The National Drug Shortage: Causes and Its Effect on Neonatal Care

Steve Plogsted, BS, PharmD, BCNSP, CNSC
Nutrition Support Pharmacist
Nationwide Children’s Hospital
Chair, Drug Shortage Taskforce
American Society for Parenteral and Enteral Nutrition
Objectives

Discuss the multiple causes of drug shortages

Discuss what is being done to correct the drug shortages

Provide potential therapeutic options when a drug is not available
Drug shortages are not a new issue

The American Society for Health-System Pharmacist (ASHP) and other have been addressing drug shortage for nearly 15 years
Background

There are many parenteral nutrition components on the American Society of Health System Pharmacists (ASHP) and FDA drug shortages list.

A recent study by the American Hospital Association found that 89 percent of hospitals have experienced nutrition product shortages. (American Hospital Association Survey on Drug Shortages. June 2011.)
Background

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is continually addressing the ongoing shortage of vitamins, electrolytes, and other IV nutrition ingredients that has critically impacted hospitals and home infusion companies nationwide.
In 2010 there were 178 drug shortages reported to the FDA of which 132 were sterile injectable drugs.

The number of reported shortages increased to 251 in 2011, 183 of which involved sterile injectable drugs.

As of February 28, 2013 there were 324 medications in short supply and of these 228 (70%) are sterile injectables.

All PN products except dextrose and water have been in short supply at some point since spring of 2010.
Causes for the Drug Shortage

The leading primary reasons for the shortages reported to FDA were problems at the manufacturing facility (43%), delays in manufacturing or shipping (15%), and active ingredient shortages (10%).

Manufacturing quality problems that have resulted in shortages can be serious, including findings of glass shards, metal filings, and fungal or other contamination in products meant for injection into patients.

However, there have been other reasons such as production delays at the manufacturer and delays companies have experienced receiving raw materials and components from suppliers.
Causes for the Drug Shortage

Discontinuations are another factor contributing to shortages. FDA can't require a firm to keep making a drug it wants to discontinue. Sometimes these older drugs are discontinued by companies in favor of newer, more profitable drugs.

With fewer firms making older sterile injectable drugs, there are a limited number of production lines that can make these drugs.

The raw material suppliers the firms use are also limited in the amount they can make due to capacity issues at their facilities.
Causes for the Drug Shortage

This small number of manufacturers and limited production capacity for older sterile injectables, combined with the long lead times and complexity of the manufacturing process for injectable drugs, results in these drugs being vulnerable to shortage.

When one company has a problem or discontinues, it is difficult for the remaining firms to increase production quickly and a shortage occurs.

The FDA provides additional information on drug shortages at [http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm#q1](http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm#q1)
Celebrity Trend Uses Nutrients Hospitals Desperately Need

Experts say: “We’ve got babies’ lives hanging in the balance while we’re worried about getting through a hangover.”

By Alexandra Robbins

It’s been called the new “it” bag. The “vitamin drip”—a trendy, expensive treatment of vitamins and nutrients delivered intravenously—is billed as a way to beautify and reenergize those who are tired, stressed out, dehydrated, or too busy to get a good night’s sleep.

X Factor judge Simon Cowell swears by it. Madonna, Cindy Crawford, and the Miami Heat’s Rashard Lewis have been rumored to be fans.

Meanwhile, unbeknownst to them, patients across the country—especially premature babies—have been malnourished because of a lack of some of the same nutrients used in the vitamin drip.
Reasons for Injectable Shortages – 2012

Source – FDA Drug Shortages

- Quality - Delays / Capacity: 42%
- Quality - GMP: 35%
- Increased demand: 7%
- Discontinuation: 7%
- Raw materials: 4%
- Loss of manufacturing site: 5%
National Drug Shortages

Number of active drug shortages

Year

- 2007: New shortages, by year reported - 114, Ongoing shortages, which began in prior years - 40, Total - 154
- 2008: New shortages, by year reported - 137, Ongoing shortages, which began in prior years - 56, Total - 193
- 2009: New shortages, by year reported - 157, Ongoing shortages, which began in prior years - 74, Total - 231
- 2010: New shortages, by year reported - 201, Ongoing shortages, which began in prior years - 127, Total - 328
- 2011: New shortages, by year reported - 255, Ongoing shortages, which began in prior years - 184, Total - 439
- 2012: New shortages, by year reported - 195, Ongoing shortages, which began in prior years - 261, Total - 456
- 2013: As of June 30, New shortages, by year reported - 73, Ongoing shortages, which began in prior years - 288, Total - 361

Source: GAO analysis of University of Utah Drug Information Service data.
Drug Shortages

Over half (55 percent, or 622) of the 1,132 shortages reported since January 1, 2007, were for drugs that were in shortage more than once.

Specifically, 240 drugs were in shortage on multiple occasions between January 1, 2007, and June 30, 2013, representing 622 individual shortages.
Drug Shortages

For shortages reported since January 1, 2007, the duration of the shortages varied, ranging from 1 day to over 5 years. The majority of shortages, 68 percent, lasted 1 year or less.

The average duration of the drug shortages over this period was 340 days—slightly less than a year.
Parenteral Shortages 2010–2014

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Issues in Supply

Manufacturers and wholesalers typically have a 15 to 40 day inventory on hand.

Pharmacies - 10 to 16 annual inventory turns.
Manufacturing Problems

Sources
Sole source raw materials
Time to establish new source

Capacity
Few manufacturers of sterile injections
Same production lines for multiple items
Limited lyophilization capacity
Multifactorial Reasons

Multiple reasons can play a role in any particular shortage

A product may be recalled due to concern for microbial contamination or particulate matter in the vials (propofol)

- 3 manufacturers of propofol, 2 had recalls, and the 3rd could not keep up with demand—U.S. imported product from Europe.

- A product may be recalled and the manufacturer may have difficulty accessing raw materials (lipid emulsion)
Business Decisions

Profitability
Manufacturing fixes
Capacity – most factories running 24/7
Fragile Supply Chain

Sterile Injectables

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

• Lack of redundancy
  – Multiple products made on existing manufacturing lines
  – Limited resiliency in manufacturing process

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

Raw material availability

20 years ago – 90% from US and Europe
Currently, 75 – 80% from China and India

Some materials are no longer accessible or only available as single source products
Example – Fragile Supply Chain

Manufacturing plant closes April 2010.

Impacts 49 drugs – 18 are chemotherapy.

Problems occurred at the same time at other facilities.

Manufacturing resumed spring of 2011, but still not up to prior capacity for some agents.
U.S. Food and Drug Administration (FDA)

Policy is to “prevent or alleviate shortages of medically necessary products”

- Product treats or prevents a serious or life-threatening illness (off-label or labeled)
- No reasonable alternatives exist (single-source)

July 19, 2012

President Obama signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA), bipartisan legislation reauthorizing user fee programs for innovator drugs and medical devices and establishing two new user fee programs for generic drugs and biosimilar biological products.

FDASIA is helping FDA take important steps to address the challenges posed by an increasingly global drug supply chain in which nearly 40 percent of finished drugs are imported and nearly 80 percent of active ingredients come from overseas sources.
FDA’s Strategy

Prioritize medically necessary agents (determined on a case by case basis)

Evaluate risks and benefits for patients

Offer assistance and advice, but up to the manufacturer to fix

Success hinges on early notification
The strategic plan includes a number of new ideas to address shortages.

Many of these strategies focus on enhancing FDA’s response and communication when we become aware of quality or manufacturing issues that could lead to a shortage.

Other strategies that FDA is considering include the development of new risk-based approaches to identify early warning signals for manufacturing and quality problems that could lead to production disruptions.
FDA Strategic Plan

In addition, the strategic plan identifies some preventive measures companies can take that place a greater emphasis on manufacturing quality and stability of supply, thereby eliminating the root causes of most shortages.
FDA Strategic Plan

Oct 13, 2013 issued a proposed regulation implementing the expanded early notification requirements included in FDASIA.

This regulation would require that all manufacturers of certain medically necessary prescription drugs give FDA advance notice of a permanent discontinuance or a temporary interruption of manufacturing. It would also extend this requirement to manufacturers of biologic products.
How Does FDA Prevent Shortages?

Regulatory discretion
   Require filters (products with particulates, glass fragments)
   Ask clinicians to double check volume (overfill)

Ask others to increase production

Expedite reviews (new product, longer expiration, new raw material, new manufacturing sites)
Shortages Prevented by FDA 2010 - 2012

Source: CDER Drug Shortages
FDA Can Only Do So Much…

FDA CAN require
* notification of supply disruptions (FDASIA)

FDA CANNOT require
* continued production
* increased production
* disclosure of distribution
“FDA takes action to ease neonatal drug shortage” (May 2013)

Federal health regulators are allowing overseas imports of critical intravenous drugs used to nourish premature infants, amid a shortage that has affected hospitals nationwide.

Drug shortages have increased dramatically in the U.S. over the past six years, particularly for generic injected drugs. They are the workhorses of Hospitals but are difficult to make and produce little profit for drug makers.
Do PN Product Shortages Affect Patient Safety

Shortages pose safety risks throughout the entire parenteral nutrition process, from procurement to patient outcomes
“Children Are Dying”

Special report: Because of nationwide shortages, Washington hospitals are rationing, hoarding, and bartering critical nutrients premature babies and other patients need to survive. Doctors are reporting conditions normally seen only in developing countries, and there have been deaths. How could this be allowed to happen?

By Alexandra Robbins
“Children are dying,” says Steve Plogsted, a clinical pharmacist who chairs the drug-shortage task force of the American Society for Parenteral and Enteral Nutrition (ASPEN). “They’re not getting any calcium or any zinc.
Nutritional Drug Shortages Take Toll on The Smallest Patients

June 14, 2013
By GILLIAN MOHNEY via WORLD NEWS
Zinc Deficiency–Associated Dermatitis in Infants During a Nationwide Shortage of Injectable Zinc — Washington, DC, and Houston, Texas, 2012–2013

Please note: An erratum has been published for this article. To view the erratum, please click here.

Weekly
January 17, 2014 / 63(02);35-37
June-July 2011 Stories about the impact of parenteral nutrition drug shortages on patients and healthcare providers (ASPEN)

Arizona Clinician Report We have had a shortage of IM B12 as well as TPN ingredients.

Arizona Clinician Report The lack of K acetate means we use more KCl. Our pts c/o of excessive thirst and I believe the high serum Cl is making them miserable (referring to NPO fistula pts). Typically these pts have wounds and higher protein needs which are difficult to meet with AA shortage.

California Clinician Report The latest threat to provision of appropriate PN involves the neonatal population. We were notified today that CAPS locally will be unable to provide L-cysteine after the next 7-10 days - that there is none available when current supply is exhausted.
Stories

1. Having to use Freamine III instead of a nonphosphate containing amino acid mixture has been a challenge for the patients who are hyperphosphatemic

2. When KCL conc was not available, having to "pool" multiple 20ml vials to provide a source bag for the compoudner = increased risk of contamination and error

3. Frequent changes in manufacturer of the "source" electrolytes in the compoudner increase the potential for errors: the compoudner is programmed to the specific gravity of the specific manufacturer's product. If the operator does not select the substitute manufacturer, an error in dose can occur

4. Having to remove calcium gluconate from PN formulations due to product not available

5. Having to "pool" 10ml aliquots of IV Multivitamins for use on compoudner due to shortage of the 50ml vials increases potential for contamination
Managing Shortages

The following are leading clinical concerns as identified in an Institute for Safe Medication Practices (ISMP) survey:

- Increasing volume of critically important medications in shortage
- Use of less desirable, unfamiliar alternatives
- Errors and poor patient outcomes due to absence or delay in treatment
- Preventable adverse events by use of alternative drugs
- Lack of advanced warning when drugs are nearly in shortage
- Precious clinical hours lost to time-consuming activities required to manage shortage
Managing Shortages

The AHA reported that virtually all responding hospitals experienced a drug shortage during 2011 and that 82% of hospitals had to delay patient treatment as a result of drug shortages.

A University of Michigan–ASHP survey estimates the labor costs for hospitals to manage drug shortages at $216 million dollars.
Managing Shortages

Drug shortages may result in higher drug costs as well as greater risks to patients.

To obtain drugs in short supply, providers may turn to suppliers they do not typically use, including authorized alternative suppliers, compounding pharmacies, or gray market suppliers—those not authorized by the manufacturer to sell the drug—who typically obtain small quantities of a drug that is in short supply and offer it for purchase at an inflated price.
Deaths Attributed to Compounding Issues Related to Drug Shortage

BIRMINGHAM, Ala.

State and federal health officials are investigating the deaths of nine patients at Alabama hospitals who were all given an intravenous nutritional supplement that investigators have found was contaminated by bacteria.

Ten other patients who received the supplement also were sickened by the bacteria, called Serratia marcescens, which is most commonly found in water, including some tap water, and sometimes in bathrooms.
The Case of the New England Compounding Center

During the fall of 2012, the New England Compounding Center (NECC) became the focus of national attention when the Framingham, MA-based company was accused of “unsafe manufacturing practices” that lead to 61 deaths and more than 749 injuries in patients infected with a fungus that led to a rare but deadly form of meningitis.

As many as 13,000 people nationwide may have been put at risk from tainted steroid injections for chronic pain from this case alone.
Managing Shortages

Outsourcing of PN
third party-CAPS
local resources
conservation

Transferring patients to an institution who has adequate supply
Therapeutic Options

Product shortage recommendations, developed by the A.S.P.E.N. Clinical Practice Committee Shortage Subcommittee and approved by the Board of Directors, help clinicians manage parenteral Nutrition therapy during this time of product shortages.
A.S.P.E.N Publications Free to the Public

- Parenteral Nutrition Trace Element Product Shortage Considerations
- Parenteral Nutrition Intravenous Fat Emulsions Product Shortage Considerations
- Parenteral Nutrition Amino Acids Product Shortage considerations
- Information to Use in the Event of an Intravenous Multivitamin Shortage
- Parenteral Nutrition Cysteine Product Shortage Considerations
- Parenteral Nutrition Electrolyte / Mineral Product Shortage Considerations
Therapeutic Options

Practice Changes
  Compounding
  Alternative salts
Foreign imports
  sodium glycerophosphate
  trace elements
  vitamins
  lipids
Conservation
ASPEN Recommendations for Conservation of PN Products

1. Consider oral or enteral administration

2. Prioritize patients, saving supplies for those most vulnerable patients

3. Eliminate adding injectable electrolytes/minerals to enteral nutrition products

4. Minimize the use of additives to daily maintenance IV fluids

5. Reevaluate replacement algorithms or treatment protocols

6. Carefully evaluate alternative supplies of individual and multiple electrolyte products that are available, including standardized, commercially available PN products
One Last Thought

National Association of Neonatal Nurses
Why are we seeing so many drug shortages in the past few years?

Many of the pharmaceutical plants that produce the medications we use in the NICU are about 50-60 years old. In 2010 there was a “perfect storm” for drug shortages related to aging production facilities and concerns for the quality of the drugs being produced. With the closing of plants around the country we experienced episodic critical shortages. Most, drugs used in the NICU are produced by one or two manufacturers. While the FDA has been able to find imported substitute products for some of the medications in short supply it has been difficult to find replacements for neonatal medications. Most medications used in the NICU are not approved for use in neonates and it has proved difficult to find foreign manufacturers willing to go through the process of approval.
What causes drug shortages?

According to the FDA, 2/3 of all drug shortages are related to concerns for quality of product. Specifically, concerns related to large particulate in injectable have led to the closing of the two major manufactures. When there are only one or two manufactures making all of the sterile injectable drugs, as is the case for most electrolytes/TPN components used in the NICU, it becomes exceedingly difficult to guarantee product if there is any problem in the production line. There have also been delays or decreases in production of raw materials needed to manufacture drugs. There is little incentive for other manufactures to pick up the production of drugs in short supply because many of the drugs are very inexpensive to purchase but expensive to produce if not produced in large quantities.
What is being done about drug shortages?

In July 2012 The Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law. The law provides the FDA with increased ability to mitigate the effects of drug shortages and to impose new requirements on manufacturers to notify stakeholders about impending shortages. It also requires the FDA to establish a task force to create and implement a strategic plan for preventing drug shortages. This strategic plan is due in July 2013.

The specifics of FDASIA can be found at:

What can clinicians do?

If you are experiencing a drug shortage that is not on FDA’s list of Drug Shortages you can report a shortage directly to the FDA here. You can follow the FDA’s website listing of current drug shortages to manage the supply at your institution. Clinicians can also sign up here to receive email notifications from the FDA about drug shortages.

You can also call or write letters to manufactures listing your concerns. American Regent and Hospira make most of the injectable medications in current short supply.
What is NANN doing?

NANN's Health Policy & Advocacy Committee considers the problem of drug shortages, along with other issues related to the safe use of drugs in neonates, a key advocacy issue for the association. NANN conducted a survey of members to find out what drug shortages were being experienced in NICUs throughout the country, and to find out the consequences of those shortages on patient care. These findings were shared with the FDA's Office of Drug Shortages at a meeting in March, 2013. NANN plans to resurvey the membership in late summer, 2013 to determine whether the drug shortage situation has improved.
Is this a temporary or permanent problem?

The hope is that this is a temporary problem. The two major distributors of neonatal injectables, American Regent and Hospira, have recently had to close their production plants secondary to quality concerns. According to the FDA, both plants will be re-opening and producing injectables as needed.
How can I find out when a particular drug will be available again?

Manufacturers are required to report information about shortages to FDA, and are required to report the reasons for shortages and the expected duration of shortages. The FDA then posts this information on their website. A list of current drugs in short supply is available. If you click on the drug of interest, you will see the following information: the company that makes the drug (and their telephone number), the specific products (dosages, etc) that are in short supply, the reason for the shortage, the estimated duration of the shortage and when the company thinks stock will be available, and other pertinent information.