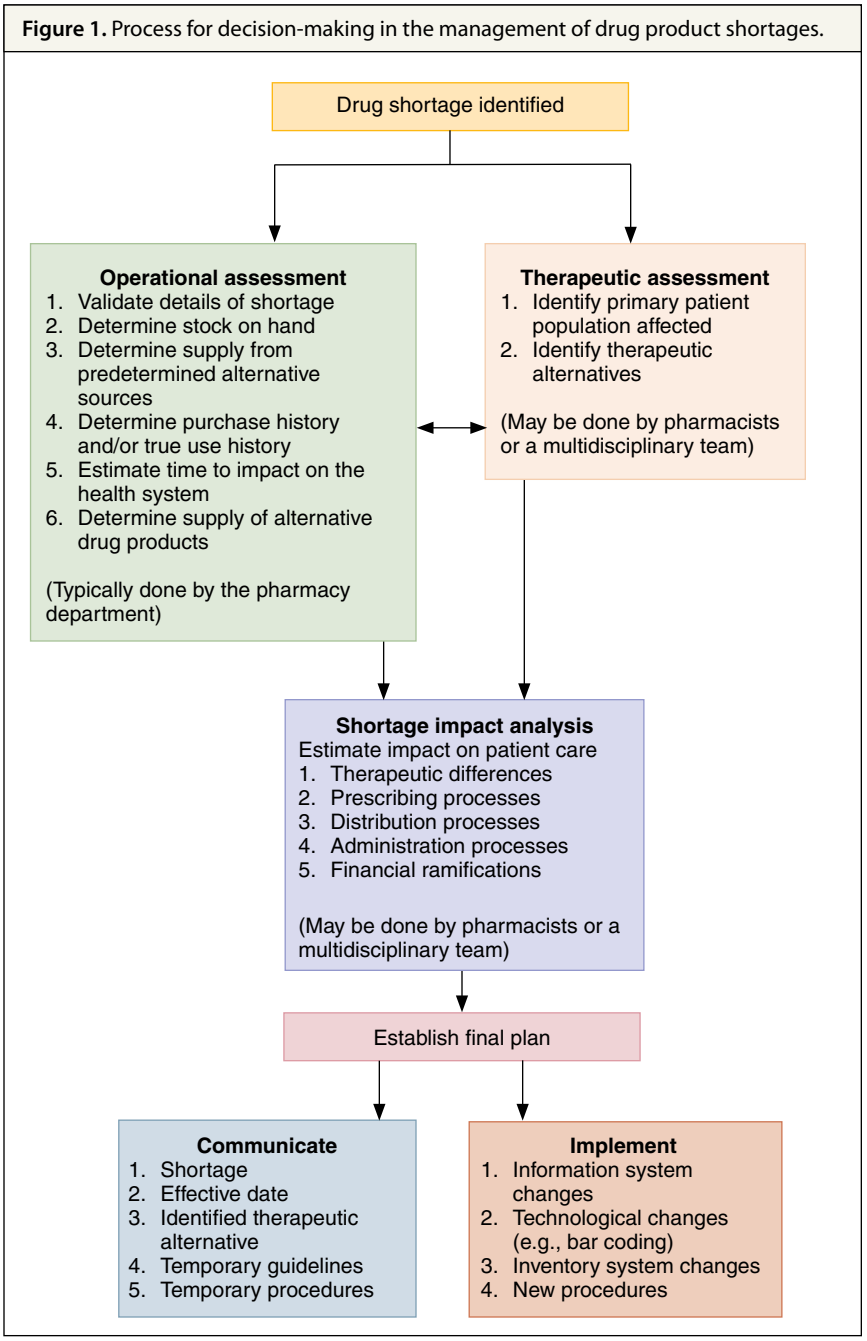
Natural disasters. Natural disasters can have a profound effect on the availability of drug products. Damage to manufacturing facilities, particularly those that are the sole source of a drug product or category of products, is likely to cause long-term shortages. Damage to manufacturing facilities in Puerto Rico in 1998 from hurricane George caused shortages of several drug products. Fires, hurricanes, tornadoes, and floods are examples of natural disasters that may temporarily compromise drug product supplies. In some instances, these shortages may be exacerbated by an escalated need for certain classes of drug products to care for victims of the disaster. In 2005, areas affected by hurricanes Katrina and Rita were affected by both an increased need for medications and the inability to obtain them.

Phased approach to planning for drug product shortages

The discovery of a shortage initiates a cascade of events surrounding drug procurement and therapeutic decision-making (Figure 1). Drug procurement considerations include validating the shortage and its anticipated duration, determining the availability of supplies from alternative sources, locating and procuring alternative supplies (if available), investigating the implications of compounding the product, and researching and providing education about alternative agents and the cost implications of all scenarios. The outcome of this process may prompt an evaluation of the shortage's potential effect on patient care and development of a strategy for effectively communicating the needed information to all professionals involved and to affected patients when warranted.

In an ideal world, there would be a system for warning providers in advance of impending drug product shortages; this would give them

Figure 1. Process for decision-making in the management of drug product shortages.



ample opportunity to proactively address and manage all aspects and implications of the shortage. In lieu of this ideal, pharmacists, when confronted with the unavailability of a drug product, want information on which to base decisions about meeting patient needs for the product. Segments of the supply chain, especially manufacturers and distributors, have been inconsistent in providing information and assistance to health systems. The difficulty in obtaining information is exacerbated by the many players, complexities, and uncertainties in the supply chain.

The pharmacy department must take a leadership role in managing shortages by developing and implementing appropriate strategies and processes for optimizing the safe and effective use of therapeutic alternatives. Health systems should develop a contingency planning strategy to prepare for the possibility of a prolonged drug product shortage.[19] Although it often is not possible to predict when shortages will occur, the process for dealing with them can be defined in advance. The health system should identify a point person to implement and monitor this process and establish an organizational approach to decision-making and communication. The institution should determine committee structures and responsibilities for decision-making during each phase of the process (e.g., pharmacy and therapeutics committee, medical executive committee).

Planning can be divided into three phases: identification and assessment, preparation, and contingency. Assessment requires a critical evaluation of the current situation and the potential effect of the shortage on the health system. An effective evaluation examines the reason for the shortage and estimates an end date; both internal and external supply availabilities are assessed.

The preparation phase consists of all activities that can be performed before the actual effects of the shortage are felt. Depending on the health system's inventory, when a back order or other notice is received, there is often lead-time before actual stock depletion. All patients whose treatment depends on the unavailable drug product and alternative therapies should be identified. Since many drug products have limited therapeutic alternatives, outages can have significant patient care and cost consequences. Health systems need to gauge the effect of those consequences on their institutions. Preparation should also include the development of methods for implementation and communication.

The contingency phase involves operations and circumstances for which preparation is limited because of incomplete information, financial constraints, or circumstances beyond the health system's control. For example, biological products are available only in increments and at a very high cost when no therapeutic alternatives are readily available or when shortages are longer than anticipated. Since direct control over availability is not possible, health systems must prepare for a product's unavailability.

Identification and assessment phase. The purchasing agent is often the person who identifies a shortage and may be the person responsible for managing drug product shortages. This person must be cognizant of aberrant fluctuations in the health system's supply chain that may indicate a potential shortage (e.g., partial orders filled, one strength difficult to obtain, most manufacturers have no more stock). If the purchasing agent is not a pharmacist, he or she must work with a designated pharmacist.

When a shortage is identified, the point person or his or her designee should conduct an assessment to evaluate its potential effect. A threat analysis using the shortage's expected duration and an assessment of the current inventory and usage patterns can be used to determine the potential consequences of the shortage.

Details and duration of shortage. Pharmacists can contact product manufacturers, distributors, FDA, CDC, and other sources to determine the reason for the shortage and its expected duration. This information may already be available on the ASHP Drug Shortage Resource Center Web site (www.ashp.org/shortages). If not, visitors to the site can report a shortage online. Predictions of when the product will be available help determine the health system's ability to endure the shortage and guide its short- and long-term management strategies.

Although the end result is the same, the time to impact and the duration of effect vary according to the reason for the shortage and where in the supply chain problems occur—from raw materials to manufacturer, manufacturer to wholesaler, or wholesaler to health system. A lack of raw materials may affect several manufacturers of the finished drug product. A manufacturer's problems may affect only its product. Effects on distributors are dependent on their inventory levels.

Inventory on hand. Once a shortage is confirmed, the pharmacy should count the inventory on hand and estimate the time period it will cover. Available inventory includes all supplies of the drug product within the health system, including the pharmacies, inpatient units, ambulatory care clinics, automated medication storage and distribution devices, floor stock, resuscitation carts, and prepared trays.

Based on available quantities and historical usage, the pharmacy should estimate how long the health system can endure a shortage. Usage history can be obtained from procurement and issue records held by distributors, the purchasing department, and the pharmacy department. Billing and automated medication storage and dispensing device records can

assist in determining actual usage within the system.

Inventory counts of all alternative drug products should be converted into common measurement units to augment estimates of use. Both current use rates and reduced rates after conservation measures are implemented should be included when assessing how long the available inventory of the shortage drug product and possible alternative products will last.

Threat to patient care and costs. A threat analysis evaluates all factors relevant to the shortage (e.g., duration, current inventory, medical necessity, alternative sources or therapies) to determine the shortage's potential effect on patient care and costs. Shortages affect safe medication practices throughout the medication distribution and administration process within a health system. When considering alternative dosage forms or therapies, pharmacists must consider changes in their procedures for look-alike and sound-alike medications, bar coding, distribution paths, and the effect on automation, contract compliance, and final product preparation.[20] The extent to which a health system will be affected by a given shortage depends on the health system's scope and level of services and its service population.

Preparation phase. Once an imminent shortage is confirmed, the health system should take steps to prepare for known and potential problems in maintaining patient care and controlling costs.

Therapeutic alternatives. The first step in the preparation phase is to identify therapeutic alternatives to the unavailable drug product. A formal process for identifying and approving therapeutic alternatives for the health system should be established. The health system should make decisions about alternative agents in collaboration with medical, nursing, and pharmacy representatives and obtain approval of the appropriate medical committees. Therapeutic alternatives should be inventoried to ensure adequate supplies to meet new demand. In many cases, supplies of the best alternative agent may be affected by the current shortage.

Communication and patient safety. Information about the drug product shortage, alternative therapies, temporary therapeutic guidelines, and implementation plans should be communicated to clinical staff by the most effective means available within the health system. Communication of this information is essential for ensuring patient safety and preventing medication errors caused by confusion over differences between drug products' dosages, onsets, durations, and other factors. Automated systems and order-entry systems must be updated with changes. Pharmacy department staff responsible for assisting prescribers with medication orders and aiding nursing staff with administration should be thoroughly informed about the alternative therapy decisions and implementation plans. Sustained communication is necessary to reach medical, nursing, and pharmacy staffs working varied shifts or services.

External relationships with other health systems. The preparation phase includes, when applicable, the establishment of collaborative arrangements with other institutions within a regional network or system. Available supplies of a potentially unavailable product and information about alternative therapies should be shared among the facilities. This option is limited for rural hospitals and for area hospitals served by a single wholesaler.

Patient prioritization. When a limited supply of a drug remains available and alternatives for specific patient groups are undesirable, a health system may prioritize the drug for specific patient groups. National organizations (e.g., CDC, medical organizations) may provide guidance on setting patient priorities. Medication-use evaluation data on prescribing and utilization trends, if available for the drug in question, may be useful in developing prioritization criteria to guide appropriate drug use. Such criteria are particularly helpful in dealing with long-term shortages such as with intravenous immunoglobulin. To limit product use for select patients or services in the health system, criteria should be developed by a multidisciplinary team. Communication is essential to ensure that adequate supplies are available to complete courses of therapy. Clear guidelines for prioritization must be provided to assist pharmacists in evaluating the appropriateness of medication orders.

Consultation with risk management and ethics staff members or committees may be useful when supplies are severely limited. For example, during the influenza vaccine shortage of 2004–05, many health systems did not have sufficient product to follow recommended CDC guidelines and further restricted use of the product to specific patient groups.

Stockpiling restraint. Inventory management is a challenge during a shortage. Despite pressure to do otherwise, stockpiling (hoarding) in advance of a feared shortage can occur; this can exacerbate the shortage and divert unneeded supplies away from other health systems with patients in need.[21] Health systems should refrain from stockpiling, which causes two distinct problems:

1. Stockpiling can cause artificial shortages when health systems drain the supply chain and exceed manufacturing capacities, and
2. Increased inventory is costly and may not be absorbed by normal usage if shortages do not occur as anticipated.

Speculative purchasing in response to a potential shortage has drawbacks, depending on the likely

cause of the shortage and where it might occur in the supply chain. Problems may arise that pose threats to, but do not reach, end users. This happens when the supply chain, from raw material to finished product, contains several months' supply; the long lead-time allows corrections that avert a shortage.

During shortages, manufacturers and distributors often allocate a product on the basis of past usage. An initial stockpile order generally has no effect on increasing an allocation.

Contingency phase. Health systems must establish clear guidelines for dealing with situations in which a product is available only from a compounding source or nontraditional source or when a critical drug is not available at all.

Risk management and liability. One potential complication of a shortage is litigation by patients who feel that they have received improper care or suffered unanticipated adverse drug events as a result of delays, prioritization, alternative therapy, or nontraditional drug product sources. This situation is most likely with agents for which no alternatives are available. Even though risk management and legal representatives may have participated in earlier phases of the process, they should be notified immediately when all options for obtaining either the drug product or acceptable alternatives have been exhausted.

Each health system must determine its philosophy on purchasing drugs from the gray-market or compounding pharmacies and on compounding agents inhouse. These decisions should be made before the pressure and emotion of a specific shortage occur. Each option and its potential effect on patient risk should be evaluated. Nontraditional drug product sources (e.g., secondary wholesalers) have extremely limited supplies, and the quality of these products may be questionable, as the provenance of the medication may be unknown. Compounding pharmacies may also present patient risks; several deaths have been associated with improperly sterilized compounded products.[9] Health systems may choose to compound products if they can meet the necessary guidelines; however, obtaining raw materials may be difficult in some cases.

Budget considerations. In the event that the drug product is available only from noncontracted manufacturers or through nontraditional distributors, the increased costs of using these sources should be estimated. Using alternative therapies may also increase costs. The financial implications should be presented through budget channels, with a request and justification for contingency funds. Additional expenditures caused by drug product shortages (e.g., overtime spent in locating product, extra or priority deliveries, inhouse compounding or packaging) must be documented to explain budget variances and to support future budget proposals.

Information coordination and communication. Clear communication with all affected clinicians about the status of a shortage is vital. Some health systems may designate a specific department to manage communications; others may find that a collaborative strategy involving various organizational departments and committees works best. Patients or family members should be counseled when a drug product shortage will delay or compromise care, especially when patients have been stabilized on the drug product and when alternatives may not be as effective (e.g., pain or blood pressure medications). The Joint Commission requires that prescribers potentially affected by drug product shortages be actively alerted.[10]

Strategies for prevention

Communication with the media, national professional or patient organizations, and government agencies can raise awareness of the shortage and its potential consequences. Notifying ASHP or FDA about a drug product shortage can initiate these efforts. Drawing attention to the shortage may encourage production by other manufacturers, collaborative efforts to develop alternative therapies, and ad hoc training opportunities on the safe and effective use of alternatives.

Government intervention

FDA is responsible for assisting with drug product shortages to the extent of its authority.[11] Its responsibilities are dispersed among several components of CDER. The extent of FDA's activities depends on whether a shortage meets "medical necessity" criteria. FDA will attempt to prevent or alleviate shortages of medically necessary products. A product is considered to be medically necessary or a medical necessity if it "is used to treat or prevent a serious disease or medical condition, and there is no other available source of that product or alternative drug that is judged by medical staff to be an adequate substitute."[12] Inconvenience to the patient and cost to the patient, institution, and manufacturer are insufficient reasons for classifying a product as a medical necessity.

A determination of medical necessity involves a risk–benefit evaluation of the compromising issue with the product versus the medical need. When FDA has determined that a shortage of a medically necessary product exists, the agency will act within its authority; actions may include discussions with pharmaceutical manufacturers to encourage additional sources, technical assistance to manufacturers experiencing cGMP difficulties, or expedited reviews of drug product marketing applications or cGMP-related improvements. FDA may take these actions whether the cause of the shortage involves business decisions to stop manufacturing the product, voluntary recalls, FDA

enforcement actions, or other factors. Information on the availability of medically necessary drug products is posted on CDER's website, and information regarding the availability of blood and vaccine products regulated by FDA's Center for Biologics Evaluation and Research (CBER) is posted on CBER's website. FDA encourages consumers and health care professionals and organizations to report product shortages. Reports of drug product shortages can be made by e-mail via CDER's Drug Shortages website (www.fda.gov/cder/drug/shortages/default.htm), and reports on vaccine and blood product shortages via CBER's Biological Products Shortage website (www.fda.gov/cber/shortage/shortage.htm). FDA's shortage team will obtain information about availability and will work cooperatively with ASHP's drug product shortage team.

Conclusion

Drug product supply issues are becoming more frequent, whether they result from manufacturing difficulties or natural disasters that affect production, reductions in the supply of raw materials, voluntary recalls, manufacturer business decisions, FDA enforcement actions to ensure public safety, or stockpiling that leads to artificial shortages. Although it is impractical to prepare for every potential shortage, proper planning can minimize adverse effects on patient care and health-system costs and prevent problems from escalating into crises. The key to success will undoubtedly be found in the effectiveness of information gathering, teamwork to assess options, and communication with providers, patients, and administrators.

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Drug Shortages Summit

Summary Report:

Appendix F

15 YEARS ISMP Helping You Keep Patients Safe
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Educating the healthcare community about safe medication practices
A federally certified Patient Safety Organization PSO
ISMP MedicationSafetyAlert!® Acute Care
September 23, 2010 ■ Volume 15 Issue 19

SafetyBriefs

Doribax-Zovirax name confusion. At a hospital where medication orders are routinely entered by unit secretaries, a handwritten physician order for **DORIBAX** (doripenem), a carbapenem-type antibiotic, was incorrectly entered as **ZOVIRAX** (acyclovir) 500 mg IV q8h (see Figure 1). For verification, a copy of each order was also

Figure 1. Zovirax or Doribax?

scanned and sent to a unit-based pharmacist covering the area. The pharmacist reviewing the order initially agreed that it appeared to be the antiviral, Zovirax, but later admitted that there was probably some bias on his part, since the order was already entered as Zovirax by the unit secretary. Also, 500 mg IV q8h would be an appropriate dose for Zovirax. However, this order was written by a pulmonologist, which seemed unusual, so the pharmacist decided to investigate. When he accessed an electronic copy of the history and physical, he did not see an indication for Zovirax, at least on the initial admission history. To determine if he needed to contact the physician, he went to the unit (a medical ICU) to read the physician's latest progress note to get a full picture of the situation. There, Doribax was clearly written. There may be a risk in having unit secretaries interpret orders and perform order entry, as they may see the drug names with which they are most familiar due to confirmation bias and/or may not be fully concentrating on the process, especially when there are high volumes of orders and frequent interruptions. Had the ordering physician been an infectious disease specialist, the order might not have been questioned. Nevertheless, due to potential carbapenem resistance, limiting the prescribing of Doribax to infectious disease physicians is best.

Ambiguous directions, wrong assumption by patient. A 67-year-old male arrived at a hospital emergency department (ED) with hypotension, tachycardia,

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Special Issue

Drug shortages: National survey reveals high level of frustration, low level of safety

An exhaustive account of frustrations, difficulties, and patient safety concerns came across loud and clear from more than 1,800 healthcare practitioners (68% pharmacists) who participated in our July-September 2010 survey on drug shortages.[1] Many respondents stated that the conditions associated with drug shortages during the past year have been the worst ever, without a glimmer of hope for any improvement in the near future. They feel unsupported by the Food and Drug Administration (FDA) and perplexed regarding why the US is experiencing drug shortages of epic proportion that are often associated with third-world countries. Respondents clearly believe the public is severely impacted by this issue, and several suggest that the problem has risen to the level of a national public health crisis.

By far, respondents were most alarmed by: the ever-increasing volume of critically important medications in short supply; the use of less desirable, often expensive, unfamiliar alternative drugs—if even available; the potential for errors and poor patient outcomes caused by absent or delayed treatment or preventable adverse drug events associated with alternative drugs or dosage forms; the lack of advanced warning about an impending shortage; and precious clinical hours lost to time-consuming activities required to manage drug shortages.

Frequency of drug shortage difficulties

During the past year, more than half of the respondents reported *frequently* or *always* encountering every one of the potential difficulties associated with drug shortages identified in our survey, which are listed in the next column in descending order starting with the most frequently encountered difficulty:

- Little or no information available about the duration of a drug shortage (85%)
- Lack of advanced warning from manufacturers or FDA to alert practitioners to an impending drug shortage and suggested alternatives (84%)
- Little or no information about the cause of the drug shortage (83%)
- Substantial resources spent investigating the shortage and developing a plan of action (82%)
- Difficulty obtaining a suitable alternative product (80%)
- Experience a significant financial impact (78%)
- Lack of a suitable alternative product (70%)
- Substantial resources spent preparing and/or administering the alternative products (69%)
- Risk of adverse patient outcomes (64%)
- Internal hoarding of medications associated with impending shortages (58%)
- Physician anger towards pharmacists/nurses/hospital in response to a drug shortage (55%).

Physicians and pharmacists, particularly pharmacy managers and directors, reported encountering the above-listed problems more frequently than nurses, especially in areas such as spending resources to investigate shortages, developing a plan of action, hoarding medications in short supply, obtaining a suitable alternative, and experiencing the financial impact of purchasing drugs off contract or through secondary markets, or higher rushed delivery costs. While all professional disciplines clearly reported grave concerns regarding the risk of adverse patient outcomes during drug shortages, physicians reported encountering this risk more frequently than others, preceded in frequency only by

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gray vision, and lightheadedness. The patient's EKG showed abnormal sinus rhythm resembling atrial fibrillation. He was admitted for observation and his cardiologist was consulted. The initial plan was to start this patient on digoxin and increase his metoprolol dose. During a medication reconciliation meeting with the pharmacist, the patient described taking **FLOMAX** (tamsulosin) 0.4 mg capsule with meals, three times a day. On the day of his admission, he said he'd only taken his "breakfast dose" before coming to the ED. He said he'd started Flomax 2 weeks before and had taken one capsule three times a day the entire time, noting that the medication bottle said "take daily after a meal." The patient admitted that he had assumed that these directions meant to take the medication after *every* meal. A decision was made to stop the Flomax and to not treat the patient with digoxin or increase his metoprolol dose. The patient returned to normal sinus rhythm, blood pressure, and heart rate by the next morning. The product label mentions that this medication should be taken once daily after a specific meal and repeated each day after the same meal. For example, "Take one capsule by mouth once daily after lunch." The patient should have received better education when picking up his prescription to ensure he understood how to properly use this medication. Vague directions on labels can lead to the incorrect assumption even by well-educated, competent patients.

HIGH-ALERT **EPINEPHrine for norepinephrine?** An error in the Bridge MedPoint System barcode software (Cerner Corporation) misnames norepinephrine as **EPINEPH**rine in one of the database fields (see Figure 1). The editable description field autoloads

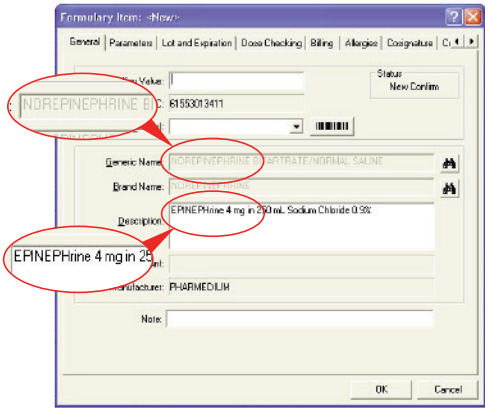

Figure 1. EPINEPHrine displays in description field when norepinephrine is selected.

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Drug shortages continued from page 1

lack of information about the causes and duration of shortages and lack of advanced warning from manufacturers or FDA.

Near misses, errors, adverse outcomes

Approximately one in three (35%) respondents reported that their facility had experienced a near miss during the past year due to a drug shortage. About one in four reported actual errors and one in five reported adverse patient outcomes during the past year due to drug shortages. More staff level practitioners (21%) reported adverse patient outcomes than administrative staff or directors/managers (18%), and as many as one in three (33%) physicians reported an adverse outcome caused by drug shortages this past year, more than pharmacists (21%) or nurses (16%). However, many respondents repeatedly commented that errors and adverse patient outcomes were not shared with them on a routine basis, were based on sporadic voluntary reporting, or were difficult to quantify. Thus, many felt the frequency of errors and adverse outcomes due to drug shortages is much greater than reported, and that not being aware of events did not mean they were not happening.

Respondents provided disquieting details regarding actual near misses, errors, and adverse patient outcomes associated with more than 50 drugs that had abruptly become unavailable, often without adequate notice. Table 1 (pages 5-6) provides just a glimpse at the many—more than 1,000!—near misses, errors, and adverse outcomes reported by respondents that occurred during the past year due to drug shortages. Especially troubling is that many of the drugs involved in the shortages are high-alert medications, such as propofol, heparin, **EPINEPH**rine, morphine, neuromuscular blocking agents, chemotherapy, 50% dextrose, and parenteral electrolyte supplements; if not a high-alert medication, many other drugs in short supply are essential and lifesaving, such as antibiotics, IV fat emulsion, and fosphenytoin.

Lack of alternative medications

Some drug shortages result in situations where a viable alternative is not available. For example, according to respondents, the shortage of amikacin and acyclovir has contributed to patient deaths from infections that were only sensitive to amikacin or treatable with acyclovir. Alternative antibiotics and antiviral medications were of little help in these situations. The shortage of various chemotherapeutic agents and adjunct therapy is another prime example. One respondent reported that stem cell transplantations were on hold because etoposide is not available. Another respondent said that important investigational drug studies have been put on hold because an adequate supply of adjunct medications required in the protocol could not be assured. Some hospitals and outpatient surgical centers have been forced to postpone surgeries indefinitely due to shortages of propofol and neuromuscular blocking agents; some have transferred patients to facilities that still have a supply of these crucial medications.

Issues with alternative medications

In other cases, alternative drugs or dosage forms/strengths are available when a drug shortage occurs, although the purchase price is often high. But even when alternatives can be identified, three serious problems were repeatedly voiced by survey respondents.

First, an alternative medication is often just that: an alternative to a drug with superior efficacy and/or a lower risk profile. For example, according to our survey respondents, alternative agents used in place of propofol for deep sedation have resulted in higher incidences of agitation and self-extubation in ventilated patients, and postoperative nausea and vomiting (related to the sedative, not analgesics) in surgical patients, which often led to extended hospitalization. To cite another example, an alternative medication may pose greater risk to patients with renal impairment than the drug in short supply.

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SafetyBriefs continued from page 2

"**EPINEPH**rine," displaying it on the bedside module, on printed worksheets, and the medication administration record (MAR) if not caught. The problem is present with four line items for norepinephrine: NDC 61553011511, 66647615733, 61553012011, and 61553016411. Cerner states the problem will be corrected in a free October update, but it's important for users to know about it now due to the potential for inaccurate documentation and false impression that **EPINEPH**rine 4 mg was given or that a 4 mg dose of **EPINEPH**rine should be reordered. Nurses might catch the error during order confirmation or via warnings when scanning **EPINEPH**rine. But relying on staff to catch all order entry errors is not a dependable error prevention strategy. We've notified Cerner of our concern and hope they will alert users as soon as possible.

UK ahead in preventing catheter misconnections. The National Patient Safety Agency (NPSA) in the United Kingdom has launched a newsletter to keep National Health Service (NHS) workers informed about the implementation of medical devices with safer connectors, in particular devices for epidural or intraspinal use that cannot accidentally connect to IV systems. NPSA issued a *Patient Safety Alert* in November 2009 which recommended using syringes, needles, and other devices with safer connectors that cannot fit/connect with intravenous Luer connectors for all spinal (intrathecal) bolus doses and lumbar puncture samples by April 1, 2011. NPSA is relying on the medical device industry to help hospitals meet this goal. Medical device and pharmaceutical manufacturers are expected to supply devices with safer connectors before the required implementation date to enable clinical evaluation and changes to occur. *Neuraxial Update* listed various commercial suppliers who are developing medical devices with designs that will be compliant with NPSA recommendations. However, not all of the suppliers will be ready in time for hospitals to meet a 6-month trial period before the April 1, 2011 date. Although no company has publicly stated it will make Luer-incompatible neuraxial connectors in the US, among the device manufacturers in the UK are some that are well-known here, including Becton Dickinson (BD), B Braun Medical, and Smiths Medical. The newsletter, including a full list of vendors, can be accessed at: www.patientsafetyfirst.nhs.uk/ashx/Asset.ashx?path=/Medicationsafety/NPSA-Neuraxial%20Update%20Newsletter-Aug%202010.pdf. Additional updates can be viewed at: www.nrls.npsa.nhs.uk/resources/?EntryId45=65259.

Drug shortages

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Certain diseases and conditions can be compromised when alternative products produce less than optimal treatment outcomes. In some instances, patients have allergies or a history of adverse reactions to the alternative medication and are left without an effective treatment option.

The next issue survey respondents raised is that the supply of alternative products can quickly become exhausted, leading to a secondary shortage of the alternative medication. For example, supplies of **HYDRO**morphone, a commonly used alternative during the morphine shortage, have become increasingly more difficult to obtain, particularly lower dose unit-of-use **HYDRO**morphone syringes. Thus, **HYDRO**morphone injection now joins morphine injection on the drug shortage list. The demand for an alternative drug may outpace the current supply, and companies that manufacture the product may not be prepared to address the sudden increased demand. The practice of hoarding drugs and viable alternatives in short supply by facilities places further demand on manufacturers.

The third pressing issue raised by respondents is the risk of an error or adverse outcome when being asked to use unfamiliar alternative drugs. What is the correct dosage range and dosing frequency of the alternative drug? How is it prepared, stored, and administered? Are there untoward side effects that require patient monitoring? With so many drugs in short supply, several respondents admitted to increasing difficulty in just remembering which products are involved and what the suitable alternatives are—let alone how to safely prescribe, prepare, dispense, and administer the alternative drugs.

Physicians are asked to prescribe unfamiliar alternative drugs on the spot when called about an order for a drug in short supply; pharmacists are asked to safely dispense alternative medications, which often require additional unplanned time to prepare; nurses report that they never know what to expect when gathering medications. Will it be **HYDRO**morphone 1 mg/mL syringes in the automated dispensing cabinet? 2 mg/mL syringes? A 10 mg/mL vial? Will a totally different drug be required as an alternative? One nurse respondent stated, "I have lost count of how many times I have caught or witnessed another nurse catch a dosing error associated with **HYDRO**morphone since we never know what to expect."

Respondents also touched upon the ethical dilemma they face when trying to prioritize use of any remaining stock of drugs involved in a shortage. Who gets the desirable medication, and who gets what may be a less desirable alternative drug? The stress of making such decisions can be seen in the brutally honest and emotional responses from the survey participants. As noted by one respondent, when a suitable alternative for a lifesaving drug is no longer available, "I guess patients just have to die." Another respondent asked, "What do I tell our breast and lymphoma patients? You *had* a curable disease but *not anymore* because there is no drug available?"

Lack of notification about shortages

Respondents expressed significant concern regarding the lack of prior notification regarding an impending drug shortage. Most pharmacists (40%) and pharmacy technicians (51%) learn about a drug shortage the hard way—when the pharmacy department fails to receive an ordered product from a wholesaler or manufacturer. The next most frequently cited sources (24-32%) for learning about shortages included internal purchasing staff, word of mouth from other hospitals or professional listserves, secondary market contacts, and the American Society of Health-System Pharmacists (ASHP) website. Some respondents told us they often feel the impact of the shortage before it is officially communicated as a shortage.

Very few (6-15%) pharmacists, pharmacy technicians, nurses, and physicians rely on the FDA website or an advanced

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Special Announcements...

Prepare for Pharmacy Week. *National Hospital and Health-System Pharmacy Week* is **October 17-23.** Now through October 31, you can purchase videos, DVDs, posters, and other essential medication safety resources from ISMP's online catalog at significantly discounted prices. For more information, please visit: http://onlinestore.ismp.org/shop/.

Date change. The date of the ISMP webinar, *Beyond "Be Careful": Maximizing Perinatal Medication Safety*, has been changed to **October 27, 2010**, from 1:30-3:00 p.m. (EDT). For more information, please go to: www.ismp.org/educational/webinars.asp.

ISMP November webinar. Join us on **November 17** (1:30-3 p.m.) for: ***HYDRO**-morphone: Balancing the Benefit and Risk for Patient Care.* As **HYDRO**morpone use has become more commonplace, so have reported errors and serious adverse events associated with misunderstandings about equianalgesic dosing, inappropriate patient monitoring, confusion among product concentrations, and mix-ups with morphine. ISMP invites all safety-minded practitioners to participate! For details, visit: www.ismp.org/educational/webinars.asp.

ISMP Canada webinar. On **October 27** (12-1 p.m.), ISMP Canada is presenting: *Hospital-Acquired Acute Hyponatremia: Prevention is Key.* The discussion will provide valuable insight into how practitioners can lessen the possibility of patient harm from hospital–acquired hyponatremia, which has caused needless tragic deaths. For details, visit: www.ismp-canada.org/education/webinars/20101027_Pediatric_Hyponatremia_H/.

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notice from a wholesaler, distributor, buying group, or drug manufacturer to learn about drug shortages. Among these entities, practitioners found the buying groups and wholesaler/distributors more helpful than FDA and the manufacturer. Some respondents suggested that drug manufacturers and distributors intentionally withhold information about an impending shortage until the last moment to prevent hoarding. This delay poses a significant threat to safety because practitioners have little time to prepare for the shortage.

Half of the physicians (50%) reported learning about drug shortages from pharmacists who call them after they have prescribed a drug in short supply, or from colleagues and the literature. Likewise, most nurses (52%) told us they learn about drug shortages primarily from the pharmacy department staff or unit manager; about 30% first learn about a drug shortage when pharmacy fails to dispense a prescribed medication.

Respondents also expressed their frustrations with drug companies that fail to disclose the cause of the shortage and underestimate how long the shortage will last. The disparity between information provided by drug companies and actual resolution of the shortage was called "unacceptable" by many.

Problems with secondary markets

Respondents voiced a growing concern that secondary markets (often called gray or black markets) seem to be able to gain access to drugs that are no longer available to healthcare providers through usual sources. These secondary markets contact pharmacists to advertise availability of scarce drugs, often at exorbitant prices. Some pharmacists expressed worry about the quality of products from secondary sources and felt that the exorbitant prices breach ethical lines, particularly when the drug in short supply is an essential lifesaving medication. Further conflict between healthcare providers and drug companies arises from what appears to be allowing select groups of individuals to still have access the drug or to be given a preferential warning about impending shortages so they can stockpile the drugs.

Next steps

The impact of drug shortages has taken an enormous toll on healthcare providers who are responsible for dealing with the problem, and the patients who are on the receiving end of the shortage. The man-hours alone spent on planning for the shortage, educating staff, restocking and coding the alternative products, dealing with secondary market vendors, and fielding calls from healthcare practitioners consumes a large portion of the pharmacists' time, stealing valuable resources from clinical activities. Some respondents believe a full-time position will be needed in the future to manage drug shortages if the situation does not improve. Overall, survey respondents conveyed a real sense of crisis and are clearly looking for external support to reduce the burden and harm associated with drug shortages.

As mentioned in our article *Drug shortages threaten patient safety*, in our July 29, 2010 issue (www.ismp.org/Newsletters/acutecare/articles/20100729.asp), ISMP and ASHP are interested in co-convening a public meeting with FDA and other key stakeholders representing the pharmaceutical industry, healthcare practitioners, regulatory authorities, and medication safety experts to explore and articulate the scope of this problem, and to develop a plan to reduce the occurrence of drug shortages and better manage them when they occur. More effective FDA oversight, a comprehensive early warning system, and patient safety and outcomes placed ahead of anyone's profit margins are goals we hope to begin to explore at this meeting. ISMP and ASHP will keep readers apprised of progress to this end. Meanwhile, in a subsequent newsletter, we plan to provide guidelines for managing drug shortages on a local level within healthcare organizations.

Reference: 1) ISMP. ISMP survey on drug shortages. *ISMP Medication Safety Alert!* 2010;15(15):4.

Table 1 appears on pages 5-6

Drug shortages continued from page 4

Table 1. Examples of Near Misses, Errors, and Adverse Outcomes Associated with Drug Shortages

Propofol
■ Unintended intraoperative awareness occurred when a patient was given too little propofol based on weight in an attempt to conserve supplies
■ Misprogrammed **PRECEDEX** (dexmedetomidine) concentration in a smart pump; the drug was not in the library because it had never been used before the propofol shortage; the patient received a 20-fold overdose for 5 hours
■ Physician unfamiliar with Precedex dosed the drug in mcg/kg/minute instead of mcg/kg/hour
■ Infused **VERSED** (midazolam) at usual propofol rate; entire bag infused within a few hours, leading to oversedation
■ A paralyzed, ventilated patient received no sedation because propofol was not available and an alternative drug was never prescribed
■ Prolonged hospitalization from intractable post-op nausea and vomiting has occurred with alternative sedation agents
■ Difficulty extubating patients due to residual effects of **ATIVAN** (**LOR**azepam)
■ Patients developed phlebitis and other known adverse reactions when etomidate was used in place of propofol
■ Respiratory spasms and airway obstruction required conversion to general anesthesia when alternative agents were used for sedation
■ Inadequate sedation with benzodiazepines led to agitation and self-extubation; one patient bit through her tongue
■ Difficulty weaning patients from the ventilator when using alternative sedation
■ Unnecessary use of general anesthesia for procedures that could be performed with deep sedation
Neuromuscular Blocking Agents
■ Compounded syringes of vecuronium and succinylcholine from the same company looked similar; auxiliary labels for vecuronium accidentally applied to succinylcholine, leading to a mix-up
■ Infused rocuronium at the rate intended for cisatracurium
■ Administered pancuronium to patient with renal failure, which resulted in excessive and prolonged paralysis and tachycardia
■ Patient given the wrong dose of a neuromuscular blocking agent when the anesthesia provider forgot that an alternative drug was being used
■ Patient received the wrong dose of succinylcholine after an alternative concentration of the drug was provided
■ Several patients receiving rocuronium got the wrong dose because the physician dosed it in mcg/kg/hour, not mcg/kg/minute
■ Wrong dose of vecuronium calculated using a written protocol intended for pancuronium
■ Early self-extubation due to shorter duration with alternative neuromuscular blocking agents
■ Cancellations of surgeries and procedures
■ Two patients developed possible rocuronium-induced pulmonary hypertension when preferred agents, cisatracurium and vecuronium, were unavailable
Morphine
■ IV **HYDRO**morphone prescribed at the intended dose for morphine and administered, resulting in the death of two patients
■ **HYDRO**morphone 0.5 mg IV was supposed to be substituted for morphine 4 mg IV, but **HYDRO**morphone 4 mg IV was given in error
■ Administered 4 mg of morphine IV believing the vial held 2 mg
■ Administered 8 mg of morphine IV instead of 2 mg; only 8 mg syringes available from manufacturer
■ Administered 10 mg (10 mg/mL) of morphine instead of 1 mg (1 mg/mL); patient required naloxone and was transferred to critical care
■ Misfilled an automated dispensing cabinet (ADC) pocket for 2 mg morphine vials with 10 mg morphine vials
■ Patient switched from morphine 6 mg IV to **HYDRO**morphone without changing the dose; patient received several 6 mg doses, which required naloxone administration and increased the length of hospitalization
■ Wrong dose of morphine administered after 4 mg/mL prefilled syringes were replaced with 5 mg/mL vials; bar-coding system overridden due to the emergent switch in strengths, which had not yet been entered into the bar-coding system
■ Increased incidence of drug diversion because pharmacy-prepared syringes of morphine and **HYDRO**morphone are less tamper-resistant than commercially available syringes
EPINEPHrine
■ Unable to keep up with the demand for **EPINEPH**rine doses during a code, as each 1:1,000 ampul needed to be diluted; patient died
■ 10-fold overdose of **EPINEPH**rine administered when nurse withdrew 10 mL of a 1:1,000 solution, assuming the vial contained a 1:10,000 solution
■ During **EPINEPH**rine shortage, 30 mL vials of topical **EPINEPH**rine were ordered by mistake and loaded into crash carts; the wrong product was reordered from the same order label several times
■ In crash carts, **EPINEPH**rine Bristojects were replaced with an **EPINEPH**rine syringe with a permanently attached intra-cardiac needle; during a code, a nurse jammed the cardiac needle through a needleless system port, which broke the valve; the tubing had to be changed during the code
■ **EPINEPH**rine with an intra-cardiac needle was needed but not available during a code; the cart had been stocked with **EPINEPH**rine 1:10,000 prefilled syringes (no cardiac needle) from a compounding company
■ An **EPINEPH**rine 1:1,000 (1 mg/mL) ampul was removed from an ADC; nurse administered the entire ampul IV along with other IV medications but should have administered 0.3 mg IM; patient developed tachycardia and elevated troponin levels necessitating transfer to another hospital
■ A patient failed to respond during a code after a nurse accidentally administered a pediatric emergency dose of **EPINEPH**rine, although the cart was stocked with **EPINEPH**rine 1:1,000 vials, diluent, and instructions for dilution
■ Pharmacy had been preparing 10 mL syringes of **EPINEPH**rine 1:10,000 (0.1 mg/mL) and atropine (1 mg/mL); nurse grabbed atropine by mistake and administered it during a code instead of the intended **EPINEPH**rine

continued on page 6

Drug shortages continued from page 5

Table 1. Examples of Near Misses, Errors, and Adverse Outcomes Associated with Drug Shortages (cont'd)

Heparin

- A nurse prepared and administered an incorrect strength of heparin infusion (30,000 units/500 mL) when the pharmacy was closed at night
- Heparin bags prepared in the pharmacy look similar to other pharmacy admixtures; heparin was administered over 90 minutes instead of vancomycin, and azithromycin was administered instead of heparin
- Prescribers who switched from IV heparin to subcutaneous enoxaparin initially prescribed the wrong dose and frequency of administration
- Vials containing the wrong strength of heparin were stocked in an ADC, leading to dosing errors
- Hoarded bags of heparin were stored in the hospital's distribution center to save space in the pharmacy, where they were accidentally dispensed to a nursing unit instead of plain IV solutions
- IV heparin was administered instead of magnesium during a code because the 10,000 units/mL heparin vials purchased to replace the 5,000 units/mL vials looked similar to magnesium vials
- A pharmacy-prepared heparin infusion containing 25,000 units/500 mL (50 units/mL) was accidentally dispensed to the NICU and administered for 2 hours instead of the intended pharmacy-prepared solution containing 0.5 units/mL

Fosphenytoin

- Phenytoin dispensed in place of fosphenytoin was administered IV into a peripheral vein too rapidly, which resulted in severe thrombophlebitis in a pediatric patient
- Phenytoin, which was reintroduced into the OR because of the fosphenytoin shortage, was administered IV too rapidly during surgery, which resulted in an arrhythmia and cardiac arrest
- Nurse programmed IV phenytoin to infuse over 2 hours instead of 1 hour (as noted on the pharmacy label due to stability issues), which caused several ports to clog; the patient required surgery to implant a new long-term central line, which delayed hematopoietic stem cell transplantation (HSCT) conditioning

Chemotherapy

- Cytarabine dosing error occurred when a pharmacist used a mixing protocol applicable to the usual 500 mg vials (50 mg/mL, not available) but was actually using an alternative strength 1,000 mg vial
- Pre-diluted methotrexate was unavailable; a vial of dry powder was reconstituted incorrectly and the patient received less than the prescribed dose
- Vin**BLAS**tine shortage led to replacement with vin**CRIS**tine for a patient with a hematologic disease, but a dosing error occurred when determining the dose for the alternative drug
- IV etoposide was converted to oral dosing, but the prescriber was not aware that the oral dose needed to be double the IV dose
- Physician prescribed the wrong dose when levoleucovorin was substituted for leucovorin
- Chemotherapy treatments delayed in a patient with a high potential for remission while attempting to find a source of the needed drug
- Switched cancer patients from leucovorin to levoleucovorin, from fluorouracil to capecitabine, and from asparaginase to pegasparagase, but the impact on overall survival and quality of life is undetermined
- Substituting **XELODA** (capecitabine) for leucovorin has resulted in serious gastrointestinal toxicity in many patients
- Chemoembolization was significantly delayed due to unavailability of mitomycin

Antibiotics

- A patient with a pseudomonas infection sensitive only to amikacin died when the drug could not be provided
- Inability to treat with amikacin in a patient with established resistance caused readmission due to treatment failure with ineffective alternatives
- A patient with viral meningitis had to be transported by helicopter from one hospital to another because IV acyclovir was not available, which increased the patient's length of hospitalization
- A patient with probable meningitis experienced a clinically significant delay in therapy while awaiting an alternative antiviral agent; the limited stock of IV acyclovir was sequestered for use in the NICU, where alternative therapies are limited
- Shortage of IV **BACTRIM** (sulfamethoxazole and trimethoprim) led to refractory cases of PCP (pneumocystis pneumonia) from alternative treatment with clindamycin and primaquine
- Clinically significant delay in treating a patient with PCP due to IV Bactrim shortage, particularly when alternatives were not available either; the patient required transfer to another hospital that had enough IV Bactrim to treat the patient

Others

- Treatment delays in hypoglycemic patients when dextrose 50% vials could not be located in an ADC, when pharmacy-prepared mini-bags stocked in the refrigerator could not be located, and when a nurse could not locate a 60 mL syringe and a large-bore needle to withdraw the dextrose from vials
- Patients on flunisolide had to be converted to mometasone; one patient was already on mometasone due to an adverse drug reaction with flunisolide; when flunisolide became available again, the patient was inadvertently converted to flunisolide
- Prefilled ondansetron syringes became unavailable necessitating use of 4 mg/mL vials, which look like hydr**ALAZINE** vials; hydr**ALAZINE** was accidentally stocked in an ondansetron bin and dispensed to a patient care unit
- Patient deteriorated after only receiving partial doses of imiglucerase due to rationing of the drug
- Hospital recently converted from IV indomethacin to IV ibuprofen because of better safety profile; after ibuprofen recall, neonate required the drug to treat a patent ductus arteriosus; neonate given indomethacin as an alternative but developed a gastrointestinal perforation associated with indomethacin treatment

Drug Shortages Summit

Summary Report:

Appendix G

15 YEARS ISMP Helping You Keep Patients Safe
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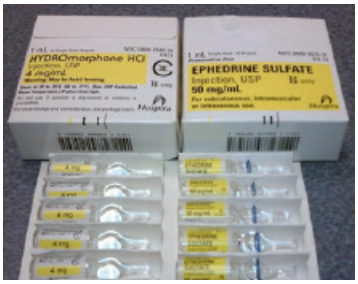
Educating the healthcare community about safe medication practices
A federally certified Patient Safety Organization PSO
ISMP MedicationSafetyAlert!® Acute Care
October 7, 2010 ■ Volume 15 Issue 20

SafetyBriefs

HIGH-ALERT **Look-alike products.** Be aware of the potential for a dangerous mix-up if you use these two Hospira products, **HYDRO**morphone and e**PHED**rine, in ampul dosage forms. During the final check of items to be sent to nursing units for stock, a near-miss error was caught by a pharmacist in which Hospira's **HYDRO**morphone 4 mg ampuls were present instead of the company's e**PHED**rine sulfate 50 mg ampuls. Both boxes and ampuls display a similar yellow and white color pattern, which was believed to have contributed to the mix-up (picture below). Either way, a mix-up would be dangerous. Obviously, barcode scanning, reading labels carefully, and independent checks by at least two pharmacy employees are primary prevention measures, but hospitals may want to purchase one product from a different vendor.



CQI imperative with smart infusion pumps. An article about continuous quality improvement (CQI) in conjunction with employment of smart infusion pumps speaks volumes about the value of establishing interdisciplinary teams and devoting financial resources to develop and refine drug libraries (Breland BD. Continuous quality improvement using intelligent infusion pump data analysis. *Am J Health-Syst Pharm.* 2010; 67:1446-1455). Over a 3-year period during which education and auditing of smart pump use was ongoing, overall use of safety software rose from 33% in November 2006 to over 98% in December 2009. Many clinically significant dosing errors were intercepted by the safety software, prompting edits by end users. Consider sharing this article with members of

continued on page 2 — SafetyBriefs ▶

Weathering the storm: Managing the drug shortage crisis

All healthcare organizations have disaster plans in place that they practice and refine in preparation for an unexpected crisis. These plans are not developed "on the fly" because healthcare providers recognize the value of planning for the unexpected and the necessity of minimizing potentially life-saving interruptions in care. The ongoing problem with drug shortages in our nation is rising to the level of "disaster" status. Drug shortages continue to take an enormous toll on healthcare providers who must deal with the problem on a daily basis, and on patients who are on the receiving end of the shortages.

According to more than 1,800 respondents to our recent 2010 survey, the conditions associated with drug shortages during the past year have been the worst ever, with little hope for improvement in the near future. Respondents were most alarmed by:

- The ever-increasing volume of critically important medications in short supply
- The use of less desirable, unfamiliar alternative drugs—if available
- Errors and poor patient outcomes caused by absent or delayed treatment or preventable adverse drug events caused by the use of alternative drugs or dosage forms
- The lack of advanced warnings about impending shortages
- Precious clinical hours lost to time-consuming activities required to manage drug shortages.

Overall, survey respondents conveyed a real sense of crisis and are clearly looking for support to reduce the organizational burden and potential patient harm associated with drug shortages. As previously mentioned, ISMP and the American Society of Health-System Pharmacists (ASHP) believe a public meeting with FDA and key stakeholders is urgently needed to develop a strategic plan aimed at reducing the occurrence of drug shortages and managing them better when they occur. More effective FDA oversight of drug shortages, a comprehensive early warning system, and patient safety and clinical outcomes placed ahead of anyone's profit margins are goals we hope to begin to explore at this meeting.

Meanwhile, healthcare organizations, guided by pharmacy leadership, can follow the recommendations below to help manage this complex problem. These recommendations are primarily culled from a prior article ISMP published on drug shortages,[1] ongoing discussions with healthcare providers, and guidelines published by ASHP in 2009.[2] Some of the recommendations denote well-known and currently followed steps; others may provide new ideas for managing the problem. Either way, the recommendations can serve as a tool to evaluate your current processes for managing drug shortages. Although it may be impractical to prepare for every potential drug shortage, proper planning can minimize the adverse effects on both patients and providers.

Identify drug shortages. Determine who will be the key person or team members to remain up-to-date on drug shortages. Typically, a pharmacy purchasing agent is given this responsibility as he/she is often the first to know about a shortage. If the purchasing agent is not a pharmacist, a pharmacist should be assigned to work closely with the purchasing agent to aid in evaluating the clinical and operational impact of the shortage and to address means of handling the problem. Be alert to potential signs of an impending shortage, such as partially filled orders or specific strengths of drugs that are difficult to obtain. Regularly search the ASHP (www.ashp.org/shortages?WT.ac=hp%5FPopLinks%5FDrug%5FShortages) and FDA

continued on page 2 — Shortages ▶

SafetyBriefs continued from page 1

your CQI team, pharmacy and therapeutics committee, and hospital administration if you are struggling to improve compliance with the use of smart pump drug libraries.

Military versus conventional time. We have received a couple of questions recently about whether conventional or military time (the 2400 clock) is safer. We would suggest using military time for one reason. It is easier to designate midnight precisely. Sometimes there is confusion as to the meaning of midnight when an order is written or electronically communicated. According to the Time Service Division at the United States Observatory, midnight is actually 00:00. Think about New Year's Eve. The New Year starts when the ball reaches the bottom of its drop, exactly at midnight, not 12:01 a.m. or even 12:00:01 a.m. So if someone writes "Start dose at midnight 4/22" is that supposed to mean start the drug on Wednesday at the beginning of 4/22 or Wednesday, at the end of 4/22? Most of us think of midnight as the end of the day, so to be precise, 2400 on 4/22 would be clearer (the end of Wednesday 4/22). Confusion between 12:00 p.m. (noon) and 12:00 a.m. (midnight) has also been reported. Of course, there are other ways to avoid midnight altogether, such as never scheduling a drug at midnight (use 10-4-10-4 for q 6h instead of 12-6-12-6 for example). Contracts usually expire at 11:59 or 12:01, and trains and planes are never scheduled to leave exactly at midnight either. But the important thing is for each hospital to decide what's right for them, then to standardize, include in policies, and publicize to all appropriate staff.

In memoriam. ISMP staff were saddened to learn of the recent passing of **Dr. Steve Lewis**, who served as Chief Medical Officer for CareFusion and was formerly a senior vice president of the Center for Safety and Clinical Excellence. Steve was a graduate of the University of South Florida, College of Medicine, where he also completed an internship in Medicine and residency in Internal Medicine. Dr. Lewis participated in several ISMP safety summits and collaboratives throughout the country and was well respected for his advocacy of medical device safety. His presence will be missed throughout the patient safety community.

Shortages continued from page 1

(www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm) websites to learn about drug shortages. Social media, collegial networks with professional organizations, participation in professional listserves and discussion groups, wholesalers, and purchasing groups may also serve as resources about impending and new drug shortages.

Learn more about drug shortages. Once an impending or actual shortage has been identified, call the manufacturer for more details about the shortage, its estimated duration, and directions for ordering drugs on allocation or for emergent situations. Wholesalers and purchasing groups may also be a good source of information about drug shortages and alternatives.

Assess inventory of drugs on hand. Begin to assess the impact of the shortage by counting your inventory on hand and estimating how long the supply will cover your needs based on historical usage of the drug.

Research the drugs in short supply. Identify clinically appropriate uses of the drug, the lowest optimal dose for current indications, and strategies to decrease drug waste and inappropriate/unnecessary prescribing. Reference historical data from any drug use evaluation (DUE) conducted in the past or consider performing a DUE to determine how the drug is actually used in your facility.

Identify potential therapeutic alternatives early. Create and employ a standard, formal process for identifying and approving therapeutic alternatives to shortage drugs. An expedited approval process is also needed when the standard process is not timely enough to meet needs based on current inventory of the shortage drug. Obtain suggestions for therapeutic alternatives from the literature, professional websites, listserves, prescribers who use the product, and other local/regional hospitals (to promote consistency for prescribers who practice at multiple sites). Ensure that any decisions made about alternative drugs are in collaboration with medical, nursing, and pharmacy representatives, as well as any other disciplines that may use the product (e.g., respiratory therapists); involve a pharmacy and therapeutics committee as appropriate. Select alternatives early so an education plan can be developed in case implementation is needed. When appropriate, develop and approve guidelines for use of the alternative drugs. Also conduct an inventory of the current supply of approved therapeutic alternatives that will be used.

Prioritize patients and place limitations on use. Based on the extent of the shortage or shortage forecast, availability of alternatives, and results of DUEs, develop temporary therapeutic guidelines that reduce waste and tailor the drug's use to groups of priority patients for whom the alternative drug may be unsafe, ineffective, or undesirable. Guidance on management of shortages and use limitations may be available from external organizations, such as government agencies (e.g., Centers for Disease Control and Prevention, departments of health [for an example associated with vaccine shortages, visit: www.health.state.mn.us/oep/healthcare/standards.pdf]), medical/professional organizations (e.g., Anesthesia Patient Safety Foundation), and specialty groups (e.g., American Society for Parenteral and Enteral Nutrition). Reassess how long the drug will be available to priority patients after conservation measures have been implemented. When appropriate, remove shortage drugs from unit floor stock and have pharmacy dispense the drugs as needed to better control use and waste.

Conduct a failure analysis and take action. Considering the medical necessity of the shortage drug, the duration of the shortage, and the current supply of the drug, assess the potential hazard to patients and the organization. Conduct a mini failure mode and effects analysis (FMEA) to identify required changes to processes and potential misuses of alternative products. (A sample format for a mini FMEA from OhioHealth Pharmacy Services is available on page 4.) Determine how to best manage the risk of serious errors and adverse reactions to alternative drugs, and take action. Consider how the use of alternative drugs could affect current prescribing

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Join **ISMP** in celebrating *National Hospital* and *Health-System Pharmacy Week* from **October 17-23.**

Special Announcements...

Step Up Your Medication Safety Efforts with ISMP. Healthcare practitioners with medication safety oversight responsibilities have an opportunity to join ISMP experts for a 2-day interactive **Medication Safety INTENSIVE** workshop in **Orlando, FL**, on **November 4-5**. Participants will gain cutting-edge knowledge, tools, and strategies to establish a focused medication safety program. For details, visit: www.ismp.org/educational/MSI/.

ISMP webinar. Join us on **November 17** for ***HYDROmorphone: Balancing the Benefit and Risk for Patient Care.*** ISMP invites all safety-minded practitioners to participate! For details, visit: www.ismp.org/educational/webinars.asp.

ISMP salutes James P. Bagian, M.D., P.E. Dr. Bagian retired last Friday from the Department of Veterans Affairs (VA) where he served as founding director of the VA National Center for Patient Safety since 1998 and Chief Patient Safety Officer. He is known worldwide for his leadership in patient safety. He has been a steadfast proponent of a systems approach to problem solving, based on prevention, not punishment. He has championed a safety culture beyond medicine's "name and blame" culture of the past. He currently serves as Chairperson of The Joint Commission Patient Safety Advisory Group, a role in which he will continue. Dr. Bagian has accepted an appointment as a professor in the medical and engineering schools at the University of Michigan and the University of Michigan Health System. We look forward to continued interaction with him.

ADC workbook. Facilities that participated in the **2009 ISMP Medication Safety Self Assessment for Automated Dispensing Cabinets** (ADC) can now view and print an associated Quality Improvement Workbook. Organizations that have used the self assessment are encouraged to utilize the workbook, which contains comparative data collected from responses submitted between June 2009 and February 2010 from 380 hospitals nationwide. The project is intended to assist organizations in identifying and prioritizing opportunities for improvement related to the safe use of ADCs. To access the workbook, go to: www.ismp.org/selfassessments/ADC/Login.asp.

Shortages continued from page 2

practices, storage of the drug, final product preparation (including directions for admixing), drug administration procedures, and the use of technology (e.g., electronic prescribing, bar-coding systems, automated dispensing cabinets, smart pump libraries). Make any necessary procedural and technological changes to support safe use of the alternative medications. Whenever possible, have pharmacy prepare and dispense alternative drugs in the most ready-to-use form. Also address any sound- and look-alike issues with an alternative drug's name and packaging, and determine if additional safety checks, alerts, and/or patient monitoring are required when prescribing, preparing, dispensing, and administering an alternative product.

Do not hoard shortage or alternative drugs. Stockpiling a medication may lead to an artificial shortage where the drug might otherwise be available in adequate supplies to meet patient needs across the nation. Further, manufacturers with products in short supply rarely honor requests for quantities larger than historically ordered; allocations to organizations are typically determined by prior use.

Establish ongoing communication with staff. Using the most effective means possible (e.g., staff meetings, newsletters, email, website, Intranet, posters/charts, alerts in electronic systems), regularly share information with clinicians about:

- The drug shortage, causes, and expected duration (if known)
- Assessment of current drug availability
- Temporary therapeutic guidelines, including use limitations for the shortage drug
- Alternative products and how they will be supplied to units
- Dosing, preparation, and administration guidelines for alternative products
- Error potential with alternative products and how to reduce risk
- Additional patient monitoring and safety steps that may be required when using an alternative drug.

Consider preparing a report which includes the above information on the most critical drug shortages, updating the report on a daily basis, and using the report to keep healthcare professionals informed about the shortages (e.g., included in clinical staff email, staff meetings, the organization's Intranet, newsletters). Pharmacy staff should be briefed daily regarding all aspects of drug shortages so they can serve as a resource to prescribers, nurses, and patients.

Engage ethics committee and risk management. When supplies of the shortage drug are critically low and suitable alternatives are not available or are suboptimal, consultation with an ethics committee may be required to help determine limitations on the use of the shortage drug. Potential or actual patient harm caused by the unavailability of a drug or a suitable alternative should be reported to risk management. (Organizations may want to engage the ethics committee and risk management staff in general terms to discuss potential ethical or risk management situations that may arise during a severe drug shortage, rather than waiting for a specific drug shortage to spur consultation.)

Establish a drug shortage network with other local healthcare providers. Build and strengthen local collaborative networks to share information regarding drug shortages and alternative products, to share emergency supplies of shortage drugs when appropriate, and to coordinate the transfer of patients to providers that still have a shortage drug available when an alternative is not suitable.

Determine an organizational position on alternative suppliers. The potential availability of shortage drugs from secondary gray markets, compounding pharmacies, or ramped up in-house compounding are complex issues that require philosophical discussions as well as quality and budgetary considerations to determine whether it is appropriate and safe to utilize these resources. Decisions regarding these issues are difficult to make under pressure, so the organizational position should be well known and documented. Require-

continued on page 4 – Shortages

Shortages continued from page 3

ments regarding quality control measures for outside vendors and criteria for when the current position might be challenged should be included.

Proactively monitor adverse events associated with drug shortages. Utilize error and adverse event reporting systems as well as a hotline, chart review, focus group meetings, discussions during pharmacy rounds, or other means to learn about hazardous conditions, near misses, and adverse events associated with drug shortages so actions can be taken to limit further risk and harm.

As a final recommendation, healthcare organizations might want to share the results of our recent survey on drug shortages with pharmacy and therapeutics committee members and key groups of organizational leaders and clinicians, including nurses and the medical staff, to help illustrate the significant impact of drug shortages, particularly the types of adverse events that are happening across the nation. The full results of our survey can be found in our September 23, 2010, newsletter at: www.ismp.org/Newsletters/acutecare/articles/20100923.asp.

References:

1) ISMP. Part II of our national survey on drug shortages: proactive guidelines to safely managing scarce supplies. *ISMP Medication Safety Alert!* April 4, 2001;6(7):1-2. Accessed at: www.ismp.org/Newsletters/acutecare/articles/20010404.asp.

2) Fox RE, Birt A, Janes KB, Kokko H, et al. ASHP guidelines on managing drug product shortages in hospitals and health systems. *Am J Health-Syst Pharm.* 2009;66:1399-1406. Accessed at: www.ashp.org/DocLibrary/BestPractices/ProcureGdlShortages.aspx.

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Table 1. Failure Mode and Effects Analysis (FMEA) for New/Alternative Drugs**

Potential Failure Mode as it Relates to Steps in the Product Use Process	Yes	No	Methods of Avoidance	Comments
Selection and Procurement				
Have specific errors associated with this product been reported in the literature (e.g., Sentinel Event Alerts, ISMP newsletters)?				
Is the product a high-alert drug?				
Does the product have an approved Risk Evaluation and Mitigation Strategies (REMS)?				
Prescribing and Ordering				
Is it likely that a calculation error could occur during prescribing, ordering, or processing?				
Does the procured product contain latex?				
Are there policies and procedures that need to be rewritten or amended before the product is approved for formulary use (e.g., IV guidelines, preprinted order sets, ordering restrictions)?				
Order Processing				
Does this product require that specific alerts (or changes in existing protocols) be configured in the pharmacy information system or smart pump drug library?				
Are there other products that look or sound like this product?				
Preparation and Dispensing				
Is it likely there would be multiple steps in product preparation?				
Are there any handling precautions associated with this product?				
Can this medication be delivered safely by the pneumatic tube system?				
Does the preparation and dispensing of this product require an independent double-check?				
Administration				
Does the product require administration (rate) over a given amount of time that if not adhered to may cause harm?				
Is there a specific skill(s) necessary for nurses to achieve before administering this product to a patient?				
Does the administration of the product require an independent double-check?				
Is it likely this product could be inadvertently administered by an alternative route (e.g., liquid oral medication in a syringe given IV)?				
Monitoring				
Is there a patient parameter that needs to be monitored to ensure efficacy or to minimize the risk of toxicity?				
Is there an effective treatment if the patient experiences undesirable side effects or an overdose?				
Other Failure Modes				

**Source: OhioHealth Pharmacy Services

Drug Shortages Summit

Summary Report:

Appendix H

Drug Shortages Summit
November 5, 2010
Hyatt Regency
Bethesda, Maryland

Antitrust Statement

ASHP and and its co-conveners of this Summit have a policy of strict compliance with federal and state antitrust laws. The group assembled here today needs to be aware of the possible antitrust exposure that may arise when competing organizations with market power meet to discuss the type of issues which are on today's agenda. The organizations assembled here today are considered competitors, and they have come together for the express purpose of carrying on joint discussions for the purpose of optimizing therapeutic outcomes and patient care. It is important that all the participants assembled understand that they cannot come to understandings or agreements on activities or positions that might: 1) raise, lower or affect prices, reimbursement levels, discounts, fees and/or other terms and conditions for doing business; 2) allocate or divide markets or territories; or 3) indicate a refusal to deal with particular customers, companies or third party payors. It is acceptable to discuss pricing models, methods, systems and other forms of voluntary consensus standards or guidelines based on objective evidence that do not lead to an agreement on restraining prices, markets or related matters. Information may be presented with regard to historical pricing activities, trends and overviews so long as such information is general in nature and does not include specific data on current prices in a particular trade area. Any discussion by this group of current or future pricing or fees, and other terms and conditions, which may lead to an agreement or consensus on prices or fees to be charged, is strictly prohibited. A violation of the antitrust laws may be inferred from discussions about pricing followed by parallel decisions by group members even in the absence of an oral or written agreement.