Mitigating Risks Associated with Supply Chain Disruptions of Intravenous Fluids Due to Disaster

October 14, 2024

Webinar EBOOK

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Anne Marie Orlando is the Senior Director, Clinical Programs at Blue.Point Supply Chain Solutions and the President-Elect for Board of Directors for the Association of Healthcare Value Analysis Professionals. Anne Marie has been a critical care nurse for over 20 years with a leadership foundation in the Interventional Cardiology and Interventional Radiology space. During her supply chain tenure, Anne Marie held a dual role of Supply Chain and Clinical Resource Director where she operationalized many clinical initiatives while maintaining fiscal accountability. At the GPO level, Anne Marie served as the Director of Clinical Services for Yankee Alliance supporting member value analysis teams and their work with clinical utilization. Anne Marie is currently the Senior Director, Clinical Programs for Blue.Point Supply Chain Solutions supporting value analysis teams in the use of the Blue.Point platform focusing on aligning product utilization and standardization with evidence-based practice.

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He is a frequent international lecturer in the areas of infectious diseases, healthcare-associated infections, outbreak response and prevention, medical device-related infections and outbreaks, endoscopes, and infection prevention and control. He holds Board Certifications in Patient Safety, Healthcare Quality, Healthcare Risk Management, Legal Nurse Consulting, Medical and Clinical Affairs, Patient Experience, Vascular Access, Antibiotic Stewardship, Infection Control, Long-Term Care Infection Control, Dental Infection Control, as a Designated Infection Control Officer, Flexible Endoscope Reprocessing, Critical Care Fundamentals, as a Patient Safety Officer, Healthcare Value Analysis, and in Healthcare Management.

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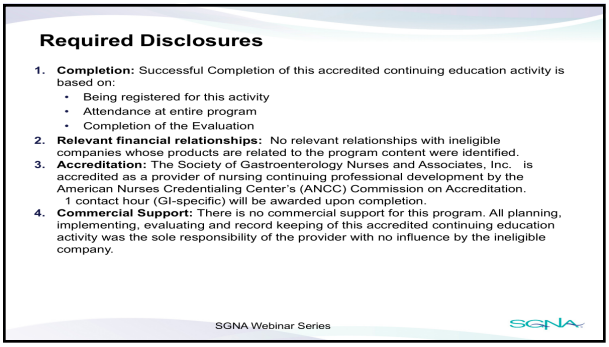

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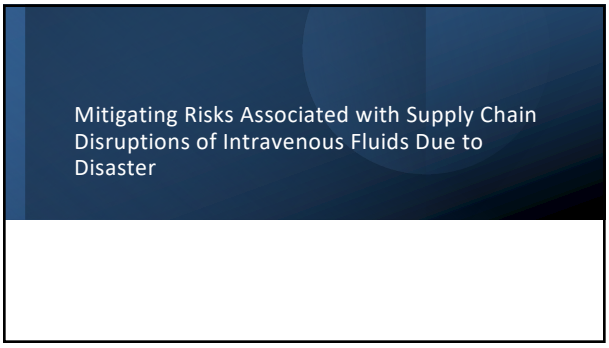

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Webinar Faculty Conflicts of Interest

Anne Marie Orlando: No Relevant Conflicts

Dr. Hudson Garrett: No Relevant Conflicts

Karen Niven: No Relevant Conflicts

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Webinar Faculty

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AHVAP Association of Healthcare Value Analysis Professionals

SGNA

Partnership in Action

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Webinar Objectives

- Review the clinical impacts of the ongoing supply chain disruption of intravenous fluids on patient care
- Discuss Supply Chain Continuity strategies to maintain clinical continuity of care
- Review an interprofessional collaborative approach to emergency preparedness for supply chain disruptions impacting GI and Pulmonology care delivery

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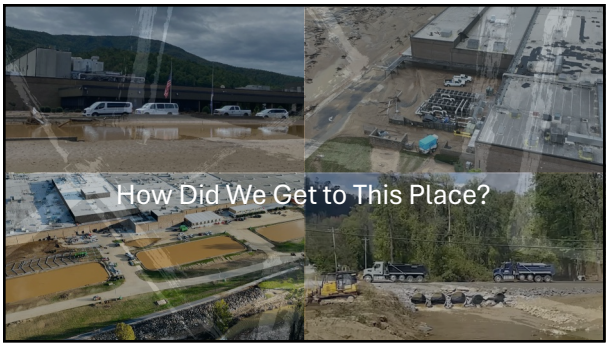

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Primary Impacts to Supply Chain

- Sodium chloride injections/solution
- Lactated ringers injections/solution
- Sterile water for injection
- Dextrose injections/solution

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Specific FDA Shortages List

- The following products are currently in shortage and may be further impacted until North Cove resumes operations:
  - Dextrose 5% IV Solution – (shortage posted on 2/14/22)
  - Dextrose 10% IV Solution – (shortage posted on 2/14/22)
  - Dextrose 70% IV Solution – (shortage posted on 10/11/24)
  - Lactated Ringers IV Solution – (shortage posted on 10/11/24)
  - Peritoneal Dialysis Solution – (shortage posted on 10/11/24)
  - Sodium Chloride 0.9% IV Solution (Normal Saline) – (shortage posted on 6/21/18)
  - Sodium Chloride 0.9% for Irrigation – (shortage posted on 4/28/23)
  - Sterile Water for Injection – (shortage posted on 11/23/21)
  - Sterile Water for Irrigation – (shortage posted on 4/28/23)

Source: Food and Drug Administration

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Core Fluid-Related Definitions

- **Small-volume parenteral solutions (SVPs):** a solution volume of 100 mL (as defined by USP) or less that is intended for intermittent intravenous administration (usually defined as an infusion time not lasting longer than 6-8 hours)
- **Large-volume parenteral solutions (LVPs):** a solution volume of greater than 100 mL (as defined by USP)

Source: ASHP Small- and Large-Volume Fluid Shortages Suggestions for Management and Conservation

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Immediate Priorities-Part 1

Prioritize IV Fluids for Critical Care Patients: Providers should carefully assess each patient's clinical need for IV fluids, prioritizing their use for critically ill patients, those undergoing surgeries, or those with conditions where IV administration is necessary for life-saving hydration, medication delivery, or electrolyte balance.

Encourage Oral Hydration When Clinically Appropriate: For patients who are able to tolerate oral intake, healthcare providers should prioritize oral hydration over intravenous fluids whenever clinically appropriate. This includes encouraging the use of oral rehydration solutions, electrolyte replacement drinks, and regular fluids to meet hydration needs. Providers should exercise their best clinical judgment and follow evidence-based guidelines for patient care treatment.

Review and Adjust Clinical Protocols: Facilities should review their clinical protocols to identify opportunities for reducing IV fluid usage when possible, particularly in routine cases where oral hydration or alternative routes of administration may be sufficient. Consider adjustments in post-operative care, where oral hydration might be introduced earlier in recovery for eligible patients.

Source: ASHP Small- and Large-Volume Fluid Shortages Suggestions for Management and Conservation

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Immediate Priorities-Part 2

Minimize Waste Through Precise Dosing and Administration: Healthcare providers should take steps to reduce wastage of IV fluids by ensuring precise dosing and administration. This includes accurately calculating fluid requirements, limiting the use of IV fluids to the exact volume needed, and preventing over-administration or unnecessary continuation of IV therapies.

Use Alternative Routes of Medication Administration: When possible, healthcare providers should consider alternative routes of administration for medications that are typically delivered intravenously. Oral, subcutaneous, or intramuscular administration of medications can help conserve IV fluids for patients who cannot tolerate these alternatives.

Educate Staff on Conservation Efforts: All clinical staff should be educated on the importance of conserving IV fluids during this shortage. Regular communication should emphasize the necessity of critical thinking in assessing the need for IV fluids and implementing strategies for conserving supplies without compromising patient care.

Source: ASHP Small- and Large-Volume Fluid Shortages Suggestions for Management and Conservation

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Infusion Rate	Bag Size
20 mL / hour or less	250 mL
21 mL/hour to 40 mL/hour	500 mL

Recommended Container Volumes Based on Infusion Rates

Source: ASHP Small- and Large-Volume Fluid Shortages Suggestions for Management and Conservation

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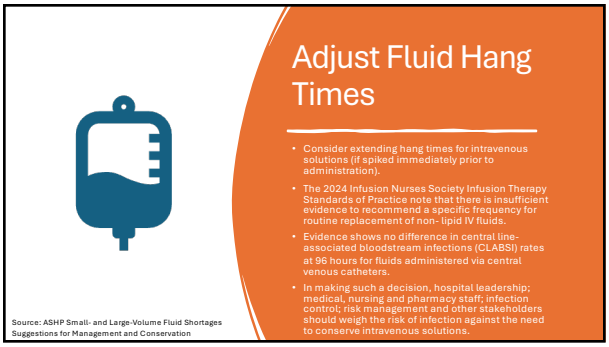

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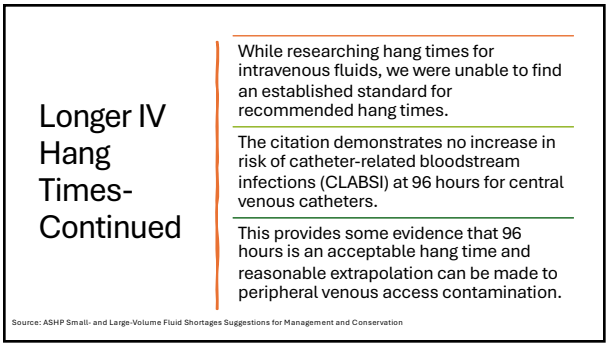

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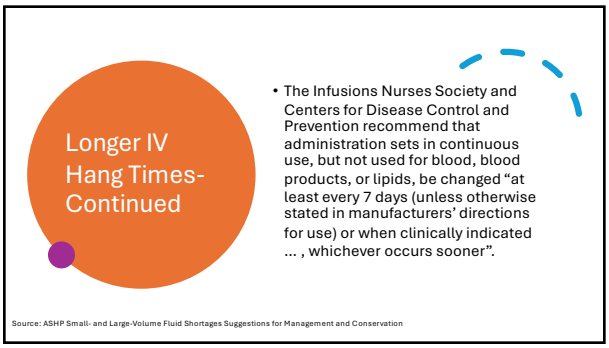

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Longer IV Hang Times- Continued

- Organizations should consider the criticality of fluid supply, and clinical risk factors and other variables when making decisions on hang times up to or beyond 96 hours.
- Connections and disconnections should be minimized when possible, and aseptic technique should be used at all times when connecting fluids to administration sets and when spiking bags.
- There are many different types of vascular access devices and organizations should consider risk factors associated with each when establishing fluid hang times.

Source: ASHP Small- and Large-Volume Fluid Shortages Suggestions for Management and Conservation

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Strategies for Conservation for Small Volume Intravenous Products

- If oral route is not feasible or indicated, some medications can be administered via intramuscular or subcutaneous injection.
- Switch products to IV push when the patient's clinical status drug properties (e.g., pH, osmolarity) allow.
- Change IV medications and electrolytes to a clinically appropriate oral product whenever possible.
- Do not make practice change plans that will require additional fluids or specific products (e.g., requiring additional mix-on-demand supplies).

Source: ASHP Small- and Large-Volume Fluid Shortages Suggestions for Management and Conservation

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Strategies for Conservation of Large Volume Intravenous Products

- Evaluate the clinical need to continue intravenous fluid replacement at every shift change and bag change.
- Assess the need to initiate "keep vein open" (KVO) orders and the need to continue those orders at every shift change.
- Review the organization's standard KVO rates and consider reducing to the lowest reasonable rate.
- Consider catheter locks with flushes for eligible patients.
- Use oral electrolyte and hydration whenever possible.
- Discontinue infusions as soon as appropriate.
- Avoid discontinuing and restarting intravenous fluids during transitions of care (such as between the emergency department and other nursing units) unless clinically necessary.
- Consider policies that allow completion of a currently hanging infusion bag before switching to a different infusion product unless clinically contraindicated.

Source: ASHP Small- and Large-Volume Fluid Shortages Suggestions for Management and Conservation

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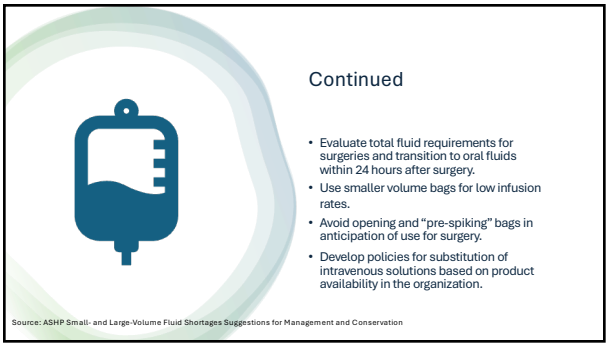

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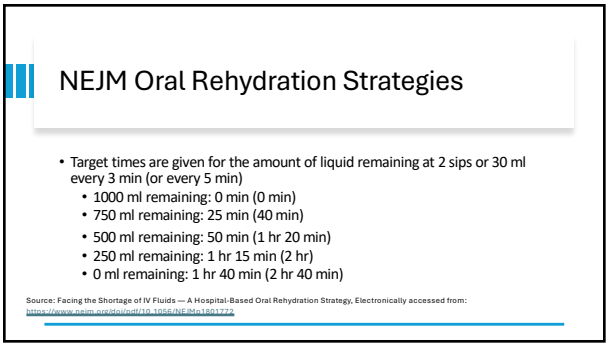

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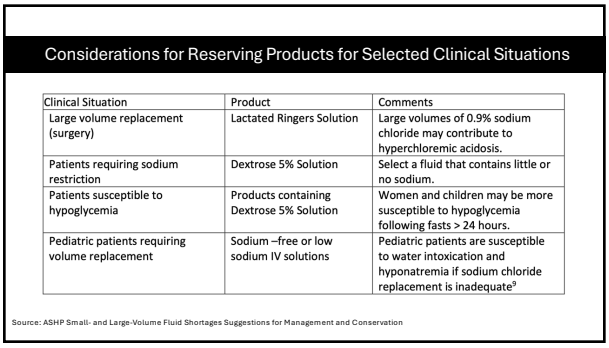

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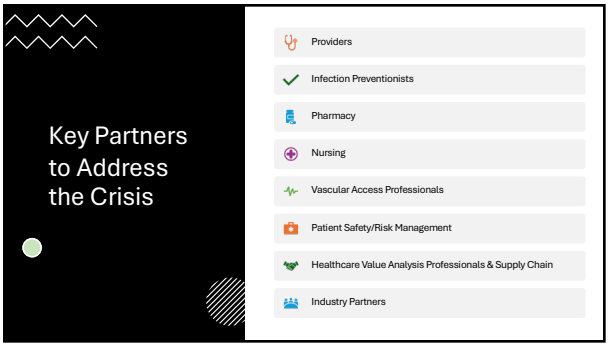

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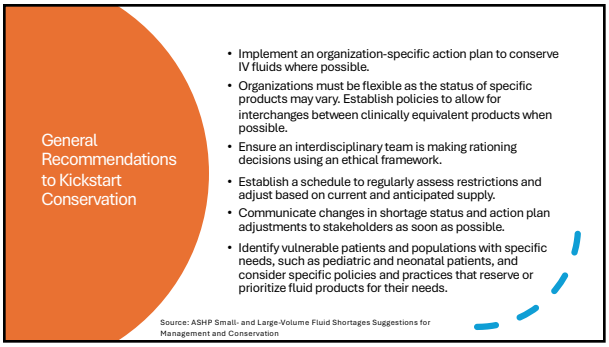

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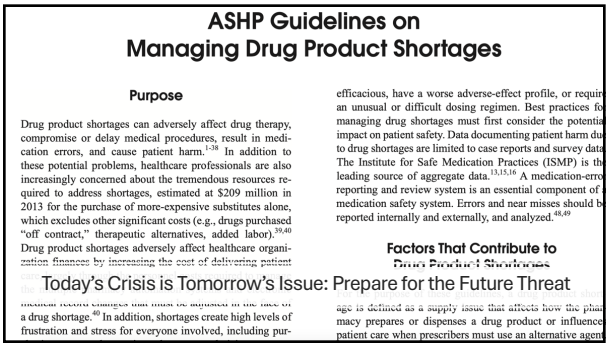

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Extensions to Expiration Dates: Current FDA Guidance

- The request for extension of expiry must be submitted by the manufacturer and manufacturer-specific stability data must be reviewed by FDA.
- At this time, FDA does not have data from the intravenous and renal fluid product manufacturers to support extension of expiry.

Source: Food and Drug Administration, electronically accessed from: https://www.fda.gov/drugs/updates-2024-hurricane-season/hurricane-helene-hasten-manufacturing-recovery-north-Carolina

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Compounded Drug Options

Compounded drugs might be appropriate if a patient's medical need cannot be met by an FDA-approved drug or the FDA-approved drug is not available. However, compounded drugs are not FDA-approved, which means they are not reviewed by FDA for safety, effectiveness or quality before they are marketed for patient use.

Compounders may make a compounded version of a drug on FDA's drug shortages list if they meet the conditions in federal law.

Source: Food and Drug Administration, electronically accessed from: https://www.fda.gov/drugs/updates-2024-hurricane-season/hurricane-helene-hasten-manufacturing-recovery-north-Carolina

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Additional Criteria

Section 503A of the FD&C Act restricts compounding, regularly or in inordinate amounts, drugs that are essentially copies of commercially available drugs.

FDA does not consider a drug to be commercially available if it is on FDA's drug shortages list.

Section 503B of the FD&C Act restricts outsourcing facilities from making essentially a copy of an FDA-approved drug.

This condition does not prohibit outsourcing facilities from preparing compounded drugs that are identical or nearly identical copies of an FDA-approved drug on the FDA's drug shortages list.

Source: Food and Drug Administration, electronically accessed from: https://www.fda.gov/drugs/updates-2024-hurricane-season/hurricane-helene-hasten-manufacturing-recovery-north-Carolina

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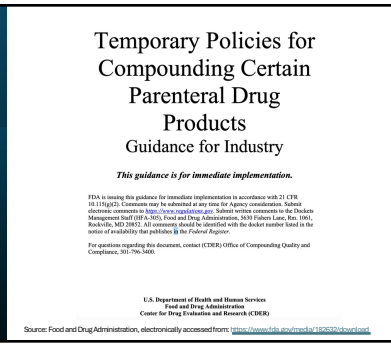
New FDA Emergency Compounding Guidance in Immediate Effect



Temporary Policies for Compounding Certain Parenteral Drug Products

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Comments may be submitted at any time for Agency consideration. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact (CDER) Office of Compounding Quality and Compliance, 301-796-3400.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Source: Food and Drug Administration, electronically accessed from: https://www.fda.gov/media/185525/download

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Infection Control Considerations

In compounding options are utilized, Infection Preventionists should be aware and closely monitor potential impacts to CLABSI infection rates.

Infection Preventionists should be engaged in any changes to policies and procedure related to vascular access and supply chain disruptions.

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Communicate!
Communicate!
Communicate !

- Adequately communicate any changes to current practice using established communication channels within your hospital or health system, such as local intranet, EHR alerts, emails, daily huddles, flyers, labeling, etc.
- Be sure that the clinical informatics team is aware of the need to make priority changes in drug records, charge description masters, and infusion pump libraries and recognize that they will not have the normal lead time that this process generally requires.
- Consider having a physician and nursing champion in addition to the pharmacy lead who can assist with routine communication, practice changes, and stock updates.

Source: ASHP Small- and Large-Volume Fluid Shortages Suggestions for Management and Conservation

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Supply Chain Strategies: Build Resilience

- Work closely with the supply chain team to obtain accurate system-wide estimates of stock on hand, particularly in health-systems where pharmacy does not supply all fluids.
- Consider using smaller volume bags or vials of saline and sterile water for reconstituting drugs in the pharmacy instead of using liter bags.

Source: ASHP Small- and Large-Volume Fluid Shortages Suggestions for Management and Conservation

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Ensure Supply Chain Channels are Maintained for Patient Safety

- Medicare will not reimburse for oral hydration in the Outpatient Prospective Payment System (OPPS).
- This applies to patients in ambulatory care settings and patients in the ED who are not admitted to the hospital.
- Avoid buying products from sources outside the traditional supply chain.
- Report suspected illegal activity by nontraditional distributors to your state board, state attorney general, or FDA's Office of Criminal Investigation.

Source: ASHP Small- and Large-Volume Fluid Shortages Suggestions for Management and Conservation

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National Stabilization Efforts

Group Purchasing Organizations (GPOs) are directly collaborating with Baxter, distributors, and other stakeholders to improve stability of the supply chain with intravenous fluids.

The Department of Health and Human Services, Food and Drug Administration, and other Federal Agencies are actively engaged in this discussion.

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Other Health-System Level Strategies to Drive Compliance

- Evaluate supplies on a health system-wide basis to redeploy solutions to areas of greatest need.
- Minimize unit stock of large volume bags to the extent possible or stock only in critical care, procedure, and emergency care areas where fluids are an essential component of supplies.
- Ensure smaller volume bags are stocked in supply areas.
- Work closely with the supply chain team to obtain accurate system-wide estimates of stock on hand, particularly in health-systems where pharmacy does not supply all fluids.

Source: ASHP Small- and Large-Volume Fluid Shortages Suggestions for Management and Conservation

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Forecasting and Realistic Expectations

- Hospitals and Healthcare Facilities should collaborate with their GPO resources and preferred Industry Partner to ensure proper forecasting is provided.
- Realistic forecasting and demand must be submitted during supply chain shortages to prevent supply chain collapse.
- All involved must exercise patience during difficult times associated with critical supply chain shortages.

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What about the National Strategic Stockpile?

- Any sterile fluid inventory maintained in the SNS is insufficient to meet even a fraction of daily national needs.
- The Strategic National Stockpile cannot realistically provide relief for ongoing shortages.

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Temporary Import Strategies

- FDA is working to temporarily import some products in shortage to help meet patient needs.
- In this situation, FDA very carefully assesses the overseas product for quality, making sure that it is safe for U.S. patients.

Temporary importation sources to help mitigate shortages

Search: Show 25 entries

Product Name	Presentation	Additional Information
0.9% Sodium Chloride Injection	250 mL, NDC 0338-9793-01	Product from Shanghai, China
0.9% Sodium Chloride Injection	1,000 mL, NDC 0338-9793-01	Product from Shanghai, China
10% Glucose Injection	250 mL, NDC 0338-9797-01	Product from Shanghai, China
5% Glucose and 0.9% Sodium Chloride Injection	1,000 mL, NDC 0338-9799-01	Product from Shanghai, China
5% Glucose Injection	250 mL, NDC 0338-9795-01	Product from Shanghai, China
5% Glucose Injection	1,000 mL, NDC 0338-9801-01	Product from Shanghai, China
50% Glucose Injection	3,000 mL, NDC 0338-9787-01	Product from Thetford, UK
70% Dextrose Injection USP	3,000 mL, NDC 0338-9789-01	Product from Allston Canada
70% Glucose Injection	500 mL, NDC 0338-9785-01	Product from Thetford, UK

Source: Food and Drug Administration, electronically accessed from: https://www.fda.gov/drugs/updates-2024-hurricane-season/hurricane-helene-hastens-manufacturing-recovery-north-Carolina

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Where Do We Go From Here?

- Today's Crisis is Intravenous Fluids, but what will it be Tomorrow? Prepare Accordingly....
- Develop Protocols for Clinical Conservation of Critical Clinical products to ensure future readiness
- Ensure Supply Chain Resilience & and Collaborate with Healthcare Value Analysis

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Additional Clinical Resources

- AHVAP Emergency Supply Chain Disruption Resource Center
- Updates on IV Fluid Supplies: American Hospital Association
- Hurricane Helene Baxter Shortages: American Society of Anesthesiologists
- Interim Guidance on PD Solution Conservation During Supply Shortage: American Society of Pediatric Nephrology
- Update on Intravenous Fluid Shortages: Association of Perioperative Registered Nurses
- Alliance Resources: End Drug Shortages Alliance
- Guidance Document for Managing Product Shortages during Disruptions in Manufacturing: National Home Infusion Association

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Selected References

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- Infections and Extended Intravenous Solution Hang Times. J Infus Nurs. 2021 May-Jun Mianecki TB, Peterson EL. The Relationship Between Central Line-Associated Bloodstream 01;44(3):157-161.
- General Chapter: USP. Pharmacuetical Compounding—Nonsterile Preparations <795>. In: USP-NF. Rockville, MD: USP; May, 2024.

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Resource Center Open and Available

Supply Chain Disruption Resource Center

IV Fluids Supply Chain Disruption Resource Center

AHVAP

AORN

AVA

Access Here: https://ahvap.memberclicks.net/ahvap-aorn-resource-center

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Stay in Touch

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Small- and Large-Volume Fluid Shortages
Suggestions for Management and Conservation

(Updated by ASHP and the University of Utah Drug Information Service, Oct 11, 2024)

This information has been compiled using publicly available information on established best practices. ASHP and the University of Utah have provided this fact sheet for informational purposes only and are not assuming any liability for the accuracy or completeness of the information provided.

Please email PracticeAdvancement@ashp.org with comments or questions.

Recent Updates:

- Frequently Asked Questions section added
- Additional considerations added for determining IV fluid hang times
- Additional links added to External Resources section, including links to recommendations by other professional organizations
- Added a link to report instances of price gouging to the Department of Justice
- Added a link and a reminder to report medication errors that result from drug shortages to the Institute for Safe Medication Practices

Introduction

This fact sheet provides potential actions for organizations to consider in managing fluid shortages. Healthcare practitioners should use their professional judgment in deciding how to use the information in this document, considering the needs and resources of their individual organizations.

Why is Conservation Necessary?

There is a national shortage of large-volume parenteral solutions, including but not limited to: sodium chloride injections, lactated ringers injection, sterile water for injection, and dextrose injections. The shortages are due to the effects of Hurricane Helene in North Carolina.

Definitions

Small-volume parenteral solutions (SVPs) — a solution volume of 100 mL (as defined by USP) or less that is intended for intermittent intravenous administration (usually defined as an infusion time not lasting longer than 6-8 hours).[1]

Large-volume parenteral solutions (LVPs) – a solution volume of greater than 100 mL (as defined by USP)

Intravenous (IV) push — The Institute for Safe Medication Practices (ISMP) defines IV push as "direct, manual administration of a medication using a syringe, usually under pressure, connected to an IV access device."[2] Best practice recommends that whenever possible the actual rate of IV push

administration specific to a given drug be noted and that terms such as IV push (unspecified), IV bolus (unspecified), slow or fast/rapid IV push should be avoided.

Ready-to-administer — A dosage form or concentration that can be administered to the patient without further manipulation

General Recommendations

- Implement an organization-specific action plan to conserve IV fluids where possible. Organizations must be flexible as the status of specific products may vary. Establish policies to allow for interchanges between clinically equivalent products when possible.
- Ensure an interdisciplinary team is making rationing decisions using an ethical framework.[3]
    - Establish a schedule to regularly assess restrictions and adjust based on current and anticipated supply.
- Communicate changes in shortage status and action plan adjustments to stakeholders as soon as possible.
- Identify vulnerable patients and populations with specific needs, such as pediatric and neonatal patients, and consider specific policies and practices that reserve or prioritize fluid products for their needs.

Conservation - Large Volume Products

- Evaluate the clinical need to continue intravenous fluid replacement at every shift change and bag change.
- Assess the need to initiate “keep vein open” (KVO) orders and the need to continue those orders at every shift change.
- Review the organization’s standard KVO rates and consider reducing to the lowest reasonable rate.[4]
- Consider catheter locks with flushes for eligible patients.
- Use oral electrolyte and hydration whenever possible.[5]
- Discontinue infusions as soon as appropriate.
- Avoid discontinuing and restarting intravenous fluids during transitions of care (such as between the emergency department and other nursing units) unless clinically necessary.
- Consider policies that allow completion of a currently hanging infusion bag before switching to a different infusion product unless clinically contraindicated.
    - For example, if an order is changed from 0.9 % sodium chloride to dextrose 5 % with 0.45 % sodium chloride, consider allowing completion of the bag of 0.9 % sodium chloride before switching to prevent waste and prolong the total infusion time of available fluids.
- Evaluate total fluid requirements for surgeries and transition to oral fluids within 24 hours after surgery.[6]
- Develop policies for substitution of intravenous solutions based on product availability in the organization. Example: an organization might allow substitution of Lactated Ringers for 0.9% sodium chloride or vice-versa depending on what is in stock. Table 1 provides a comparison of common intravenous fluid components.
- Use smaller volume bags for low infusion rates (see Table 2).
- Consider reserving some products for specific clinical situations as outlined in Table 3.
- Avoid opening and “pre-spiking” bags in anticipation of use for surgery.
- Use other large volume electrolyte replacement solutions where appropriate.
- Consider extending hang times for intravenous solutions (if spiked immediately prior to administration). The 2024 Infusion Nurses Society Infusion Therapy Standards of Practice note that

there is insufficient evidence to recommend a specific frequency for routine replacement of non-lipid IV fluids.[7] Evidence shows no difference in central line-associated bloodstream infections (CLABSI) rates at 96 hours for fluids administered vis central venous catheters.[8] In making such a decision, hospital leadership; medical, nursing and pharmacy staff; infection control; risk management and other stakeholders should weigh the risk of infection against the need to conserve intravenous solutions. See FAQs section for more information.

- Review use of sterile water for rinsing equipment or utensils used during nonsterile compounding. USP Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations specifies that purified water, distilled water, or reverse osmosis water should be used to rinse equipment or utensils.[9]
- Review use of sterile water for reconstituting conventionally manufactured oral solutions. Follow product labeling instructions for water requirements. Note that reconstituting conventionally manufactured nonsterile products according to product labeling is not considered compounding according to USP Chapter <795>. However, compounding nonsterile preparations does require the use of USP-compliant purified water or better-quality water.[9]

Conservation - Small Volume Products

- Review the use of fluids as supplies. Many areas use SVP fluids to start intravenous lines, administer blood, or flush lines. During these shortages, consider using single-use flush syringes when possible, although these products can also be affected by shortages.
    - Switch products to IV push when the patient's clinical status drug properties (e.g., pH, osmolarity) allow. Follow ISMP Safe Practice Guidelines for Adult IV Push Medications.[2]
    - Adhere to the CDC use guidelines for single-use vials.[10]
- Change IV medications and electrolytes to a clinically appropriate oral product whenever possible.
    - Work with the organization's P&T committee, or equivalent, to review current IV to oral (PO) policies.
    - Policies may need to be expanded to include other drug classes.
- If oral route is not feasible or indicated, some medications can be administered via intramuscular or subcutaneous injection.
    - Adhere to recommended maximum volumes for a single injection; doses may need to be divided into more than one syringe.
- Consider alternative intravenous solutions when therapeutic interchange is not clinically important (e.g., maintaining line patency, for blood administration, etc.).
- Review the stock of small volume bags and vials to determine stock on hand that is compatible with proprietary bag-and-vial systems.
    - Do not make practice change plans that will require additional fluids or specific products (e.g., requiring additional mix-on-demand supplies).

Operational Strategies – Large Volume Shortages

- Evaluate supplies on a health system-wide basis to redeploy solutions to areas of greatest need.
- Minimize unit stock of large volume bags to the extent possible or stock only in critical care, procedure, and emergency care areas where fluids are an essential component of supplies.
- Ensure smaller volume bags are stocked in supply areas.
    - If conservation of SVP bags is necessary, stock only in areas where medications must be prepared so that supplies can be consolidated.

- Work closely with the supply chain team to obtain accurate system-wide estimates of stock on hand, particularly in health-systems where pharmacy does not supply all fluids.
- Consider using smaller volume bags or vials of saline and sterile water for reconstituting drugs in the pharmacy instead of using liter bags.
- For situations where small volumes are required but small volume packages are not available (e.g., lactated ringers solution), aliquots of fluids drawn into syringes in the pharmacy may allow a bag of fluid to be used on multiple patients if syringe pumps can be used.
    - For example: 50 mL syringes drawn out of a liter bag of lactated ringers solution may allow a single liter bag to be used for multiple patients during a minor or short procedure.
    - Follow USP Chapter <797> and state rules and regulations for determining applicable beyond-use dates.[11]
- Medicare will not reimburse for oral hydration in the Outpatient Prospective Payment System (OPPS). This applies to patients in ambulatory care settings and patients in the ED who are not admitted to the hospital. Medicaid patients are reimbursed in accordance with state-based policy.
- Avoid buying products from sources outside the traditional supply chain. Report suspected illegal activity by nontraditional distributors to your state board, state attorney general, or FDA's Office of Criminal Investigation. Report price gouging to the Department of Justice.

Operational Strategies – Small Volume shortages

- Transition to commercially manufactured premix medications when available.
- If switching to IV push, ensure sufficient supplies of diluent vials, syringes, and needles are available to accommodate these doses.
- Leverage admixtures available from 503B outsourcers when available.
    - Also communicate with 503B outsourcers to understand how their supply may be affected by shortages.
- Consider changes in the electronic health record (EHR) to allow the use of either dextrose or saline for admixture of drugs compatible with both solutions. This will help create better flexibility based upon which products are available at the time.
    - Use EHR alerts or forced functions when a drug is compatible in only one diluent.
    - Implement or encourage the use of barcode scanning of admixture ingredients to ensure the correct solution is used and documented.
- Consider preparing and dispensing medications that may be administered IV push in ready-to-administer concentrations packaged in syringes.
    - External references are available with information on concentrations and administration rates. See the ***External Resources*** section for additional information.
- If your organization can utilize syringe infusion pumps, consider preparing and dispensing non-IV push medications in ready-to-administer syringes to be infused via syringe pump.
- If empty bags are available, and all other options have been exhausted, consider compounding SVPs of 5% Dextrose or 0.9% Sodium Chloride. This may not be possible if the fluid shortage includes both SVPs and LVPs. See FAQs section for more information.
    - The preferred method for these preparations is to use 1 L bags of commercially available 5% Dextrose or 0.9% Sodium Chloride to repackage into smaller bag sizes (50, 100, or 250 mL).
    - Peristaltic pumps may be used for compounding and will help ensure accuracy and minimize employee fatigue and over-use injuries.

    - Follow USP Chapter <797> and state rules and regulations for determining applicable beyond-use dates. [11]
- If compounded or repackaged bags have been frozen to extend dating, thoroughly inspect the bag before dispensing to ensure the bag did not crack or split during frozen storage.
    - Only compound in an empty container that adequately reflects the final volume: for example, 100 mL of solution in a 100 mL empty container.
        - If necessary to compound in a bag with larger capacity than the final volume of solution, the pharmacy label should be affixed so that it covers the empty capacity printed on the bag. For example, if compounding 50 mL total volume in a 150 mL container the pharmacy label should cover the 150 mL print on the bag.
- Ensure that the temperature for refrigerators and freezers are continuously monitored.
    - Double check that they are plugged into emergency power outlets.

Infusion Pumps / Informatics Strategies

- Allocate appropriate clinical informatics resources to manage critical shortages.
- Review order sets and preference lists for fluid orders that have been selected by default, including KVO orders, and update when possible.
- Individual prescribers may have manually overridden order-set defaults and to a personal preference list. Develop a process to identify these personal selections and update them when possible. Overriding personal versions may require manually adjusting each saved version.
- Consider alerts to notify clinicians when fluids are ordered for patients tolerating oral hydration.
- Ensure existing pump libraries are up to date to ensure safe and consistent practices.
- It may be necessary to change or add to drug libraries. If so, use clinical, safety/quality, and informatics teams to ensure that any additions or changes have been vetted through appropriate channels.
- Drug records, order-sets, and treatment protocols will need to be reviewed for changes based on available products.
    - These may include solutions used for medication dilution or solutions available for line patency.
- Reflect use of smaller volumes in infusion pump libraries, electronic order sets, and standard fluid labels as needed.
- Take the opportunity to review, revise, or develop good infusion pump practices and protocols.
- Consider where and when other types of ambulatory infusion pumps can be used.
- Try to maintain standardization whenever possible, especially if the same pumps are used for both adult and pediatric patients.

Communication Strategies

- Adequately communicate any changes to current practice using established communication channels within your hospital or health system, such as local intranet, EHR alerts, emails, daily huddles, flyers, labeling, etc.
- Be sure that the clinical informatics team is aware of the need to make priority changes in drug records, charge description masters, and infusion pump libraries and recognize that they will not have the normal lead time that this process generally requires.

- Consider having a physician and nursing champion in addition to the pharmacy lead who can assist with routine communication, practice changes, and stock updates.

Safety Considerations

- Compounding sodium chloride solutions from sterile water for injection and concentrated sodium chloride injection is labor-intensive and may worsen the existing shortage of concentrated sodium chloride injection. For urgent short-term sodium and fluid replacement therapy, consider adding concentrated sodium chloride to dextrose or other commercially available large volume parenterals.
- Avoid use of sodium chloride irrigation solution administered intravenously. Limits on particulate matter differ between these two products.
- Make sure all healthcare professionals administering medications have access to IV push policies and guidelines and have been trained and assessed for competency in administering medications via the IV push route. Use available best practices and concepts for IV push administration.[2]
- Consider an IV push administration competency assessment tool if one is not already in place.
- Do not allow the use of "stock" bags that could potentially be used for multiple patients.
- If transitioning medications to syringes for syringe infusion pump administration, make sure staff are adequately trained to use the technology.

ISMP Medication Error Reporting

ASHP encourages the reporting of any medication errors related to drug shortages to the Medication Error Reporting page on the ISMP website.

External Resources

- Hurricane Helene Updates: Baxter Healthcare Corporation.
- Hurricane Helene: Baxter's manufacturing recovery in North Carolina: Food and Drug Administration, 2024
- Hospital-Based Oral Rehydration Strategy: NEJM, 2018
- Temporary Policies for Compounding Certain Parenteral Drug Products: FDA, 2024
- Adult and pediatric IV push medication reference: Vizient, Inc. 2023
- ISMP Safe Practice Guidelines for Adult IV Push Medications: ISMP, 2015
- Intravenous Push Administration of Antibiotics: Hosp. Pharm, 2018.

Resources and Recommendations from Other Professional Organizations:

- Updates on IV Fluid Supplies: American Hospital Association
- Hurricane Helene Baxter Shortages: American Society of Anesthesiologists
- Interim Guidance on PD Solution Conservation During Supply Shortage: American Society of Pediatric Nephrology
- Update on Intravenous Fluid Shortages: Association of Perioperative Registered Nurses.
- Alliance Resources: End Drug Shortages Alliance
- Guidance Document for Managing Product Shortages during Disruptions in Manufacturing: National Home Infusion Association

Acknowledgements

ASHP thanks Erin Fox, PharmD, MHA, BCPS, FASHP, and the ASHP Section of Inpatient Care Practitioners Advisory Group on Compounding Practice for their contributions to this resource.

Frequently Asked Questions

Can hospital pharmacies compound IV fluids that are in short supply?

FDA guidance allows hospital pharmacies (categorized as 503A pharmacies) to compound versions of drugs that are essentially copies of commercially manufactured drugs if they are posted on the FDA Drug Shortages List. While this may be possible in some limited quantities, the amount that a hospital pharmacy can compound is not likely to be nearly enough to meet the normal daily use of these fluids in a hospital setting. The products necessary to compound fluids, such as sterile water for injection, concentrated sodium chloride, and empty sterile containers, are also in short supply or likely to be available only in limited quantities. Pharmacies choosing to compound using concentrated sodium chloride solution should take extra precautions and implement in-process double checks due to the risk of serious harm if sodium chloride solutions are compounded incorrectly.

Will Baxter extend expiration dates for products in short supply?

Expiration dates can only be extended when a manufacturer conducts stability testing and can show the product is still acceptable for use. The testing results are submitted to the FDA who will review the data and grant the extended expiration dates. Baxter representatives and Department of Health and Human Services (HHS) officials have indicated these tests are likely to be performed on some products and recommend that any fluids at or near expiry be sequestered in the event that an expiration date extension is granted. To request the expiration date extension of a specific lot number of a product, contact Baxter at: medinfo@baxter.com.

Will the FDA authorize importation of fluids from other countries?

FDA and HHS officials have stated that they are exploring all options to help relieve the fluid shortages, including importation. Some products have already been authorized for importation. Check the FDA's Hurricane Helene page for the latest information.

What is the basis for suggesting longer hang times for IV fluids?

While researching hang times for intravenous fluids, we were unable to find an established standard for recommended hang times. The citation demonstrates no increase in risk of catheter-related bloodstream infections (CLABSI) at 96 hours for central venous catheters.[8] This provides some evidence that 96 hours is an acceptable hang time and reasonable extrapolation can be made to peripheral venous access contamination. The Infusions Nurses Society and Centers for Disease Control and Prevention recommend that administration sets in continuous use, but not used for blood, blood products, or lipids, be changed "at least every 7 days (unless otherwise stated in manufacturers' directions for use) or when clinically indicated … , whichever occurs sooner".[7] Organizations should consider the criticality of fluid supply, and clinical risk factors and other variables when making decisions on hang times up to or beyond 96 hours.[12,13] Connections and disconnections should be minimized when possible, and aseptic technique should be used at all times when connecting fluids to administration sets and when spiking bags. There are many different types of vascular access devices and organizations should consider risk factors associated with each when establishing fluid hang times.

Will the United States Pharmacopeia (USP) provide considerations for extending the beyond-use dates of compounded preparations to reduce waste like they did during the COVID-19 public health emergency?

While ASHP cannot comment on whether USP will provide any resources during this shortage, there is some important context to understand about the COVID-19 *Operational Considerations* resource provided by USP. An updated version of Chapter <797> Pharmaceutical Compounding—Sterile Preparations had already been published and was expected to become final. The revision included beyond-use dates (BUDs) that were longer than the previous version of the chapter. However, the updated chapter was appealed and ultimately remanded back to the compounding expert committee for further review and stakeholder engagement. The granted appeals did not include the section related to BUDs. The BUD changes were expected to become final with the next update to the chapter, which was updated in 2023 to the now-current version. Therefore, USP had a basis to include the updated, longer BUDs as part of its *Operational Considerations* document to support compounders during drug shortages that occurred during the pandemic. USP may offer some resources during this shortage, however it is unlikely that longer BUDs will be included.

Can the Strategic National Stockpile (SNS) help provide sterile fluid supplies to healthcare practitioners?

Any sterile fluid inventory maintained in the SNS is insufficient to meet even a fraction of daily national needs; we do not expect the SNS will realistically provide relief for ongoing shortages.

Table 1. Comparison of Selected Intravenous Fluid[14-19]

Product	mOsm/L	Na (mEq/L)	Cl (mEq/L)	Dextrose (g/L)	K (mEq/L)	Ca (mEq/L)	Lactate (mEq/L)	Mg (mEq/L)	Ace-tate (mEq/L)	Gluconate (mEq/L)
0.9% Sodium Chloride	308	154	154	---	---	---	---	---	---	---
0.45% Sodium Chloride	154	77	77	---	---	---	---	---	---	---
Dextrose 5% plus 0.2% Sodium Chloride	321	34	34	50	---	---	---	---	---	---
Dextrose 5% plus 0.45% Sodium Chloride	406	77	77	50	---	---	---	---	---	---
Dextrose 5% plus 0.9% Sodium Chloride	560	154	154	50	---	---	---	---	---	---
Dextrose 5%	252	---	---	50	---	---	---	---	---	---
Lactated Ringers Solution	273	130	109		4	2.7	28	---	---	---
Lactated Ringers and Dextrose 5% Solution	525	130	109	50	4	2.7	28	---	---	---
Normosol-R	295	140	98	---	5	---	---	3	27	23
Plasmalyte-A	294	140	98	---	5	---	---	3	27	23

Table 2. Recommended Container Volumes Based on Infusion Rates

Infusion Rate	Bag Size
20 mL / hour or less	250 mL
21 mL/hour to 40 mL/hour	500 mL

Table 3. Considerations for Reserving Products for Selected Clinical Situations[20-22]

Clinical Situation	Product	Comments
Large volume replacement (surgery)	Lactated Ringers Solution	Large volumes of 0.9% sodium chloride may contribute to hyperchloremic acidosis.
Patients requiring sodium restriction	Dextrose 5% Solution	Select a fluid that contains little or no sodium.
Patients susceptible to hypoglycemia	Products containing Dextrose 5% Solution	Women and children may be more susceptible to hypoglycemia following fasts > 24 hours.
Pediatric patients requiring volume replacement	Sodium –free or low sodium IV solutions	Pediatric patients are susceptible to water intoxication and hyponatremia if sodium chloride replacement is inadequate[9]

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Temporary Policies for Compounding Certain Parenteral Drug Products

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Comments may be submitted at any time for Agency consideration. Submit electronic comments to *https://www.regulations.gov*. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact (CDER) Office of Compounding Quality and Compliance, 301-796-3400.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2024
Compounding

Temporary Policies for Compounding Certain Parenteral Drug Products

Guidance for Industry

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Food and Drug Administration
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Contains Nonbinding Recommendations

Temporary Policies for Compounding Certain Parenteral Drug Products Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

As of October 10, 2024, pursuant to section 319(a) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)), Department of Health and Human Services (HHS) Secretary Becerra has determined that public health emergencies (PHEs) exist as a result of the consequences of Hurricane Helene in the States of North Carolina, Florida, Georgia, Tennessee, and South Carolina, and as a result of the consequences of Hurricane Milton in the State of Florida.[2] In late September 2024, Hurricane Helene had a devastating impact on one of the largest manufacturers of certain intravenous and peritoneal dialysis solutions in the United States. The Food and Drug Administration (FDA or the Agency) is working with the manufacturer and alternative suppliers to increase supply and reduce the risk of new shortages of critical drug products.

This guidance describes the FDA's regulatory and enforcement priorities regarding the compounding of certain parenteral drug products by outsourcing facilities and by State-licensed pharmacies and Federal facilities that are not registered with FDA as outsourcing facilities. This policy is intended to remain in effect only for the duration of the supply disruption related to the above referenced PHEs, or for another period of time as FDA may announce. As relevant needs and circumstances evolve, FDA intends to update, modify, or withdraw the policies in this guidance and the drug products that are the subject of this policy.

This guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately to help ensure patient access to certain parenteral drug products, such as intravenous fluids, which are essential in the care of patients, including those who are critically ill and those undergoing surgery. While this guidance is being implemented immediately due to the urgent

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research at the Food and Drug Administration.
[2] A list of HHS PHE declarations is located at: https://aspr.hhs.gov/legal/PHE/pages/default.aspx.

public health need, it remains subject to comment in accordance with the Agency's good guidance practices.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Although compounded drug products can serve an important patient need, they can also pose a higher risk to patients than FDA-approved drug products. Compounded drug products are not FDA-approved, which means they are not reviewed by FDA for safety, effectiveness, or quality before they reach patients. The Agency recommends FDA-approved drug products be used to treat patients whenever possible.

Section 503A of the FD&C Act (21 U.S.C. 353a) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from the following three sections of the FD&C Act: (1) section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements).

One of the conditions in section 503A of the FD&C Act is that each drug product must be compounded for an identified individual patient based on the receipt of a valid prescription order, or a notation, approved by the prescribing practitioner, on the prescription order that a compounded drug product is necessary for the identified patient.[3] The prescription requirement is a critical mechanism to distinguish compounding under section 503A of the FD&C Act from conventional manufacturing, or compounding by outsourcing facilities, and helps ensure that drug products that pharmacies compound under section 503A of the FD&C Act are provided to a patient only based on individual patient need. Another condition in section 503A of the FD&C Act is that a licensed pharmacist or licensed physician does not compound regularly or in inordinate amounts any drug products that are essentially copies of commercially available drug products.[4]

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[3] See section 503A(a) of the FD&C Act. See also the guidance for industry *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (December 2016). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] See section 503A(b)(1)(D) of the FD&C Act. FDA does not consider products on FDA's drug shortage list to be commercially available. See section 503A(b)(1)(D) of the FD&C Act, and the guidance for industry *Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (January 2018).

Section 503B of the FD&C Act (21 U.S.C. 353b) describes the conditions that must be satisfied for human drug products compounded by an outsourcing facility to be exempt from the following three sections of the FD&C Act: (1) section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 582 (21 U.S.C. 360eee-1) (concerning drug supply chain security requirements). Section 503B of the FD&C Act restricts outsourcing facilities from compounding drugs that are not on FDA's drug shortage list. In particular, bulk drug substances used to compound a drug that is not on FDA's drug shortage list must be on a list of substances established by the Secretary for which there is a clinical need (the 503B Bulks List),[5] and outsourcing facilities may not compound a drug that is essentially a copy of one or more approved drugs.[6] Additionally, outsourcing facilities are required to register with FDA, are inspected by FDA according to a risk-based schedule, and are subject to CGMP requirements. CGMP requirements include a requirement to conduct stability studies to support the assignment of a product expiration date.[7]

III. TEMPORARY POLICY FOR CERTAIN PARENTERAL DRUG PRODUCTS COMPOUNDED BY PHARMACY COMPOUNDERS NOT REGISTERED AS OUTSOURCING FACILITIES

Although FDA is monitoring the global pharmaceutical supply chain and working, within its authorities, with manufacturers of approved parenteral drug products to bolster supply, temporary flexibility is needed to help ensure that treatment options remain available to hospitals and health systems during this period.

To the extent that hospitals and health systems have a need for compounded drug products, FDA encourages them to obtain such products from outsourcing facilities. As noted above, outsourcing facilities register with FDA, are subject to CGMP requirements, and are inspected by FDA according to a risk-based schedule. This helps to mitigate the risk that their drug products will be contaminated or otherwise made under substandard conditions.

However, hospitals and health systems may have difficulty obtaining adequate supplies of certain FDA-approved parenteral drug products or adequate supplies of comparable drug products made by an outsourcing facility.

[5] See section 503B(a)(2)(A) of the FD&C Act.
[6] See section 503B(a)(5) and (d)(2) of the FD&C Act.
[7] See section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)). CGMP requirements for the preparation of drug products are set forth in 21 CFR parts 210 and 211.

Therefore, as a temporary measure, FDA does not intend to take action against a State-licensed pharmacy that is not registered as an outsourcing facility, including a hospital or health system pharmacy,[8] for providing a compounded drug to a hospital or health system without obtaining a patient-specific prescription,[9] or for compounding a drug that is essentially a copy of a commercially available drug,[10] if all of the following circumstances are present.

1. The drug product appears on the list of drugs on FDA's website at https://www.fda.gov/media/182634/download?attachment.[11]

2. The compounded drug product is labeled with a default beyond use date (BUD) in accordance with the table in Appendix A.[12]

3. If the pharmacy and the hospital or health system are not owned and controlled by the same entity, the pharmacy requests that the hospital or health system provide, to the extent allowed by applicable laws, the records that identify the patients to whom the drugs were administered and document such request within 1 month of sending the compounded drug to the hospital or health system.

4. Before providing the drug product to the hospital or health system, a State-licensed pharmacy notifies the following State authorities, and the State authorities inform the pharmacy that they do not object to the pharmacy providing the drug product to the hospital or health system without first obtaining a patient-specific prescription:

    a. The State authority that regulates pharmacy compounding in the State where the pharmacy is located, and,

    b. If different, the State authority that regulates pharmacy compounding in the State where the hospital or health system is located.[13]

5. Other conditions of section 503A and other requirements in the FD&C Act are met. In particular, a drug is deemed to be adulterated "if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health."[14] Drug products prepared, packed, or held under insanitary conditions could become contaminated and cause serious

[8] The policy in this guidance is separate from FDA's previously issued draft guidance for industry *Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (October 2021) (when final, this guidance will represent the FDA's current thinking on this topic) and does not include a condition for use within 24 hours. FDA has adopted the policies in this guidance for immediate implementation as a temporary measure.
[9] Section 503A(a) of the FD&C Act.
[10] Section 503A(b)(1)(D) of the FD&C Act. FDA does not consider a drug to be commercially available if it is currently on FDA's drug shortage list.
[11] We recommend checking this list periodically for updates.
[12] When preparing these drug products, it is important that pharmacies consider storage and handling conditions per United States Pharmacopeia standards and approved labeling for the comparable FDA-approved drug product.
[13] FDA recommends that State-licensed pharmacies consult with State authorities regarding local requirements.
[14] Section 501(a)(2)(A) of the FD&C Act (21 U.S.C. 351(a)(2)(A)).

adverse events, including death.[15] Additionally, section 501(b) of the FD&C Act requires a drug recognized in the United States Pharmacopeia (USP) to meet the standards of strength, quality, and purity in the official monograph or to be clearly labeled to designate how it differs from USP standards.

FDA recommends that hospitals and health systems maintain records of both the entity supplying the hospitals and health systems with such drugs and the patients who receive the drugs. FDA also encourages hospitals and health systems to provide to the pharmacy, to the extent allowed by applicable laws, records that identify the patients to whom the drugs were administered. Such records may be important to allow follow-up if there are adverse drug events or product quality issues associated with drugs the pharmacy has provided.

FDA encourages health care professionals to report adverse drug events experienced with the use of compounded drug products to the pharmacies that produced the drug products as well as to FDA's MedWatch Safety Information and Adverse Event Reporting Program (available at https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program):

- Complete and submit the report online at FDA's MedWatch Online Voluntary Reporting Form web page (at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm); or
- Download and complete the Form FDA 3500 MedWatch: The FDA Safety Information and Adverse Event Reporting Program (available at https://www.fda.gov/media/76299/download), and, then submit it via fax at 1-800-FDA-0178.

IV. TEMPORARY POLICY FOR CERTAIN PARENTERAL DRUG PRODUCTS COMPOUNDED BY OUTSOURCING FACILITIES

As a temporary measure, FDA does not intend to take action against an outsourcing facility for compounding a drug product that is essentially a copy of an approved drug,[16] for using a bulk drug substance that is not on FDA's 503B Bulks List,[17] or for not meeting CGMP requirements

[15] For more information, see the guidance for industry *Insanitary Conditions at Compounding Facilities* (November 2020).

[16] See section 503B(a)(5) and (d)(2) of the FD&C Act. At this time, FDA does not intend to take action against an outsourcing facility for filling orders for a drug product that is essentially a copy of an approved drug product, provided the drug appeared on the list of drugs on FDA's website at https://www.fda.gov/media/182633/download?attachment within 180 days of the outsourcing facility compounding, distributing, or dispensing the drug. A drug is not essentially a copy of one or more FDA approved drugs if it is identical or nearly identical to an approved drug on FDA's drug shortage list.

[17] See section 503B(a)(2)(A) of the FD&C Act. At this time, FDA does not intend to take action against an outsourcing facility for compounding a drug product using a bulk drug substance that is not on the 503B bulks list if the drug compounded from the bulk drug substance appeared on the list of drugs on FDA's website at https://www.fda.gov/media/182633/download?attachment within 180 days of the outsourcing facility compounding, distributing, or dispensing the drug.

with regard to product stability testing and the establishment of an expiration date, as described below, when all of the following circumstances are present.

1. The drug product appears on the list of drugs on FDA's website at https://www.fda.gov/media/182633/download?attachment.[18]

2. The outsourcing facility's practices regarding stability testing and expiration dates meet the conditions for enforcement discretion described in Appendix B (Stability/Expiration Dating for Drug Products Compounded by Outsourcing Facilities) and Appendix C (Conditions Under Which FDA Generally Does not Intend to Take Regulatory Action Regarding Stability Testing and Expiration Date Requirements for Drug Products Compounded by Outsourcing Facilities).[19] These conditions include:

    a. The outsourcing facility uses a default beyond use date of not more than 28 days at room temperature and not more than 42 days refrigerated when a sterility test has not been completed before release;
    b. The outsourcing facility initiates limited stability testing[20] once the aggregate batch[21] size of the product is expected to exceed 5,000 units;[22] and

3. The outsourcing facility initiates container-closure integrity testing[23] with the first batch.[24]

4. Other conditions of section 503B and other requirements in the FD&C Act are met. Section 501(b) of the FD&C Act requires a drug recognized in USP to meet the standards of strength, quality, and purity in the official monograph or to be clearly labeled to designate how it differs from USP standards.

FDA encourages health care professionals to report adverse events experienced with the use of compounded drug products to the outsourcing facilities that produced the products as well as to

[18] We recommend checking this list periodically for updates.
[19] Except for provisions related to batch sizes, the policy described in Appendix B and Appendix C of this guidance is consistent with FDA's previously issued draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (January 2020). When finalized, the draft guidance will represent FDA's current thinking on the CGMP topics it addresses. FDA has adopted the policies in this guidance for immediate implementation as a temporary measure.
[20] As described in Appendix B. While stability testing is being conducted, the outsourcing facility can continue to use the default BUD and continue production until stability testing is complete.
[21] As used here, consistent with Appendix B, *aggregate batch* refers to the sum of all units produced from any number of batches over the 6-month period for which a drug product report is submitted. For more information about product reports, see the guidance for industry *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (December 2016).
[22] As used here, consistent with Appendix B, *units* are immediate containers (e.g., vial, syringe, IV bag, tube).
[23] As described in Appendix A.
[24] When preparing these drug products, it is important that outsourcing facilities consider known storage and handling conditions per USP standards and approved labeling for the comparable FDA-approved drug product.

FDA's MedWatch Safety Information and Adverse Event Reporting Program (available at https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program):

- Complete and submit the report online at FDA's MedWatch Online Voluntary Reporting Form web page (at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm); or
- Download and complete the Form FDA 3500 MedWatch: The FDA Safety Information and Adverse Event Reporting Program (available at https://www.fda.gov/media/76299/download), and then submit it via fax at 1-800-FDA-0178.

APPENDIX A: BEYOND USE DATES FOR DRUG PRODUCTS COMPOUNDED BY PHARMACY COMPOUNDERS NOT REGISTERED AS OUTSOURCING FACILITIES

Processing Conditions	Storage Conditions	
	Controlled Room Temperature (20° to 25°C)	**Refrigerator (2° to 8°C)**
• Finished drug product is aseptically processed; and • A sterility test has not been completed before release	4 days	6 days
• Finished drug product is terminally sterilized; • A verified sterilization cycle that uses biological indicators is employed; and • A sterility test has not been completed before release	10 days	12 days
• Finished drug product is aseptically processed or terminally sterilized and has a completed, passing sterility test before release[1]	20 days	22 days

[1] The default beyond use dates in this row include the time necessary to complete a sterility test, which may include rapid sterility test methods as well as sterility testing described under United States Pharmacopeia (USP) General Chapter <71> *Sterility Tests*.

APPENDIX B: STABILITY/EXPIRATION DATING FOR DRUG PRODUCTS COMPOUNDED BY OUTSOURCING FACILITIES

Stability Program and Beyond Use Dating

A stability program must be established to assess the stability characteristics of finished drug products, and the results of stability testing must be used to determine appropriate storage conditions and expiration dates (21 CFR 211.166). Stability testing is used to ensure that a drug product will retain its quality (e.g., strength) and remain sterile, if applicable, through the labeled expiration date. A stability program for compounded drug products should use past experiences, available literature, and fundamental scientific principles to establish the parameters for the program. An expiration date is established through the conduct of a stability program that includes testing to assess the product's performance against specifications after aging to the desired expiration date (21 CFR 211.137); the conditions outlined in the International Council for Harmonisation (ICH) guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003)[1] are recommended.

FDA understands that a compounded drug's batch size may be small and the frequency of batch production may vary considerably. The policies regarding stability testing and expiration dating in this guidance recognize these potential aspects of compounded drug production while addressing concerns regarding the quality of these products using a risk-based approach.

FDA generally does not intend to take regulatory action against an outsourcing facility regarding stability testing requirements if all of the following apply:

- The approved drug product labeling of at least one of the components specifies how to assign an *in-use time*.
- The compounded drug product has been prepared and labeled with an in-use time in accordance with the approved product labeling.
- The in-use time is used as the expiration date, provided the in-use time does not exceed the expiration date of any of the approved drug products used to compound the drug. If two or more approved drug products with in-use times are used in the compounded drug product, the shortest in-use time is used as the expiration date for the compounded drug product.

In addition, taking into account the unique aspects of compounding, FDA generally does not intend to take regulatory action against an outsourcing facility under the conditions described in the remainder of this appendix and in Appendix C, such as using a beyond use date (BUD) established through limited stability testing or, for certain lower risk situations, using a default

[1] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

BUD as the expiration date, in lieu of establishing an expiration date through the conduct of a full stability program required under part 211 (21 CFR part 211),[2] if all of the following apply:

- The compounded drug's BUD does not exceed appropriately established expiration or retest-by dates for any of the components used to compound the drug.

- If the drug is compounded from an approved drug product, and the approved product labeling recommends one type of storage (e.g., refrigeration through the expiry date, such as 18 months), but also provides for storage at another condition (e.g., stable at room temperature for a time frame shorter than the expiry date, such as up to 14 days), the compounded drug product is not labeled with a BUD that is longer than the relevant storage time frame in the approved product labeling (e.g., the BUD of the compounded drug does not exceed 14 days for room temperature).

Whether you use an expiration date or BUD to be used as an expiration date according to the provisions outlined below and in Appendix C, generally under CGMP requirements the two studies below must be completed before a batch is released (see §§ 211.166 and 211.167). Each study only needs to be conducted once for each formulation and container-closure system, and a bracketing or matrixing approach can be considered to minimize the amount of testing. See Appendix C for more information regarding bracketing approaches.

- **Container-closure integrity testing** is normally conducted on samples aged to or beyond the desired BUD or expiration date to ensure that sterility is maintained over that time period prior to release of the first batch. However, for the purpose of the enforcement policy described in this guidance, an initial container-closure integrity test may be performed prior to release of the first batch using unaged samples to demonstrate ability of the container-closure system to maintain sterility at release. If using this approach, subsequent container-closure integrity tests on samples aged to or beyond the desired BUD or expiration date must be initiated upon release of the first batch.[3]

- **Antimicrobial effectiveness testing** for drug products labeled or intended to be multiple dose is conducted on samples aged to the proposed BUD or expiration date. (Note that antimicrobial effectiveness testing is container-closure specific.)[4] Antimicrobial effectiveness testing must be conducted before a batch is released.

The table in this appendix highlights the conditions under which FDA generally does not intend to take regulatory action against an outsourcing facility for assigning a BUD to be used as an expiration date in lieu of conducting full stability studies required under part 211.

[2] To meet the conditions under section 503B of the FD&C Act, the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI)).
[3] See USP General Chapter <1207> *Package Integrity Evaluation—Sterile Products* for more information on container-closure integrity testing.
[4] See USP General Chapter <51> *Antimicrobial Effectiveness Testing* for more information.

a. Sterile limited stability testing

For aggregate batches ≤5,000 units, FDA generally does not intend to take regulatory action if the relevant default BUDs provided in Appendix C are used for the expiration date and the conditions set forth in Appendix C are met. Alternatively, for small batches, FDA generally does not intend to take regulatory action if limited stability testing is conducted to support a BUD longer than the relevant default BUDs in accordance with Appendix C, and that BUD is used as an expiration date in lieu of conducting full stability studies required under part 211. For larger batches (>5,000 units in an aggregate batch), FDA generally does not intend to take regulatory action regarding stability testing if the relevant conditions for the limited stability testing outlined in Appendix C are met. If, at any time during a 6-month reporting period, the total number of units compounded exceeds the 5,000-unit limit, the conditions applicable to batches ≤5,000 units do not apply.

Table. BUDs for Sterile Compounded Drug Products, by Aggregate Batch Size

Aggregate Batch Size (over 6-month reporting period)	**Default BUD (no testing)**	**BUD Based on Limited Stability Testing**
≤5,000 units	Default BUD, which may be further limited by literature or other scientific information. See Appendix C for the conditions that must be met.	Data-driven stability program. See Appendix C for the conditions that must be met.
>5,000 units	N/A. Default BUDs are not applicable to large aggregate batch sizes, unless stability testing has been initiated, but not yet completed.	Data-driven stability program. See Appendix C for the conditions that must be met.

APPENDIX C: CONDITIONS UNDER WHICH FDA GENERALLY DOES NOT INTEND TO TAKE REGULATORY ACTION REGARDING STABILITY TESTING AND EXPIRATION DATE REQUIREMENTS FOR DRUG PRODUCTS COMPOUNDED BY OUTSOURCING FACILITIES

A. Default Beyond Use Date (No Testing) for Sterile Drug Products: Aggregate Batch Size ≤5,000 Units

The Food and Drug Administration (FDA) generally does not intend to take regulatory action against an outsourcing facility regarding the requirements for stability studies and expiration dates under 21 CFR 211.166 and 211.137 if (1) a beyond use date (BUD) has been assigned according to the criteria based on processing conditions in the table in this appendix; (2) literature or other scientific information, including relevant commercially available product labeling for a similar drug (e.g., components, dosage form, route of administration, primary container-closure type), does not indicate that the drug product may not be physicochemically stable over the time period listed; and (3) the BUD is used as the expiration date.[1]

Table. Default BUDs for Aggregate Batch Size ≤5,000 Units With Given Processing and Storage Conditions

Processing Conditions	Contains a Preservative?	Storage Conditions	
		Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)
• Finished drug product is aseptically processed; and • A sterility test has not been completed before release	No	6 days	9 days
	Yes	28 days	42 days
• Finished drug product is terminally sterilized; • A validated sterilization cycle that uses physical, chemical, or biological indicators is employed; and • A sterility test has not been completed before release	No	14 days	28 days
	Yes	28 days	42 days
• Finished drug product is aseptically processed or terminally sterilized and has a completed, passing sterility test before release	No	28 days	42 days
	Yes	42 days	42 days

[1] To be eligible for the exemptions provided under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI) of the FD&C Act)).

B. Enforcement Policy Regarding the Use of Limited Stability Testing to Assign a BUD

Stability testing is intended to confirm the stability performance of a non-sterile or sterile compounded drug product held under the labeled storage conditions for the duration of the BUD. Procedures established for assessing the stability of drug products compounded by outsourcing facilities must achieve the following (21 CFR 211.122, 211.160, and 211.166):

- Incorporate stability-indicating test methods that are reliable, meaningful, and specific.
- Evaluate samples of the drug product in the same container-closure system and with the same or representative label and adhesive that will be affixed to the container in which the drug product is marketed.
- Evaluate samples for stability that are representative of the batch from which they were obtained and are stored under suitable conditions.
- Incorporate testing to evaluate antimicrobial effectiveness for drug products labeled or intended to be multiple dose. If antimicrobial effectiveness has been previously established for the formulation and container-closure system, a test for preservative content may be used in lieu of a full antimicrobial effectiveness study.

FDA generally does not intend to take regulatory action against an outsourcing facility regarding stability testing and expiration date requirements if the outsourcing facility uses the approach outlined below describing a number of lots and a set of tests—which should be conducted at lot release as part of normal operations—to be performed at the time of the desired BUD. This section B does not apply to non-sterile unpreserved aqueous drug products because of the higher risk of microbiological proliferation.

The following conditions apply:

- Samples are evaluated following aging under the long-term storage conditions (i.e., temperature and humidity) in the International Council for Harmonisation (ICH) guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).[2]
- The data from each time point are evaluated against the established specifications for the compounded drug product.
- The BUD is not longer than 12 months.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- If the data for any test fall outside of the established specifications, the BUD is restricted to the last time point at which the data remained within specifications, or the default BUD (described above) is used.

Because of the possibility that a sample may not meet specifications at the final time point, FDA strongly recommends the inclusion of testing at least once at an interim time point. If the data at the final time point do not confirm the stability of the product at the desired BUD (e.g., some measurements fall outside of the established specifications), but the data at the interim time point are acceptable (i.e., measurements meet the established specifications), a BUD equal to the interim time point meets the second condition above.

Under this policy, samples from one lot are tested. Each unit subjected to one or more tests that compromise the integrity of the primary container-closure is only tested at a single time point (i.e., not at additional time points). If a single unit is to be used for multiple discrete tests to minimize destructive testing, the unit dosage is subdivided into multiple aliquots that are not held longer than the time to complete the testing (typically not longer than 48-72 hours) and the aliquots are placed into appropriate testing containers (e.g., high performance liquid chromatography vials or sample tubes) that protect the sample from being compromised (e.g., from exposure to air, light, evaporation).

Sterile compounded drug products

a. Nondestructive tests

The following tests are conducted:

- Appearance.
- Color and clarity.
- Visible particulates.

b. Destructive chemical tests

The tests to be conducted include:

- pH, if applicable (e.g., for aqueous formulations).
- Assay.
- Subvisible particles (10 micrometers (μm) to –100 μm).[3]

c. Sterility or container-closure integrity tests

To confirm that sterility is maintained over the proposed BUD, container-closure integrity testing (such as described in United States Pharmacopeia (USP) General Chapter <1207> *Package Integrity Evaluation—Sterile Products*) or a sterility test (see USP General Chapter <71>

[3] Applicable only to intrathecal, intravenous, intra-arterial, ophthalmic, intramuscular, sterile otic, and subcutaneous preparations.

Sterility Tests) is conducted. When performed, container-closure integrity testing is conducted on a number of units that is suitable for the chosen test method.

C. Bracketing

Use of bracketing in stability studies allows for more streamlined evaluation of drug products for which there are multiple strengths or volume presentations produced. Bracketing assumes that the stability of intermediate strengths (or intermediate fill volumes) is adequately represented by the extremes tested.[4] For multiple drug products to be eligible for bracketing stability studies, the candidate formulations should vary only in strength (or concentration) or fill volume. Although individual excipient amounts may vary, all excipients (in worst-case amounts) should be in all bracketed formulations. Proportional formulations are not required. The same container-closure system must be used (21 CFR 211.166). If three or more strengths, concentrations, or volume presentations exist, intermediate cases for stability studies as follows may reflect an appropriate use of bracketing:

- If 3 or 4 drug product strengths, concentrations, or volume presentations are produced, test the high and low extremes (e.g., if available strengths include 2.0 milligrams (mg)/milliliter (mL), 3.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL, test 2.0 mg/mL and 10.0 mg/mL).

- If 5 to 10 drug product strengths, concentrations, or volume presentations are produced, test the high and low extremes and 1 intermediate case.

- If more than 10 drug product strengths, concentrations, or volume presentations are produced, test the high and low extremes and 2 intermediate cases.

It is critical that determination of the extremes be done with care. For example, with respect to volume fill, the appropriate extremes are not necessarily always the highest and lowest fluid volume fills. Rather, the head space-to-fluid volume ratio may better represent the appropriate extreme depending on the container volume used in the various presentations.

Bracketing as described in this section does not apply to microbial testing of sterility, endotoxins, or bioburden. Bracketing may be appropriate for water activity testing and antimicrobial effectiveness testing when used in conjunction with a preservative content testing strategy.

[4] See ICH guidance for industry *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products* (January 2003) for more information on bracketing and matrixing.

ASHP Guidelines on Managing Drug Product Shortages

Purpose

Drug product shortages can adversely affect drug therapy, compromise or delay medical procedures, result in medication errors, and cause patient harm.[1-38] In addition to these potential problems, healthcare professionals are also increasingly concerned about the tremendous resources required to address shortages, estimated at $209 million in 2013 for the purchase of more-expensive substitutes alone, which excludes other significant costs (e.g., drugs purchased "off contract," therapeutic alternatives, added labor).[39,40] Drug product shortages adversely affect healthcare organization finances by increasing the cost of delivering patient care, largely through the personnel costs required to manage the multiple pharmacy automation systems and electronic medical record changes that must be adjusted in the face of a drug shortage.[40] In addition, shortages create high levels of frustration and stress for everyone involved, including purchasing agents, pharmacists, pharmacy technicians, nurses, physicians, and patients.[15,41,42] Pharmacy leaders need to educate all members of the healthcare team as well as organizational leadership about the complex and challenging nature of the drug shortage problem as well as what is being done to manage shortages.

Managing drug product shortages is particularly complex for practitioners in hospitals and other acute care settings 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 drugs and technologies. These healthcare 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 informing 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 or mass casualty incidents.[43] The purpose of these guidelines is to provide a framework for healthcare teams in patient care settings that can be used to develop policies and procedures that minimize the effects of drug shortages on quality of care. These guidelines are focused on minimizing the impact on patient care because it is impossible for healthcare organizations to prevent drug shortages from happening. Although drug shortages are a symptom of broader problems in the U.S. drug product marketplace, these issues are beyond the scope of this document.[44-47]

Patient Safety

Drug shortages are a cause of significant patient safety concerns. Medication errors are more likely to occur (1) when a pharmacy alters how a product is ordered, prepared, or dispensed or (2) when prescribing practices change to less-familiar alternative agents, especially agents that are less efficacious, have a worse adverse-effect profile, or require an unusual or difficult dosing regimen. Best practices for managing drug shortages must first consider the potential impact on patient safety. Data documenting patient harm due to drug shortages are limited to case reports and survey data. The Institute for Safe Medication Practices (ISMP) is the leading source of aggregate data.[13,15,16] A medication-error reporting and review system is an essential component of a medication safety system. Errors and near misses should be reported internally and externally, and analyzed.[48,49]

Factors That Contribute to Drug Product Shortages

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 1 or a combination of factors throughout the supply chain. The supply chain includes producers of raw materials, manufacturers, regulators, wholesalers/distributors, prime vendors, group purchasing organizations, healthcare organizations, and the patient. Factors that contribute to drug product shortages include the unique market for drug products, manufacturing and quality problems, production delays and lack of manufacturing capacity, manufacturer business decisions, shortages of active pharmaceutical ingredients (APIs) or raw materials, restricted distribution and allocation of drug products, and inventory practices.

Unique Market for Drug Products. Drug products are a unique commodity because they do not follow the fundamental economic laws of supply and demand. A first-line agent remains a first-line agent, regardless of price. Unlike other markets, consumers (i.e., patients) have little or no control over prescription product selection in healthcare organizations. In addition, because there is no required disclosure of information regarding manufacturers or manufacturing sites, purchasers of drug products are unable to make educated purchasing decisions based on the quality of a supplier. Purchasers of drug products are unable to make selections based on the quality of a supplier because there is no required transparency regarding the manufacturer or manufacturing site of a drug product.[50]

Manufacturing and Quality Problems. The majority of drug shortages are caused by a production delay due to a failure of quality management at the final product's manufacturing site.[51] For example, the most recent data available show that 46.6–55.1% of sterile injectable anti-infective and cardiovascular drug shortages from 2012 through 2014 were from manufacturing plants that received a warning letter from the Food and Drug Administration (FDA) for failure to comply with manufacturing standards.[44] Quality is not rewarded in the drug product marketplace, because manufacturing is not transparent. The current pass-fail system of FDA approval

provides no opportunity for purchasers to favor companies with higher manufacturing standards over companies with lower standards.[51] Although FDA has plans to require manufacturers to provide quality metrics, such as batch failure rates or the number of complaints, neither FDA nor purchasers of drug products have any method to review even these simple metrics.[52] FDA has focused its responsibility for quality on the Office of Pharmaceutical Quality, whose mission is to ensure that quality medications are available for the American public.[53]

Production Delays and Lack of Capacity. Manufacturing capacity issues or delays were the cause of 30% of drug product shortages from 2011 through 2013.[54] Many production delays actually stem from quality problems that delay production for a single manufacturer, and other manufacturers do not have the capacity to make up for the difference. Generic drug products are particularly susceptible to shortages because, unlike branded products, redundancy is typically not built into the production process. Generic products are typically manufactured on lines that prepare multiple products. An additional manufacturing line is generally not available as a contingency for generic products.[55] These types of shortages frequently occur with generic injectable agents, as tight profit margins and the complexities of production limit the number of manufacturers and lead to high market shares; in many cases, a single manufacturer may have over 50% of the market share for specific therapeutic categories.[51] A small number of manufacturers (fewer than 7) comprise the vast majority of all injectable drug products,[51] and more than one third of injectable drug products are produced by just 1 or 2 manufacturers.[51,55]

Manufacturer Business Decisions. 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. Frequently, the decision to manufacture a new product forces production tradeoffs because many generic manufacturers function at full capacity.[51,56]

Shortages of APIs or Raw Materials. Shortages of APIs or raw materials are rare but can result in drug product shortages.[51,55] An API shortage can be particularly disruptive if there is only 1 supplier; however, manufacturers' sources of API are considered proprietary and are rarely publicly disclosed.

Restricted Distribution and Allocation of Drug Products. Most healthcare organizations obtain the majority of their drug products through wholesale distributors. Restricted distribution methods that bypass the normal supply chain can also contribute to shortages. Manufacturers may limit the availability of and access to specific drug products to selected pharmacies, clinicians, and patients complying with manufacturer agreements based on market approval requirements and/or postmarketing surveillance. A manufacturer can also place restrictions on the availability of products by requiring healthcare organizations to order directly from the manufacturer or through a specialty distributor to receive an allocation.

Inventory Practices. Inventory reductions permitted by advanced communication and transportation efficiencies within the supply chain may amplify the effects of a shortage on healthcare organizations. Most manufacturers, distribution centers, and healthcare organizations use just-in-time inventory management to reduce the cost of inventory on hand, increase inventory turns, minimize expenses, and optimize cash flow. This strategy is recognized as sound business management but allows unexpected shortages at any stage in the supply chain to significantly impact purchasers and patients. Some manufacturers and distributors use inventory management strategies that minimize end-of-quarter or end-of-year product inventories or limit shipment based on yearly quotas.[57] Poor ordering practices, stockpiling before announced price increases, hoarding caused by rumors of an impending shortage, and unexpected delivery delays may also affect inventory levels in individual healthcare organizations. 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 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.

Planning for Drug Product Shortages

The pharmacy department can lead effective drug shortage management by ensuring that its organization has the necessary infrastructure and a well-defined management strategy in place before a shortage occurs. To effectively respond to drug product shortages, several essential elements of infrastructure must be in place before a shortage occurs: a drug shortage team, a resource allocation committee, and established processes for approving alternative therapies and addressing ethical considerations.

Drug Product Shortage Team. The first step is to identify an interdisciplinary team of key staff who can make decisions and access information. The drug product shortage team needs to understand the organization's processes for change and how to expedite results. At a minimum, the drug product shortage team should be able to identify persons responsible for the following activities: data gathering and monitoring; purchasing alternatives; changing storage, preparation, and dispensing procedures; deciding to conserve or ration; implementing technology changes; and communications. The drug shortage team should develop a list of ad hoc stakeholders to consult for specific shortages. A specific point person should be designated to lead drug shortage efforts, but no single person can manage all drug shortage planning and response activities alone.

Resource Allocation Committee. Although consideration of the ethical implications of drug shortages may be discussed within the organization's existing committee structure (e.g., the ethics committee), a resource allocation committee should be formed to directly oversee the allocation of scarce resources such as drug products. The resource allocation committee should include, at a minimum, representatives from the departments of pharmacy, nursing, social work, and medicine; a patient representative; and a representative from the organization's ethics committee.[58] When a drug short-

age affects a specific therapeutic area, other departments or disciplines may need to be represented, and a clinician with expertise in that area should provide representation on the committee. Committee members should be identified in advance and be available to assume membership on the committee when the need arises.[58,59] All members of the committee should disclose any bias or potential conflicts of interest in advance if possible.[60]

The committee should carefully determine appropriate patient characteristics and clinical evidence for prioritization and rationing of medications.[58,59,61,62] Because drug shortages will evolve, ethics protocols should allow for feedback and amendment.[62] Standardizing the ethics framework in advance avoids the need for bedside decisions and allows clinicians to contemplate complexities and appropriate rationales before difficult choices need to be made.[60,62,63] Protocols should also address how to manage the distress clinicians can experience when making such difficult decisions.[60]

Interruption of clinical trials is another potential consequence of drug shortages that has potential ethical implications. Organizations must ensure that study sponsors and principal investigators are aware of drug shortages that may affect clinical trials. Healthcare organizations should appropriately allocate remaining medications, halt trial enrollment, or continue patients on the standard-of-care treatment only as necessary until the drug shortage has resolved.[58]

Process for Approving Alternative Therapies. A formal process for identifying and approving therapeutic alternatives for the healthcare organization should be established. The healthcare organization's decision-making process about alternative agents should involve timely collaboration among representatives of medicine, nursing, pharmacy, and other affected disciplines, and those decisions should be approved by the appropriate medical committees as promptly as possible. Organizations should follow the same steps and processes used in changing any drug product in their system to ensure that key steps in managing automation and technology are not missed.

Process for Addressing Ethical Considerations. As drug shortages have become more common, healthcare organizations and providers have become more adept at identifying and utilizing therapeutic alternatives. Nevertheless, situations arise in which it is difficult to simply substitute an alternative agent, if available at all.[58] Drug shortages have become a barrier to clinicians providing the most appropriate and evidence-based care to patients and may create mistrust between patients and providers.[64,65] The appropriate management of drug shortages requires carefully balancing what is good for an individual and what is good for a group of individuals or society.[60,61]

As the number of drug shortages has grown, several ethical frameworks for appropriately rationing these resources have been proposed.[58,60,66] One method that reflects the fundamental healthcare principles of justice, beneficence, and nonmaleficence is an adaptation of Daniels and Sabin's[67] "accountability for reasonableness," amended by several authors to address drug shortages.[58,60,61] Because there isn't 1 ethical framework to provide complete guidance for all drug shortage dilemmas, the framework should be adapted by organizations to address their particular circumstances.[63] The main principles of this method are as follows:

- *Transparency:* details of the process are made public and available for scrutiny.
- *Relevance:* a neutral observer would be able to apply the process to a broad range of differing situations.
- *Appeals and revision:* those who feel wronged by the process have a way to appeal and have the original decision reversed if appropriate.
- *Enforcement:* the process is mandatory, and its results are required to be applied.
- *Fairness:* the process is to be applied to all, regardless of the type of patient or prominence of clinician treating that particular patient.[58,60,66]

Just as the therapeutic management of drug shortages requires healthcare organizations to prospectively institute guidelines or restrictions, ethical procedures and protocols should be developed and put into place before the need for them arises.[65] Variations in these protocols may be necessary for different classes and uses of drugs; the rationing of anti-infectives and oncological agents, for example, is quite different.[59-61,66]

Responding to Drug Product Shortages

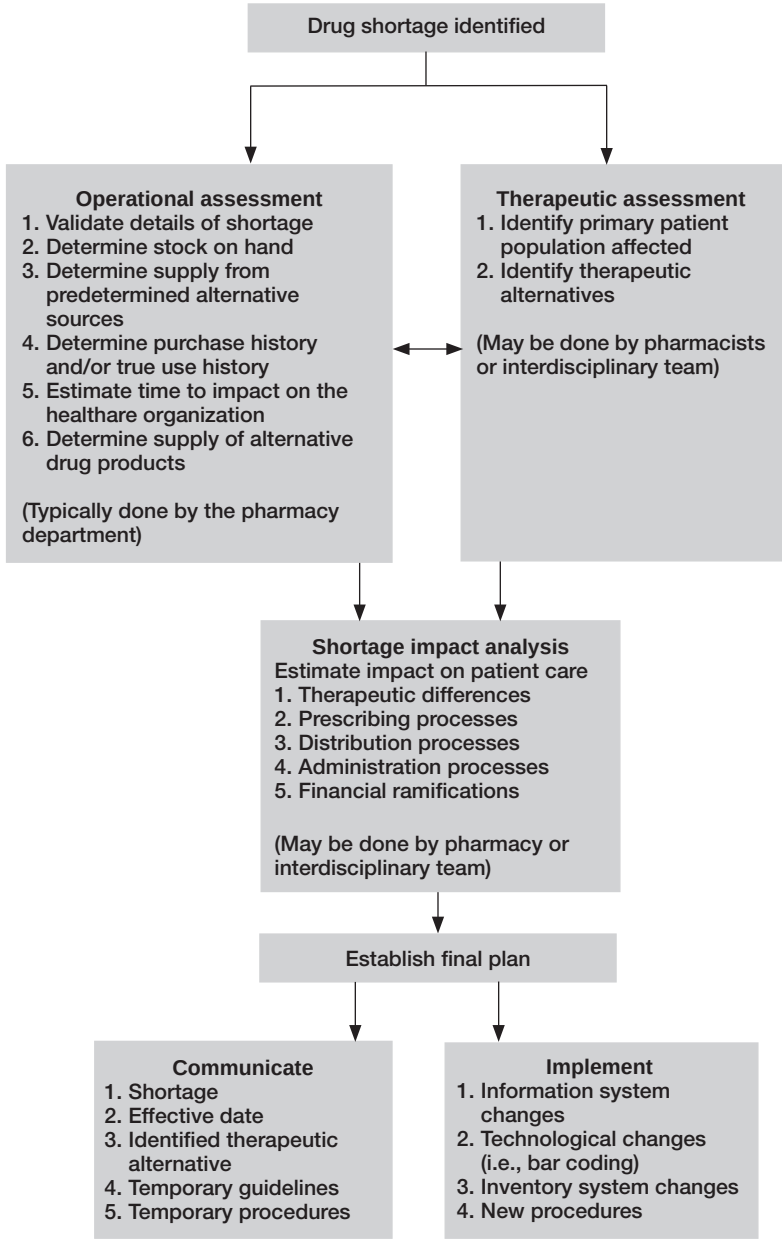
The identification of a shortage initiates a cascade of events surrounding drug procurement and therapeutic decision-making (Figure 1). When a shortage is identified, the drug product shortage team should conduct an operational and therapeutic assessment to evaluate its potential impact. A shortage impact analysis based on the 2 assessments and an evaluation of procedural and financial implications should be used to assess the potential impact on patient care. The drug shortages team should use that impact analysis to develop a final action plan for approval and implementation. An institution's success in responding to shortages is typically dependent on how well the system can change drug products in their system under nonshortage conditions.

Operational Assessment

The operational assessment should be performed by the point person or that person's designee, working with others as necessary. The assessment validates the details of the shortage, estimates the supply of the drug product in shortage available on hand and from alternative sources, evaluates past usage, and estimates the supply of alternative therapies.

Details and Duration of Shortage. The pharmacy team can contact product manufacturers, distributors, FDA, the Centers for Disease Control and Prevention (CDC), and other sources to determine the cause of the shortage and its expected timing and duration. This information may already be available on the ASHP Drug Shortage Resource Center website (www.ashp.org/Drug-Shortages) or the FDA Drug Shortages website (www.fda.gov/Drugs/DrugSafety/DrugShortages). If it is not, visitors to the sites should report the shortage online. Predictions of when the product will be available help the healthcare organization develop its short-

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



and long-term strategies. Because the status of a shortage can change quickly, follow-up communications with manufacturers may be required to obtain updates on previous estimates of product availability.

Inventory on Hand. Once a shortage is identified, pharmacy staff should assess the inventory on hand and estimate the time period it will cover. Available inventory includes all supplies of the drug product within the healthcare organization, including the pharmacies, inpatient units, ambulatory care clinics, automated medication storage and distribution devices, floor stock, code carts, and prepared trays. The pharmacy should estimate how long the healthcare organization can endure a shortage based on available quantities and historical usage, converting inventory counts of alternative drug products into common measurement units (e.g., common dose, days of therapy) to augment estimates of use.

Therapeutic Assessment

The therapeutic assessment can be performed by the point person, that person's designee, or other members of the drug shortage team as necessary. The assessment identifies the primary patient populations affected and identifies therapeutic alternatives.

Patient Prioritization. When a limited supply of a drug remains available and alternatives for specific patient groups are undesirable, a healthcare organization may prioritize use of the drug for specific patient groups. National organizations (e.g., CDC or an organization of healthcare specialists) may provide guidance on patient prioritization. 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. Additional criteria, such as therapeutic use (curative versus palliative), may also be helpful in guiding appropriate use of the drug. Such criteria are particularly helpful in dealing with long-term shortages. To restrict product use for select patients or services in the healthcare organization, criteria should be developed by an interprofessional team. An ethical framework for allocating particularly scarce or lifesaving products is essential as is evidence-based decision making with regard to alternatives.[58,63]

Therapeutic Alternatives. Therapeutic alternatives should be inventoried and availability assessed to ensure adequate supplies to meet new demand. In many cases, supplies of the best alternative agent may be affected by the response to the shortage. If therapeutic alternatives are not on the formulary or not currently stocked in the system, there should be a process to expedite adding the new product to all systems (e.g., the electronic health record [EHR], smart pump libraries, automated dispensing cabinets [ADCs]). If a compounded medication is an appropriate alternative, organizations must decide whether resources are available to compound inhouse or if the best solution is to purchase the compounded medication from an FDA-registered outsourcing facility.

Shortage Impact Analysis

A shortage impact analysis evaluates all factors relevant to the shortage (e.g., duration, current and available inventory, medical necessity, affected patient populations, alternative therapies) to determine the shortage's potential impact on patient care and costs. Such analyses should include a threat analysis for severe shortages to determine whether surgeries or other treatments must be canceled. Healthcare organizations should develop a mitigation strategy for patients whose treatments are no longer available. This strategy may include sending patients to another facility that has the drug in stock or developing a process to postpone elective surgeries. Shortages affect safe medication practices throughout the medication distribution and administration process within a healthcare organization. When considering alternative dosage forms or therapies, pharmacists must consider changes in look-alike/sound-alike procedures, barcoding, distribution paths, and the impact on automation, contract compliance, and final product preparation.[68] Healthcare organizations should evaluate the time required to implement any changes into electronic systems. The extent to which a healthcare organization will be affected by a given shortage depends on the severity of the shortage's impacts; the organization's scope, level of services, and service population; and the organization's agility in switching drug products given the constraints of information system changes (e.g., EHR, smart pump libraries, ADCs).

Financial Ramifications. Drug shortages result in increased costs due to a variety of causes: the higher cost of off-contract purchases of drug products or more-expensive alternative agents and the increased personnel costs to develop plans, relocate or compound drug products, and make changes to the EHR and other information systems. Healthcare organizations should make every effort to track all drug and personnel costs related to shortages as well as lost revenue from canceled treatments or surgeries. An accounting of these costs is helpful when explaining budget variance or proposing plans for additional staff or funds.

Final Action Plan

The healthcare organization should develop a final action plan prior to sending a comprehensive communication about the shortage. The final action plan can be used to double-check all elements of the management plan. The plan should state whether a conservation approach will be used to conserve remaining supplies or smaller future allocations or if the shortage will require use of an alternative agent. Examples of management and conservation strategies include par adjustments, centralization of inventory (e.g., removing from ADCs and floor stock), repackaging into smaller dosage units, extending beyond-use dating (when approved by FDA and manufacturer or verified through *United States Pharmacopeia* chapter 797-compliant process), i.v.-to-p.o. conversion, discontinuing nonessential therapy, limiting use of product to uses supported by evidence, and using a different strength or size of product. In some cases, a combination of these actions will be necessary for optimal clinical efficacy. For shortages that require canceled surgeries or treatments, the rationing plan for remaining supplies should be included. The organization should coordinate a specific time for making changes in information systems (e.g., EHR, smart pump libraries, ADCs, and other databases) and ensure that sufficient staff are available to re-enter orders, move stock between ADCs, or take other follow-up actions. Finally, it is essential that everyone understand their roles and the timing required for effective implementation as well as the dynamic nature of drug shortages that may require revisions to the plan.

Communication

Clear communication with all affected clinicians about the status of a shortage is vital. Administrators should also be included in communications, particularly if the shortage may result in canceled surgeries or treatments or significantly increased costs. Multiple communication methods are better than a single strategy. The EHR can also play a communication role to provide prescribers information at the time of medication order. The shortage management team should understand each member's role and share information quickly, efficiently, and in a timely manner. Information should be shared prospectively about both anticipated and confirmed shortages to allow appropriate preparation. Communication within the pharmacy department should include all staff members, including pharmacy technicians. Pharmacists who specialize in a specific clinical area (e.g., intensive care, transplantation) can be especially helpful in relaying information about shortages to their healthcare colleagues during rounds. All pharmacy shifts should receive the same message, and the communication methods should be adapted to the organization's culture, using multiple methods whenever possible (standing meetings, texts, emails, intranet, blogs). Communications to affected prescribers and other healthcare providers should include those in training (e.g., students and residents). Some healthcare organizations may designate a specific department to manage communications; others may find that a collaborative strategy involving various organizational departments and committees works best.

Disclosure to Patients. Healthcare organizations should establish policies and protocols regarding the disclosure of drug shortage information to patients and the extent of such disclosures.[59,65] 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 alternatives may be less effective.[58,63,69,70] Disclosure may vary depending on the type of clinical situation. In an emergent situation, decisions about disclosure need to balance transparency and other critical factors involved in providing care. In the case of an elective procedure, it must be decided how patients will be provided an understanding of the potential risks from less efficacious drugs or those with more adverse effects.[65] When the patient's need for a drug will recur, communications should address, before drug initiation, the possibility that the full course of treatment may not be available. Concerns that the full course of the regimen may not be available may warrant consideration of alternatives.

Communication with Media. Media outlets may be interested in reporting on severe shortages; working with the media can highlight the impact that drug shortages have on patient care. Organizations and individuals should work with

their public affairs officers before speaking to the media and should keep in mind that updates may be necessary, especially when a shortage resolves. For all communications, it is important to balance timeliness and completeness and to be transparent about how decisions to ration are made and whether there is a method for appeals or exceptions.

Inventory System Changes

Stockpiling Restraint. Inventory management is a challenge in the face of a shortage. Stockpiling (hoarding) and speculative purchasing in advance of an anticipated shortage can exacerbate the shortage, disrupt efficient distribution, and divert supplies away from healthcare organizations with patients in need.[71] Healthcare organizations should refrain from stockpiling drugs anticipated to go into shortage as well as alternatives. Stockpiling causes 2 distinct problems: (1) stockpiling can cause artificial shortages when healthcare organizations drain the supply chain and demand exceeds manufacturing capacity, and (2) stockpiled 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 as well, depending on the likely cause of the shortage and where it might occur in the supply chain. Problems may arise that appear to pose a shortage threat but never reach end users, because the supply chain, from raw material to finished product, may contain several months' supply; that long lead time allows corrections that avert the shortage. Finally, during shortages, manufacturers and distributors often allocate product on the basis of past usage, so an initial stockpile order generally has no impact on increasing an allocation.

Purchasing from Outside Pharmacies and Inhouse Compounding. Healthcare organizations 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. Each healthcare organization must determine its philosophies on purchasing drugs from the gray market or compounding pharmacies and on inhouse compounding. 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. Pedigree requirements of the Drug Supply Chain Security Act may alleviate these concerns as they are implemented.[72] Products from compounding pharmacies may also present risks to patients (e.g., inefficacy, adulteration, lack of sterility); tragically, several deaths have been associated with improperly sterilized compounded products. Healthcare organizations may choose to compound products if they can meet the necessary guidelines; however, obtaining raw materials may be difficult in some cases.

Conclusion

Drug product supply issues are a frequent problem affecting healthcare organizations. Organizations can mitigate the effects of shortages by establishing an infrastructure for dealing with shortages before they occur. Although it is impractical to prepare for every potential shortage, proper planning can reduce adverse effects on patient care and healthcare organization costs and prevent problems from escalating into crises. The keys to success will undoubtedly be found in the effectiveness of information gathering; teamwork to assess options; ability to rapidly make changes in information systems; and communication with providers, patients, and administrators.

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Developed through the ASHP Council on Pharmacy Management and approved by the ASHP Board of Directors on June 19, 2018. These guidelines supersede the ASHP Guidelines on Managing Drug Product Shortages dated January 15, 2009.

ASHP gratefully acknowledges the contributions made to previous versions of these guidelines by Annette Birt, M.B.A., M.P.H.; Ken B. James, Pharm.D.; Heather Kokko, Pharm.D.; Sandra Salverson, Pharm.D., BCPS; and Donna L. Soflin, B.S.Pharm.

ASHP gratefully acknowledges the following organizations and individuals for reviewing these guidelines (review does not imply endorsement): American Association of Pharmacy Technicians; American Pharmacists Association; Canadian Pharmacists Association; Idaho Society of Health-System Pharmacists; Ellena Anagnostis, M.S., Pharm.D., BCPS; Jason Babby, Pharm.D.,BCPS; Bona E. Benjamin, B.S.Pharm.; Kate Bidwell, Pharm.D., BCPS; Jennifer L. Brandt, Pharm.D., FASHP; Ryan Burke, Pharm.D.; John S. Clark, Pharm.D., M.S., BCPS; Shelita Dattani, Bsc.Phm., Pharm.D.; Michael D. Dickens, Pharm.D.; Elizabeth Duncan, Pharm.D.; Ashley Duty, Pharm.D., M.S.; Katie Gauen, Pharm.D.; Anne Gonzales-Luna, Pharm.D.; Stephen M. LaHaye, Pharm.D., BCPS; Molly Billstein Leber, Pharm.D., BCPS, FASP; Jim Lile, Pharm.D., FASHP; Charles E. "Kurt" Mahan, Pharm.D., Ph.C.; Susan Mankad, Pharm.D.; Michelle McCarthy, Pharm.D., FASHP; Brenna Mehta, Pharm.D.; Cristian Merchan, Pharm.D., BCCCP; Kathleen Morneau, Pharm.D., BCPS; Judy Neville; Robert S. Oakley, FASHP; Lois F. Parker, B.S.Pharm., FASHP; Stacey Pattie, Pharm.D., BCPS; Stephanie Peshek, FASHP; James Ponto, M.S., BCNP, FASHP; Emily Prabhu, Pharm.D., BCPS; Ed C. Rainville, Pharm.M.S.; James R. Rinehart, M.S., FASHP; Catherine L.

Shely, Pharm.D.; Elizabeth Snipes, Pharm.D.; Christopher Snyder, Pharm.D.; Ami Vyas, Ph.D., M.B.A., M.S.; Geralyn Waters, Pharm.D.; Roger Woolf, Pharm.D.; and Amy M. Young, Pharm.D.

Dr. Fox is a member of the *AJHP* Editorial Board. The authors have declared no other potential conflicts of interest.

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The bibliographic citation for this document is as follows: American Society of Health-System Pharmacists. ASHP guidelines on managing drug product shortages. *Am J Health-Syst Pharm.* 2018; 75:1742-50.

Facing the Shortage of IV Fluids — A Hospital-Based Oral Rehydration Strategy

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Puerto Rico produces 44% of the intravenous (IV) fluid bags used in the United States.[1] On September 20, 2017, Hurricane Maria struck the island, causing a humanitarian crisis and widespread devastation that escalated a critical shortage of IV fluids throughout the United States. Initially, small-volume bags — 50- and 100-ml bags used to dilute medications — became scarce. Today, the larger 500- and 1000-ml IV-fluid bags are also in short supply. U.S. hospitals are scrambling to develop strategies for rationing IV fluids to ensure availability for the patients who need them most.

Hurricane Maria is only the latest challenge to the U.S. IV-fluid supply. Since 2014, U.S. hospitals have faced varying degrees of IV-fluid shortages, whose causes were multifactorial. IV-fluid production is complex and highly regulated in order to ensure quality and safety, which makes it expensive for hospitals and compounding pharmacies to produce their own. Most of the IV fluid used in the United States is produced by only three manufacturers, so availability is vulnerable to even small fluctuations in supply. In addition, hospitals buy IV fluids through large group-purchasing organizations representing hundreds of hospitals so that they can negotiate with manufacturers for lower prices or better access to scarce resources. Some observers argue that these organizations' market power keeps prices so low that they create a disincentive for manufacturers to increase production or for small producers to enter the market.[2]

Given these supply-side constraints, the U.S. IV-fluid supply will be vulnerable for the foreseeable future. It is therefore critical for U.S. hospitals to develop both short- and long-term alternatives to IV-fluid use.

Emergency departments (EDs) are substantial consumers of IV fluids in the United States. The 59-bed ED at Brigham and Women's Hospital treats more than 62,000 adult patients each year and, in the 5 months from September 2017 through January 2018, used 8519 liters of IV fluids — nearly 30% of the hospital's total consumption. As the current IV-fluid shortage worsened, the team in the Division of International Emergency Medicine and Humanitarian Programs of the Department of Emergency Medicine was asked to develop an oral rehydration protocol for ED patients with mild dehydration. The protocol outlined in the box has since been adopted hospital-wide.

Oral rehydration therapy has been studied for nearly 60 years. It has been shown to reduce mortality from diarrheal illnesses by 93%[3] and to reduce the case fatality rate of cholera from 30% to 1%.[4] It is less expensive than IV-fluid therapy, and its use results in fewer admissions and shorter lengths of stay.[5] A 2006 meta-analysis showed that oral rehydration was equivalent to the administration of IV fluid for the management of dehydration due to gastroenteritis in children.[5] Data on use in adults have revealed similar efficacy, although in smaller studies. Oral rehydration therapy has been widely adopted in low- and middle-income countries where IV fluids are expensive and resources limited. Conversely, despite this evidence, oral rehydration has not been widely used in adults in high-income countries, probably owing to the widespread availability and ease of use of IV fluids.

Our protocol is based on research[3-5] and protocols for oral rehydration in low-resource settings and in the United States and on our experience as emergency physicians with more than 50 combined years of work in health care delivery in low- and middle-income countries around the world.

Patients who meet the criteria for deployment of our protocol are adults with mild dehydration from conditions such as pharyngitis, gastroenteritis, pregnancy-related vomiting, and upper respiratory tract infection. Patients with severe dehydration or who are unable to take liquids by mouth for other reasons (e.g., small bowel obstruction) are excluded; these patients constitute the minority of our ED patients who traditionally receive IV fluid. The hospital also created a new

Brigham and Women's Hospital Oral Rehydration Protocol

Use for patients with mild dehydration — in general, patients with the following conditions:

- Acute gastroenteritis
- Pregnancy-related hyperemesis
- Mild viral upper respiratory infection or pharyngitis

Exclusion Criteria:

- Moderate or severe dehydration
- Inability to receive oral intake for another reason

Protocol Steps:

1. Order oral rehydration fluids in the electronic health record (EHR); add antiemetic, pain control, or both if needed. Consider benzocaine or menthol lozenges in addition to acetaminophen or ibuprofen for pharyngitis. If there is significant nausea or pain, wait 20 min after medications to begin drinking (can start immediately otherwise).
2. The EHR order will direct the nurse to bring the patient two 500-ml pitchers of desired drink (flavored oral electrolyte solution or dilute sports drink or juice).
   - Provide patient with straw as well as 30-ml medicine cup.
   - Instruct patient to drink two large sips or 30 ml every 3–5 min. Use timers on cell phones or ask family to assist.
   - Explain target hydration goals (see below) and provide a tracking sheet. Draw lines on pitcher for target volumes (e.g., "250 ml left"). Patient or family member should complete the tracking sheet.
   - Return to reencourage oral intake as needed.
3. Troubleshooting:
   - If oral intake is insufficient, determine why and give additional antiemetic, pain control, or both as needed.
   - If taste is a problem and dehydration mild (or not due to gastroenteritis), consider alternative liquid options, such as half-strength sports drink, dilute juice, or ginger ale.
4. For pregnancy-related hyperemesis, oral intake can often help. Encourage patients to try to eat a few crackers if possible.

Target Hydration Goals*:

Target times are given for the amount of liquid remaining at 2 sips or 30 ml every 3 min (or every 5 min)

- 1000 ml remaining: 0 min (0 min)
- 750 ml remaining: 25 min (40 min)
- 500 ml remaining: 50 min (1 hr 20 min)
- 250 ml remaining: 1 hr 15 min (2 hr)
- 0 ml remaining: 1 hr 40 min (2 hr 40 min)

* Patients with vomiting should be encouraged to maintain a slower rate of intake until they tolerate the fluid well. Patients without vomiting can drink faster, as tolerated. After an intake of 250 ml has been successfully completed without vomiting, and if nausea is well controlled, intake can increase to four sips or 60 ml every 3–5 min.

order in our electronic medical record and order-entry system, called Oral Rehydration Fluids, that streamlines the process.

Under our protocol, we aim to have patients take 500 to 1000 ml of oral fluids while in the ED, since patients who drink this volume successfully can most likely continue oral rehydration at home. Providers are encouraged to offer analgesics, antipyretics, and antiemetics as needed to improve the tolerance of oral hydration. Patients may start drinking immediately if they are able, or they may wait 20 minutes for symptom improvement after administration of these comfort medications. Patients are offered their choice of drinks, including artificially flavored oral electrolyte solution, water, dilute juice, or dilute sports drinks. If electrolyte disturbances are suspected on the basis of the clinical presentation, the oral electrolyte solution is preferred. Using powdered formulations of sports drinks reduces the storage space needed. The variety of fluid options reduces reliance on a single brand-name product. As with IV strategies, clinical judgment must be used when choosing oral hydration in patients with coexisting conditions such as renal disease, diabetes, or heart failure.

Each patient is provided a straw, a 30-ml medicine cup, and 1000 ml of the patient's preferred fluid. Patients are instructed to drink 30 ml (two large sips) every 3 to 5 minutes and may ask family members or use a cellphone to time the sips. Providers explain the drinking goals (see box) and draw lines on the pitchers to delineate target volumes (e.g., "250 ml left").

The patient or a family member completes a tracking sheet to monitor total intake. Patient and family participation is key to success. Encouragement is offered regularly. Patients with insufficient oral intake are reevaluated and given additional antiemetics and pain control as needed. If the patient doesn't like the taste of the chosen drink, another drink is tried. The patient may increase the pace after tolerating the first 250 ml. Patients who vomit should wait 20 minutes before starting to drink again.

To ensure implementation of our protocol, providers were sent an email message by hospital leadership detailing the IV-fluid shortage and the oral rehydration protocol. ED nursing leaders trained nurses and ED technicians and posted flyers throughout the ED. We also provided additional training and reminders about the oral rehydration protocol to our faculty and residents.

We are now studying the impact of our protocol on IV-fluid use. According to our preliminary data, IV-fluid use by volume decreased by just over 30% in the first week after the oral hydration protocol was distributed throughout the hospital. In the 3 weeks after protocol implementation, the fraction of ED patients with IV-fluid orders decreased by 15%.

There are potential limitations to our protocol. Oral rehydration can take longer than IV hydration and requires more effort from the patient. However, it also causes less pain because there is no IV catheter insertion, and our protocol's emphasis on structured time goals and drinking small amounts can encourage patients to stay hydrated in a manner that they can continue at home. Although oral rehydration can be effective in moderate to severe dehydration, with the use of a nasogastric tube if needed, currently our protocol targets mild dehydration only. It could be expanded to include more severe cases if the IV-fluid shortage worsened.

We share this protocol as a replicable model for other U.S. hospitals looking for strategies during the IV-fluid shortage. Experience in low-resource settings worldwide has proven the efficacy of oral rehydration therapy, and vulnerabilities of the U.S. IV-fluid supply chain are expected to continue. We believe that widespread use of oral rehydration protocols would therefore be a rational practice change and a mainstream model for use in the United States even after the current IV-fluid shortage crisis ends.

Disclosure forms provided by the authors are available at NEJM.org.

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This article was published on March 21, 2018, at NEJM.org.

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DOI: 10.1056/NEJMp1801772

Navigating Hospital Drug Shortages

Bringing the Team Together

Among the many challenges for healthcare organizations created by the COVID-19 pandemic was drug shortages. The anticipatory purchasing of drugs around the world due to the uncertainty of COVID-19 and skyrocketing hospitalizations drove drug demand to an unprecedented high. Meanwhile, availability was reduced because manufacturers shut down to prevent the spread of COVID-19 and other supply chain disruptions. Although the shortages were predominantly related to drugs directly impacting patients with COVID-19, other drug classes were affected as well. The sudden surge in the number of critically ill and mechanically ventilated patients led to huge demands for sedatives, opioids, vasopressors, and paralytics. Concerns about aerosol-generating procedures led to the replacement of albuterol nebulized treatments with albuterol metered dose inhalers. Each of these factors contributed to scarcity of essential, lifesaving drugs. The pandemic also highlighted the fragility of a drug supply chain that relied mostly on just-in-time manufacturing that was already at capacity.

While shortages of essential drugs plagued patients and clinicians before the COVID-19 pandemic, the pandemic-related healthcare crisis laid bare the inadequacies of drug manufacturing and distribution. Hospital systems across the world devised innovative strategies to address these drug shortages during the pandemic. We review the available evidence and provide guidance on adopting a multipronged and multiprofessional approach to managing future drug shortages.[1]

It takes a team to manage drug shortages during a pandemic, and engaging key stakeholders early in the course is crucial. Anticipation of impending drug shortages and evaluation of current inventory is important, as is timely escalation and interdisciplinary engagement, followed by close communication with all involved parties.[2,3]

It takes a team to manage drug shortages during a pandemic, and engaging key stakeholders early in the course is crucial. Anticipation of impending drug shortages and evaluation of current inventory is important, as is timely escalation and interdisciplinary engagement, followed by close communication with all involved parties.

Identifying Drug Shortages, Evaluating Current Inventory, and Identifying Alternatives

It is vital to foresee impending drug shortages by recognizing red flags in the health system's supply chain (e.g., orders partially filled, a manufacturer with no stock). Monitoring national Listservs and even social media might identify drug shortages impacting other parts of the country, which may be a harbinger of a more widespread shortage.

Once a potential or actual shortage has been identified, its likely effect should be ascertained by assessing current inventory and historical usage patterns and then comparing to the anticipated duration of the shortage to determine the possible consequences and next steps. When assessing how long the shortage and any alternative products will last, estimates should be based on both current use rates and reduced rates after restriction measures are implemented.

Alternative therapeutic options must also be explored with multiprofessional collaboration, including medical, nursing, pharmacy, and respiratory therapy representatives as the extent of shortage is estimated. Identified alternatives should also be inventoried to ensure that adequate supplies are available to meet increased demand, especially during domino shortages, where drug A becomes unavailable and drug B is used as a replacement; anticipation of a subsequent drug B shortage should then be considered. Education on unique aspects of these alternatives should also be provided to clinicians, especially if these alternatives are not commonly used, are high-risk medications, or have unique side effect profiles.

Contingency Plans

Instituting backup plans to mitigate the impact of drug shortages is critical. Certain drugs may be available only from a compounding pharmacy, from another nontraditional source, or not at all. Specific federal laws, such as the Drug Quality and Security Act, apply to the use of drugs from compounding pharmacies, and it is important to assess compliance before these products are used. Each health system should establish a well-defined policy on purchasing drugs from the gray market or compounding pharmacies, and clear guidelines should be incorporated for managing situations in which a critical drug is not available at all.

Depending on available resources, health systems may choose to compound shortage products if they can meet certain requirements and if raw materials are available. Procuring scarce drugs or alternative products from nontraditional sources is likely to have financial implications, and estimates of additional costs should be prepared and presented to obtain contingency funds. Documented expenditures due to drug shortages can help explain budget variances and support future budget proposals.

Escalation to All Involved Parties

After identifying the drug shortages, the concerns should be escalated to appropriate authorities, and the information should be shared among all affected disciplines. Formation of a drug shortage committee under the auspice of the hospital Pharmacy and Therapeutics Committee consisting of prescribers, pharmacists, and other clinicians is helpful. The committee should meet at frequent intervals to discuss current drug shortages and management strategies. Timely and frequent communication with medical, nursing, pharmacy, and respiratory therapy representatives can help to mitigate frustration, stabilize relationships, and minimize the risk of errors in drug prescribing, dispensing, and administration. A point person from pharmacy should be designated to allow practitioners to communicate ongoing patient safety concerns or other identified problems.

In addition to email communication, incorporation of alerts in the electronic medical record (EMR) system may help with healthcare professional notification. The alternative use alert (AUA) should be used to provide healthcare professionals guidance on ordering. The verbiage could be decided based on the nature of the shortages. For example, if a parenteral formulation is not available, an enteral option

could be included, if applicable. Oral solutions could be identified to be reserved for patients with enteral feeding tubes, the pediatric population, or patients who cannot tolerate solid dosage form medications.

If one agent is not available in a therapeutic class, another agent within the same drug class that has evidence supporting its use would be identified as an alternative. Ordering panels within the EMR can also be designed to guide the shortage with drop-down menus or choices to guide the ordering process in the event of drug shortages. A hospital drug shortage committee should meet at least weekly to discuss shortage status updates. EMR drug shortage alerts and AUAs should be modified on a weekly basis based on the status reports.

Management Strategies

It is estimated that drug shortages cost U.S. hospitals $359 million a year.[4] Therefore, it is critical for health systems to take steps to mitigate drug shortages. Here are some suggested steps of an appropriate management strategy:

1. Estimate duration of drug shortage.
2. Determine how long existing stock will last based on average daily use.
3. Determine the need for a therapeutic alternative(s).
4. Determine whether usage restrictions are needed to conserve drug (e.g., reserved for pediatric patients, available route of administration).
5. Identify whether an interhospital drug loan is possible or necessary.
6. Communicate with drug manufacturers, wholesalers, and distributers on available drug supplies.
7. Develop usage criteria to ensure that the most vulnerable patients get treatment priority.
8. Operational pharmacists should focus on obtaining drugs, working closely with clinical pharmacists who communicate with clinicians to focus on judicious use of the current supply and the use of appropriate alternative agents, when appropriate.
9. Clinicians, including clinical pharmacists, should use evidence-based conservation strategies in managing drug shortages by using treatment guidelines and protocols or EMR ordering panels.
10. Hospital executives and policymakers should be included in drug shortage communications.

Creating a drug shortage dashboard can also be helpful. Medications should be grouped together based on their therapeutic class. Data on current inventory, usage, procurement, and restrictions should be compiled and analyzed on the dashboard on a daily basis during shortages. The dashboard should be shared and easily accessed by all members of the multiprofessional drug shortages committee to maintain transparency.[5,6]

Mitigating Future Drug Shortages

Once a shortage has been resolved, the multiprofessional team should be informed so normal prescribing patterns can resume. Depending on the duration of the shortage, reminders regarding normal prescribing patterns may need to be included. Another strategy for mitigating future drug shortages is to create drug shortage documents or pathways as part of hospital policies. These could be living documents located within the hospital policy site, which can then be easily accessed by anyone in the event of repeated drug shortages.

Institutional living documents can draw on already available public resources. SCCM's Drug Shortages and Medication Safety Committee provides resources on drug shortage topics at sccm.org/drugshortages. The American Society of Health-System Pharmacists (ASHP) has a guideline on managing drug shortages.[7] The Federal Drug Administration (FDA) provides an up-to-date drug shortage database at fda.gov/drugshortages.

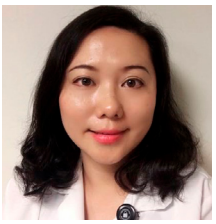
Conclusion

A multiprofessional, systematic approach should be in place in the event of any drug shortage. Communication is paramount to ensure appropriate pharmacotherapy. Alternate dosage forms, therapeutic alternatives, limited duration of therapy, and limiting indications should be implemented to mitigate shortages. Institutions should establish guidelines for drug shortages with easy access to everyone, using resources from Listservs, social media, ASHP, FDA, and SCCM to help maintain optimal care, especially in urgent lifesaving crises. ▲

Stay up to Date on Drug Shortages

Visit sccm.org/drugshortages for general resources and specific guidance on the following shortages:

- Alternative Medications for Procedural Sedation
- Electrolytes
- Sodium Bicarbonate
- Intravenous Loop Diuretics
- Intravenous Antiepileptics
- Heparin Sodium Solution for Injection
- Parenteral Benzodiazepines
- Parenteral Advanced Cardiac Life Support Medications



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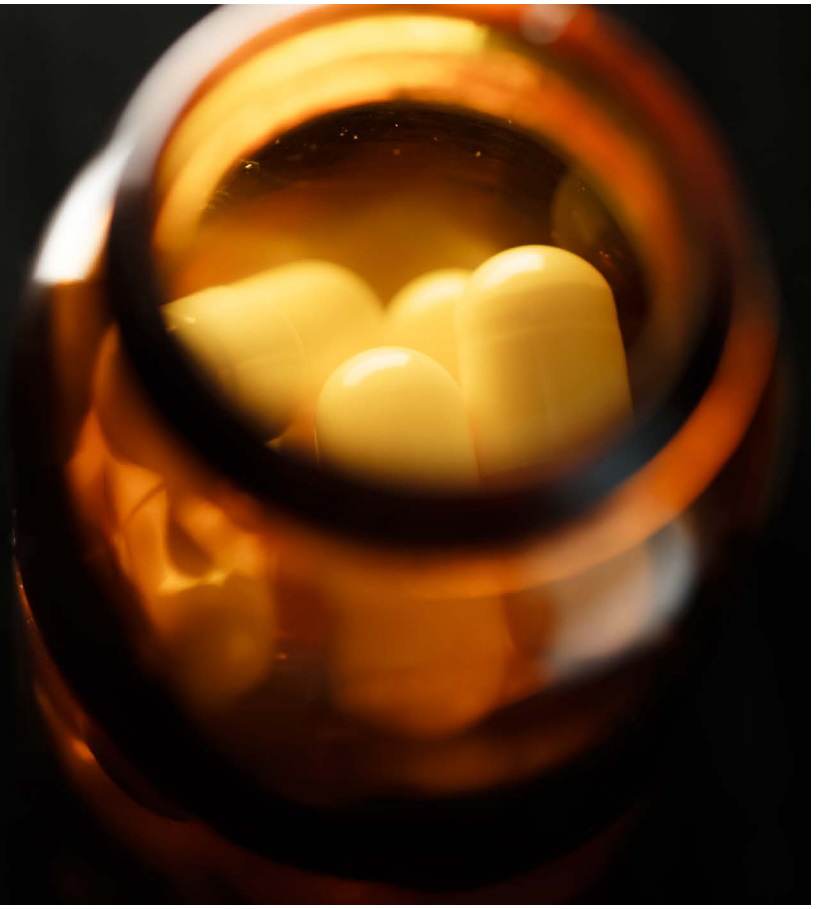
Multidisciplinary Management of Drug Shortages and Associated Ethical Dilemmas



Drug shortages have posed significant patient safety issues in the past, including during the COVID-19 pandemic as shortages affected immunomodulators (e.g., tocilizumab), antivirals (e.g., remdesivir), sedatives, and opioid analgesics.[1,2] Clinicians often face the ethical dilemma of rationing and substituting alternative drugs while maintaining quality of care and utilizing allocation systems to address critical shortages. Often, no acceptable substitute drug exists. Hospitals with clinical pharmacists and ethics committees are required to have allocation plans in place so that frontline clinicians do not have to make tough management/allocation decisions at the bedside.

Several organizations provide a list of current shortages or guidance to address shortages.[3-5] The American Society of Health-System Pharmacists published a guideline in 2018 on managing drug shortages that outlines strategies to plan for drug shortages such as the creation of a drug product shortage team, resource allocation committee, process for approving alternative therapies, and addressing ethical considerations.[3] The Society of Critical Care Medicine's Drug Shortages and Medication Safety Committee has developed a series of drug shortage alerts designed to assist the multidisciplinary team in implementing a consistent and safe approach to managing drug shortages.[4]

Multidisciplinary Drug Shortages Committee

Creating a multidisciplinary drug shortages committee to monitor and make rapid evidence-based decisions during drug shortages is essential for every hospital and healthcare system. Some hospitals may have a scarce resource allocation committee (or workgroup) rather than a specific drug shortages committee that is specifically focused on addressing drug shortages. However, most hospitals have a system-wide committee that oversees several subcommittees. A clear line of communication to other multidisciplinary committees is essential, as is defining the roles and relationships between the multidisciplinary drug shortages committee and other committees.

The scarce resource allocation committee (or workgroup) or the drug shortages committee may not be able to provide a recommendation for every drug shortage without expert input. However, these committees can create processes and procedures to rapidly implement and deploy management strategies. Multidisciplinary participation is crucial to ensure that all stakeholders are aware of a specific drug shortage and are involved in the plan to address the shortage.

Multidisciplinary participation will also facilitate the creation of processes to ensure the dissemination of information regarding a drug shortage, including the plan. Because most hospitals and healthcare systems rely on electronic medical records, including information technology specialists in the process can play a vital role in addressing drug shortages.

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Information technology specialists can help with creating drug shortage alerts, best practice alerts, or usage reports. Access to these tools in a timely manner is crucial.

Ethical Approaches to Drug Shortages

Clinicians are often faced with ethical dilemmas and questions when dealing with drug shortages. Ethical dilemmas can arise due to factors such as lack of an alternative therapeutic interchange or delaying patient care. This was evident during the recent shortages of several chemotherapy agents, such as carboplatin, cisplatin, fluorouracil, and methotrexate, which disrupted care and delayed initiation of treatment in patients with cancer. The critical care community has managed several drug shortages during the past two decades.

For example, norepinephrine was in a severe shortage in 2011.[6] Clinicians resorted to alternative agents such as phenylephrine or vasopressin. Vail et al conducted a retrospective study to assess patient outcomes during this shortage and found that patients admitted to the hospital with septic shock during the norepinephrine shortage had higher mortality.[6]

The critical care community had to address several shortages during the COVID-19 pandemic. Drug shortages affected several classes of medications because of increased use, higher patient volumes, restrictions on exports, halt in production due to lockdowns, or understaffing.[7] Drug shortages affected immunomodulators, parenteral opioids, parenteral sedative agents, neuromuscular blockers, intravenous contrast, and continuous renal replacement therapy fluid solutions.

Several special articles and editorials have discussed the importance of transparency to the healthcare team and patients.[8-10] Rosoff et al highlighted several ethical approaches for managing drug shortages.[8] The American Society of Clinical Oncology published a guidance document for ethics principles and implementation strategies for drug shortages.[9]

Hospitals and healthcare systems may address drug shortages in different ways. Drug shortages committees may involve healthcare ethics consultants in discussions, thereby ensuring stakeholder participation in the decision-making process.

Traditional notions of professional ethics are based on the idea that a healthcare professional should always advocate for a patient and act in the patient's best interest. Drug shortages may hinder clinicians' ability to fulfill these moral obligations to patients—specifically, to provide beneficent care, minimize harm (nonmaleficence), and promote equity and principles of justice.

Ethical approaches to drug shortages should include:

- **Transparency and disclosure:** Drug shortages committee recommendations and decisions should be transparent to bolster trust and increase adherence to restriction or use criteria. Comprehensive communication between healthcare teams and patients is of paramount importance throughout the process. A delineated feedback process at the practitioner level should be implemented to solicit ideas for mitigating drug shortages and use of alternatives.
- **Equity, inclusion, and fairness:** Having allocation guidelines in place will help avoid bias or preferential treatment of certain groups of patients. It is important to include patients from minority and disadvantaged groups in discussions involving shared decision-making and to ensure adequate comprehension in their language of choice. Patients with low health literacy levels may need additional guidance if they cannot engage in self-determination when presented with information about drug scarcity and alternative therapeutic options.
- **Enforcement, consistency, and review:** Hospitals and healthcare systems should create policies and procedures that guide allocation decisions and ensure consistency. Adherence to policies should be monitored regularly through medication use evaluations. Supplies should be closely monitored so that the allocation plan can be modified based on supply estimates.

Conclusions

Drug shortages are an ongoing problem and can contribute to disruption in patient care. Ethical dilemmas arise as a result of drug shortages in both the adult and pediatric settings. Involvement of healthcare ethics consultants in decision-making processes is crucial. Hospitals and healthcare systems should have multidisciplinary scarce resource allocation committees or drug shortages committees that can help create and implement policies and guidelines to address drug shortages in a timely manner. Comprehensive communication among team members as well as transparency and adherence to the principles of equity and fairness can help alleviate problems associated with drug shortages. ▲

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Importance of Effectively Communicating Drug Shortages

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DRUG SHORTAGES HAVE BECOME PERVASIVE. THE WAYS IN WHICH HOSPITALS AND HOSPITAL SYSTEMS MANAGE ONGOING SHORTAGES VARY WIDELY ACROSS THE UNITED STATES AND THE WORLD. Unfortunately, these shortages have affected the most vulnerable patients in the intensive care unit, an effect that is exacerbated by the ongoing COVID-19 pandemic. A study found that, from 2001 to 2016, of almost 2000 reported drug shortages, 51% were drugs used in critical care.[1] As critical care professionals, we are forced to pivot frequently to adapt to available medications while minimizing the impact to patient care.

Communicating drug shortages to frontline physicians, advanced practice providers, and pharmacists remains a challenge because the line of communication is large and complex. Information must travel from the manufacturer to the distributer to the system pharmacies to the frontline clinicians and, in many cases, more intermediaries. Outside of an individual hospital or hospital system, drug shortages are initially reported by manufacturers to distributers or directly to hospitals. Often there is no advance warning of a potential shortage to allow hospitals to develop alternative

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plans. The American Society of Health-System Pharmacists (ASHP) held a Drug Shortages Summit, where it was determined that there is inadequate communication of drug shortages and that reports of drug discontinuations or interruptions are usually not received until a shortage has fully evolved.[2]

However, the Food and Drug Administration (FDA) Safety and Innovation Act, passed in 2012, now requires manufacturers of drugs that are life-supporting, life-sustaining, or used in emergency medical care or surgery to notify the FDA of potential drug discontinuances and the reason for the discontinuance, whether permanent or temporary. Manufacturers must inform the FDA at least six months prior to the date of interruption or as soon as practicable.[3] The FDA reports these shortages on its website,[4] but this reporting relies on manufacturers communicating shortages in a timely manner. The ASHP also maintains a website to communicate drug shortages to hospital systems.[5]

Hospital pharmacies typically have a task force or committee tasked with keeping track of and managing drug shortages. These committees often meet on a weekly basis to monitor current inventory, availability, and trends of commonly used medications. If a pharmacy were to alert frontline clinicians to all of the drugs on shortage, there would be a distinct element of clinician fatigue and the list would likely be ignored. For example, at Northwestern Memorial Hospital, the shortage list routinely contains more than 100 different drugs and is reviewed weekly. The Shortages Committee determines which shortages are severe enough to require a change in prescribing practices and thento be communicated to clinicians. Messaging typically includes the nature of the shortage, the medication impacted, concentration and route of impacted medication, expected length of shortage, and alternatives.

Drug shortages are communicated through several different outlets, with messages tailored to different groups. Shortages can be communicated via team meetings, email, or hospital intranet. The electronic medical record (EMR) system can also be leveraged to communicate shortages by utilizing best practice advisories or including restriction information in the order. However, implementing changes into the EMR can be cumbersome and not worthwhile, especially for shortages that are expected to be short-lived.

Providing quality care during the era of drug shortages is certainly challenging. Managing these drug shortages can be even more challenging and is extremely complex. It is vital that hospital pharmacies not only monitor these shortages carefully but communicate them along with alternatives to frontline clinicians to allow for the best patient care. Relevant shortage information, however, must be targeted to the right clinician at the right time. If the information is not relevant to the clinician, it will be ignored and future updates that may be relevant will be ignored as well.

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Sterile Water for Injection Shortages
Frequently Asked Questions

(Compiled by ASHP and the University of Utah Drug Information Service January 31, 2018)

This information is has been compiled using publicly available information on established best practices. ASHP and the University of Utah have provided this fact sheet for informational purposes only and are not assuming any liability for the accuracy or completeness of the information provided.

Background

Sterile water (SW) for injection vials are commercially available in sizes ranging from 5 mL to 100 mL. Most, if not all, of these presentations are on back order with resupply dates ranging from late January to March 2018. The shortage of SW for injection vials has increased the demand for SW for injection bags ranging in size from 250 mL to 3,000 mL. There have also been intermittent shortages of these larger-sized products. There are currently two major manufacturers of SW for injection vials: Fresenius Kabi and Pfizer. Pfizer's production has been limited due to manufacturing delays. Fresenius Kabi has not provided a reason for the shortage; however, typically when one manufacturer makes less than the usual amount of a product, other manufacturers are unable to meet the market demand.

Sterile water for injection vials are primarily used to reconstitute medications available as lyophilized powders. While the prescribing information for some medications may indicate alternative sterile liquids for reconstitution, most specify that SW for injection must be used. Without a consistent supply of SW for injection, healthcare personnel need to decide between selecting other therapies as treatments or using a sterile liquid other than SW for injection despite a lack of definite information about the effects on drug stability and compatibility. The consequences of using a sterile liquid not listed in product labeling to reconstitute medication vials may include poor dissolution of the powder, precipitation, or deactivation of the active pharmaceutical ingredient before further dilution or administration.

The University of Utah Drug Information Service and ASHP have been collecting information about the SW for injection shortage and coordinating with stakeholders to develop strategies to mitigate it. Both organizations have been in contact with the FDA, compounding experts, and pharmaceutical manufacturers to collect as much information as possible to share with pharmacy professionals.

ISMP Medication Error Reporting

ASHP encourages the reporting of any medication errors related to drug shortages to the Medication Error Reporting page on the Institute for Safe Medication Practices (ISMP) website.

Frequently Asked Questions

What is being done about the SW for injection shortage?

- ASHP has been in contact with the FDA and recently facilitated the addition of many SW for injection presentations to the FDA Drug Shortages Database.
- The University of Utah Drug Information Service and ASHP will continue to provide the most up-to-date information in the ASHP Drug Shortage Database.

What can pharmacists and institutions do about the SW for injection shortage?

- Actual ability to purchase available products often depends on hospital contracts and existing customer relationships. Contact your wholesaler or a manufacturer's representative to determine what amount, if any, your institution can purchase.
- Pharmacists should consider ways to conserve SW for injection when possible. This may include strategies like finding products that do not require reconstitution with SW for injection (commercially available premixes, dual-chamber flexible containers) or batching the preparation of medications that require reconstitution to minimize waste of SW for injection.
- Review use of SW for injection vials in your organization to ensure remaining supplies are reserved exclusively for the reconstitution of medications.
- Alteplase unit-of-use 2mg vials require SW for injection for reconstitution. Instead of dispensing a SW for injection vial with each unit-of-use alteplase vial, consider bulk batching of frozen alteplase syringes to preserve SW for injection vials.[1, 2, 3, 4]

Can sterile liquids other than SW for injection be used to reconstitute medications?

- Check product labeling of frequently used medications to identify which, if any, may be reconstituted with sterile liquids other than SW for injection.
- Neither the FDA nor pharmaceutical manufacturers can make recommendations outside of product labeling. Primary literature or tertiary sources may have information about the suitability of alternatives to SW for injection.
- Sterile water for irrigation is NOT FDA labeled for any use as an injection in patients. Sterile water for injection, USP, must pass a particulate-matter test that sterile water for irrigation, USP, does not have to pass.[5]
- Bacteriostatic water for injection contains preservative and should not be used in place of SW for injection, especially in instances where injections may be given intrathecally or epidurally, or in specific patient populations (e.g. neonates).
- The inappropriate use of normal saline to reconstitute medications can result in hyperosmotic solutions that may, when administered by IV push, cause infusion-site reactions. [6, 7, 8, 9]
- Normal saline reconstitution of medications for IV push administration may produce solutions at or near the solution's saturation point. An example is reported crystallization in high-concentration cefazolin sodium after reconstitution with normal saline. [10]

Can large bags of SW for injection be repackaged into empty sterile vials or syringes?

- Before repackaging SW for injection in bulk, be sure to check product labeling to determine whether the bag of SW for injection is a Pharmacy Bulk Package (PBP) (typically 2,000 mL or 3,000 mL).
- There may be limited utility to repackaging PBPs of SW for injection into vials or syringes. An FDA guidance states that the beyond-use time for repackaged drugs should not exceed the in-use time mentioned in the product labeling; four hours is the standard in-use time for PBPs unless otherwise stated in the product labeling.[11]
- Smaller SW for injection bags (1,000 mL or less) are not likely classified as PBPs; however specific product labeling should be consulted. If the bag is not considered a PBP and there is no in-use time established in the package labeling, USP <797> should be followed when setting beyond-use dates for sterile preparations.

Can large bags of SW for injection be used to reconstitute medication vials?

- Yes. Single-use containers should be labeled with the date and time of first entry, and discarded after an in-use time of six hours if kept within an ISO 5 environment.
- If using a PBP of SW for injection to reconstitute medications in vials, remember to label the bag of SW for injection with the date and time of first entry, and discard any amount of SW for injection remaining in the PBP after four hours.[11]
- When feasible, consider batch reconstitution of medications within the allowable in-use time to minimize waste of SW for injection

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*Please note that this is the only current repackaging guidance available. The FDA does intend to release a separate guidance on this issue specific to hospitals/health-systems, so some requirements may change

ATS Clinical Recommendations: 10 Steps for Hospitals Facing Intravenous Fluid Shortages

Hurricane Maria, a Category 5 status hurricane recorded as the tenth-most intense hurricane in Atlantic Ocean history, devastated parts of Puerto Rico and the Caribbean in September 2017. This caused widespread power outages, affecting more than 100 drug and medical device manufacturers. This natural disaster superimposed on continued market consolidation has created unprecedented supply disruptions of critical medications, including intravenous (IV) fluids. These shortages and the potential effect on hospital supply lines have been widely reported (1); however, management strategies and conservation methods remain a struggle for many institutions.

This shortage has largely impacted small diluent IV fluid products, commonly defined as having a solution volume ≤ 100 mL and intended for intermittent IV use (2). These products are typically not exclusively used in the preparation of many IV antibiotics. Supply disruptions have now extended to large IV diluent products (those with volumes greater than 100 mL), which are frequently utilized as bolus or maintenance fluids. These IV fluid shortages have put further pressure on hospital systems already suffering from significant supply disruptions with numerous other IV products including opioids, benzodiazepines, electrolytes, amino acids, emergency syringes (i.e. sodium bicarbonate, epinephrine), and local anesthetics.

In the event that your hospital or healthcare system is currently experiencing or is expected to experience critical shortages of IV fluids, electrolytes, or amino acids, here are 10 steps to consider adopting:

1. Convert all possible medications from IV to oral (PO) form
    - Institutions should consider formal intravenous to oral protocol implementation (click this link to view an IV to po protocol)
    - Common medications for IV to PO conversion include: antibiotics (e.g. azithromycin, beta-lactams, fluoroquinolones, metronidazole), antiepileptics (e.g. levetiracetam), proton-pump inhibitors, vitamins (e.g. thiamine [100 mg], folic acid)
2. Intravenous push administration antibiotics
    - Many antibiotics administered by ad-mixed IV piggyback can be administered as small volume reconstituted IV push
    - Many beta-lactam antibiotics may be considered for IV push administration. Common agents that are FDA-approved for administration by IV push include: aztreonam, cefazolin, cefoxitin, cefotaxime, ceftazidime, cefuroxime and meropenem
3. Use of premixed frozen antimicrobials, if available, to decrease use of small volume diluent products
4. Preserve unused IV fluids

- Be cognizant of discontinuing or switching to another product (e.g. 0.9% sodium chloride to dextrose 5% in sodium chloride 0.45%) before current infusion completed
- Upon switching to alternative product, ensure remainder is utilized (if clinically appropriate) before starting of new IV fluid
- Educate bedside nursing staff to keep unused IV fluids spiked and primed until expiration of product or tubing in the instance of therapy re-initiation

5. Consider severity of electrolyte disturbance and need for IV versus PO replacement
   - Restrict IV electrolyte replacement to patients with life-threatening electrolyte abnormalities or those with strict NPO status
   - Utilize enteral replacement for electrolytes (e.g. potassium, phosphorus)
6. Implement specific breakpoint criteria for utilization of intravenous electrolytes
   - Recommend electrolyte replacement dosing based on serum electrolyte concentrations (e.g. serum phosphorus concentration of less than 1.6 mg/dL)
7. Reconfigure electronic health record to guide appropriate prescribing
   - Utilize alternative diluent bag sizes based on current availability while maintaining safe concentrations for product stability
   - Implement soft alerts (denoting supply is low with guides to alternative therapy) as well as hard blocks (restricts ordering of product) in your institution's clinical decision support system
8. Limit utilization of parenteral nutrition (PN)
   - Initiation of PN should be based on assessed nutritional risk and status and duration of nothing by mouth (NPO) status (3)
   - Early discontinuation upon tolerance of enteral tube feeds or solid oral diet (3)
9. Consider enteral hydration in place of IV hydration for patients with a functioning gastrointestinal tract who are not critically ill
   - Commercially available products include, but are not limited to, the following: Trioral™, Oralyte®, and Pedialyte®
10. Consider delay of elective surgeries to conserve supplies

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