Operational Considerations for Sterile Compounding by Pharmacy Compounders Not Registered as Outsourcing Facilities During Public Health Emergencies and Natural Disasters

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This USP document is for informational purposes only and is intended to address operational considerations during public health emergencies and natural disasters that impact drug supply chains and compounding operations. This should not be construed as indicating any planned future revisions to official text of the *USP–NF*. Parties relying on the information in this document bear independent responsibility for awareness of, and compliance with, any applicable federal, state, or local laws and requirements. USP has no role in enforcement. USP will continue to monitor public health emergencies and natural disasters and will update this document accordingly.

Summary of updates:

- **October 16, 2024:** USP developed a document for Operational Considerations for Sterile Compounding by Pharmacy Compounders Not Registered as Outsourcing Facilities During Public Health Emergencies and Natural Disasters.

Background

USP General Chapter <797> *Pharmaceutical Compounding – Sterile Preparations* provides official standards for compounding quality sterile preparations. The chapter sets forth standards to minimize the microbial contamination risk for compounded sterile preparations (CSPs).

- During a public health emergency or natural disaster, demand on compounding operations is expected to increase and impose challenges on compounding entities. USP supports state boards and other regulators using risk-based enforcement discretion related to the implementation of USP compounding standards.
- USP has developed the operational strategies below in anticipation of challenges that may arise during public health emergencies and natural disasters. The following operational considerations may supplement but should not replace a facility's policies and procedures. This document is not a USP compendial standard, rather, it is an informational document developed with input by the USP

Compounding Expert Committee (CMP EC), based on their scientific and professional expertise, and with input from key stakeholders.

- Facilities should carefully consider the impact on the CSP and the environment and implement risk-mitigating strategies to help ensure the quality of CSPs. USP recommends that compounders also check with state boards and other regulatory bodies to determine the existence of waivers or interim requirements.

Compounding Drugs on Shortage

Compounded drugs might be appropriate if a patient's medical need cannot be met by an FDA-approved drug or, under certain circumstances, if 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 dispensed for patient use. Compounding must be done in accordance with federal and state requirements.

Before compounding, consider sourcing from approved alternate suppliers or outsourcing facilities.

If entities desire to compound a drug on FDA's drug shortages list, compounders should use all available resources, including USP compounded preparation monographs when available. See available complimentary USP compounded preparation monographs here.

When compounding the following preparations (except when diluting commercial products to create the preparations), all specifications in the USP drug monographs below must be met and documented:

- *Dextrose Injection*
- *Lactated Ringer's Injection*
- *Sodium Chloride Injection*
- *Sodium Chloride Irrigation*
- *Sterile Water for Injection*
- *Sterile Water for Irrigation*
- *Water for Injection*

Considerations for Compounding Intravenous Fluids

Compounders must keep abreast of any interim guidance or temporary policy issued by regulators during the public health emergency or natural disaster and adjust their operations accordingly. Compounders must note if regulators permit compounding of specific intravenous (IV) fluids during this period.

Compounders should operate in accordance with the following considerations if compounding of intravenous fluids is required during a public health emergency or natural disaster:

Fluid Conservation Strategies for CSPs

Compounders should take inventory of components available and allocate resources to compounding the most critical CSPs that are in shortage, focusing on fluid conservation strategies.

- Ensure staff are aware of and are complying with stewardship strategies and discuss conservation methods with nurses, anesthesia personnel, and others administering IV fluids.
- Compounders should open the appropriate volume IV bag to meet patient needs to avoid waste.
- Maximize use of proprietary bag and vial systems and only dock and activate at the point of care.
- Withdraw reconstitution volume from the final infusion container, when compatible.
- Compounders should attempt to reduce wastage of conventionally manufactured single-dose IV fluid containers during compounding if the entire amount of IV fluid in the container will not be used in one operation. When compounding with a conventionally manufactured single-dose IV fluid container, the container must be entered or punctured in ISO class 5 or cleaner air, so that it may be used up to 12 h after initial entry or puncture as long as the labeled storage requirements during that 12-h period are maintained.
- Sequester unopened expired fluids in case regulators allow extended dating.
- Consider additional mitigation strategies that may be available from professional organizations.

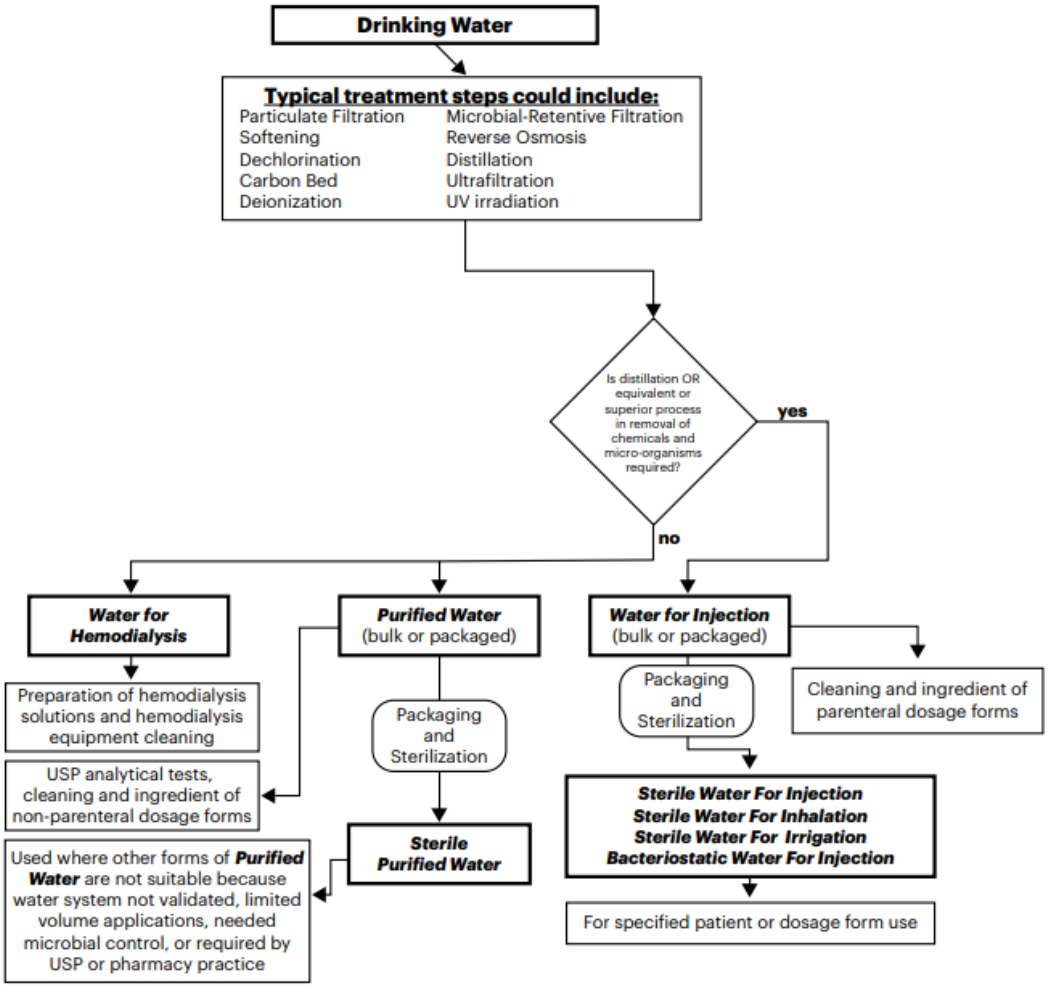
Practices to Avoid

- Avoid anticipatory compounding where possible to conserve components for the most critical CSPs which are on shortage.
- Avoid the use of *Sterile Water* for activities where other grade water may be used. For example, for rinsing equipment when compounding nonsterile preparations, *Purified Water*, distilled water, or reverse osmosis water should be used. Similarly, when reconstituting oral solutions, refer to the product's labeling for alternate grades of water rather than the use of sterile water.
- Avoid pre-spiking bags.
- Do not store opened single-dose ampules during compounding for any time period.
- Avoid unsafe practices (e.g., batch preparation from large volume bag at bedside). Follow CDC Injection Safety Guidelines.
- Avoid the use of IV flushes for purposes other than flushing. Do not reconstitute or dilute a medication using a Normal Saline flush syringe.

Water for Compounding

- Compounders must ensure that:
  - The selection of the type and specifications of water used in compounding of IV fluids is appropriate for intended use. The USP specifications for the types of water used must be met. See *USP* <1231> *Water for Pharmaceutical Purposes* for more details.
  - Water production and quality meet applicable governmental requirements.
- *Sterile Water for Irrigation* must not be used to compound medicines intended for intravenous administration. *Sterile Water for Irrigation* does not have specific limits for particulate matter, unlike *Sterile Water for Injection*.
- *Sterile Water for Irrigation* labeled by the manufacturer "not for injection" cannot be converted to *Sterile Water for Injection*, due to several reasons, including particulate matter and endotoxin limits. Further, <797> requires that "All APIs and other components used must be evaluated for suitability for use in sterile drug preparation. Components labeled with "not for pharmaceutical use", "not for injectable use", "not for human use" or an equivalent statement must not be used to compound for these purposes."
- Household Reverse Osmosis systems cannot be used to make sterile water.
- *Sterile Water for Irrigation*, USP, is prepared from *Water for Injection* that is sterilized and suitably packaged. It contains no antimicrobial agent or other added substance. *Water for Injection* is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or with the drinking water regulations of the European Union or of Japan or with the World Health Organization's Guidelines for Drinking Water Quality. Per <1231> *Water for Pharmaceutical Purposes*, *Sterile Water for Irrigation*, USP, "may be used in other applications that do not have particulate matter specifications, where bulk *Water for Injection* or *Purified Water* is indicated but where access to a validated water system is not practical, or where somewhat larger quantities are needed than are provided as *Sterile Water for Injection*."

Figure 1. Water for Pharmaceutical Purposes, from USP <1231>



Assignment of Beyond-Use Dates

When a public health emergency or natural disaster impacts drug supply chains, there may be supply disruptions, shortages of drug products, and increased demand for compounded preparations. In considerations of resource constraints and increased waste of drugs, compounders should apply beyond-use dates (BUDs) conservatively based on both chemical and physical stability and microbiological considerations. Compounders must be aware of and comply with any temporary guidance documents or temporary policy from regulators regarding BUDs for specific preparations, as they may differ from the BUD limits in USP standards.

- **If compounding facilities are able to maintain sterile compounding operations consistent with the standards in <797>:** the BUD limits outlined in General Chapter <797>, or any applicable monograph, must be used, unless otherwise required by regulators.

SUMMARY: <797> BUD Limits

- **Category 1: CSPs must be prepared in an ISO Class 5 or better primary engineering control (PEC) that may be placed in an unclassified segregated compounding area (SCA) and have shorter BUDs.**
  - ≤ 12 hours at controlled room temperature
  - ≤ 24 hours in a refrigerator

- **Category 2: CSPs must be prepared in a cleanroom suite and may be assigned longer BUDs.**

  Aseptically processed, no sterility testing, only sterile starting components
  - 4 days at controlled room temperature
  - 10 days in a refrigerator
  - 45 days in a freezer

  Aseptically processed, no sterility testing, one or more nonsterile starting component(s)
  - 1 day at controlled room temperature
  - 4 days in a refrigerator
  - 45 days in a freezer

  Aseptically processed, passed sterility testing
  - 30 days at controlled room temperature
  - 45 days in a refrigerator
  - 60 days in a freezer

  Terminally sterilized, no sterility testing
  - 14 days at controlled room temperature
  - 28 days in a refrigerator
  - 45 days in a freezer

  Terminally sterilized, passed sterility testing
  - 45 days at controlled room temperature
  - 60 days in a refrigerator
  - 90 days in a freezer

- **Category 3: CSPs may be assigned longer BUDs than the limits set for Category 2 CSPs up to a maximum of 180 days when compounded in accordance with all Category 3 CSP requirements. Category 3 CSPs undergo sterility testing, supplemented by endotoxin testing when applicable, and have more requirements than Category 2 CSPs for personnel qualification, use of sterile garb, use of sporicidal disinfectants, frequency of environmental monitoring, and stability determination.**

  Aseptically processed, sterility tested, and passing all applicable tests for Category 3 CSPs
  - 60 days at controlled room temperature
  - 90 days in a refrigerator
  - 120 days in a freezer

  Terminally sterilized, sterility tested, and passing all applicable tests for Category 3 CSPs
  - 90 days at controlled room temperature
  - 120 days in a refrigerator
  - 180 days in a freezer

- **If compounding facilities are not fully operational as outlined in the standards in <797>**:
  - When anticipatory compounding is necessary, compounding should occur in a PEC within a cleanroom when possible, rather than an SCA, to maximize BUDs and minimize waste.
  - Secondary engineering control (SEC) not operational, but PEC operational:
    - Consider compounding only Category 1 CSPs
  - PEC not operational:
    - Consider immediate-use compounding per <797> *Section* 1.3 *Immediate-Use CSPs*

CSPs compounded for direct and immediate administration must be administered within **4 hours** following the start of preparation and are not subject to the requirements for Category 1, Category 2, or Category 3 CSPs when all requirements for immediate-use CSPs are met.

Requirements for Immediate Use CSPs
Aseptic techniques, processes, and procedures are followed, and written standard operating procedures (SOPs) are in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other conventionally manufactured products or CSPs.
Personnel are trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility's SOPs.
The preparation is performed in accordance with evidence-based information for physical and chemical compatibility of the drugs (e.g., approved labeling, stability and compatibility studies).
The preparation involves not more than **3 different sterile products.**
Any unused starting component from a single-dose container must be discarded after preparation for the individual patient is complete. Single-dose containers must not be used for more than one patient.
Administration begins within 4 hours following the start of preparation. If administration has not begun within **4 hours following the start of preparation,** it must be promptly, appropriately, and safely discarded.
Unless administered by the person who prepared it or administration is witnessed by the preparer, the CSP must be labeled with the names and amounts of all active ingredients, the name or initials of the person who prepared the preparation, and the exact 4-hour time period within which administration must begin.

Storage and Temperature Excursions

Natural disasters and public health emergencies may affect the storage conditions of CSPs. To determine whether temperature excursions or storage conditions have compromised CSPs, compounders should reference both General Chapter <659> *Packaging and Storage Requirements* and General Chapter <1079.2> *Mean Kinetic Temperature in the Evaluation of Temperature Excursions During the Storage and Transportation of Drug Products*.

Additionally, BUDs must not be additive. The storage time of a CSP must not exceed the original BUD placed on the CSP for its labeled storage condition. For example, a CSP that is assigned a BUD based on storage at room temperature cannot subsequently be refrigerated or frozen in order to extend the original BUD assigned. Likewise, the BUD of a frozen CSP must not be extended based on storage at room temperature when it is thawed.

When freezing or thawing frozen products or preparations, consider the chemical and physical stability of the preparation or drug product and the integrity of the container closure system.

<659> Temperature and Storage Definitions

Controlled cold temperature: The temperature maintained thermostatically between 2° and 8° (36° and 46° F), which allows for temperature excursions between 2° and 15° (36° and 59° F) that may be experienced during storage, shipping, and distribution, but not to exceed 24 h, such that the allowable calculated mean kinetic temperature (MKT) is NMT 8° (46° F) with no excursions below 2° (36° F) or above 15° (59° F). These limits (time and temperature) and the calculated MKT must be documented (see *Mean Kinetic Temperature in the Evaluation of Temperature Excursions During Storage and Transportation of Drug Products* <1079.2>). Additionally, controlled cold excursions may only occur one time during the possession of the product within the supply chain unless directed otherwise by the manufacturer. The length of time the product is held at 2° and 15° (36° and 59° F) should be supported by stability data. Other limits may be permitted if the manufacturer so instructs as supported by the manufacturer's stability data and/or thermal cycling studies.

Controlled room temperature: The temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25° (68°–77° F). MKT may be used during an excursion provided: 1) MKT does not exceed 25° (77° F); 2) excursion between 15° and 30° (59° and 86° F); 3) transient excursions are NMT 40° (104° F); and 4) excursion time is NMT 24 h. These limits (time and temperature) and the calculated MKT must be documented. Articles may be labeled for storage at "controlled room temperature" or at "20°–25°", or other wording based on the same MKT. (See <1079.2>.) An article for which storage at *Controlled room temperature* is directed may, alternatively, be stored and shipped in a cool place or refrigerated, unless otherwise specified in the individual monograph or on the label. Storage time in controlled cold or cool place cannot be used to calculate excursion temperature outside of controlled room temperature ranges.

Freezer: A place in which the temperature is controlled between −25° and −10° (−13° and 14° F). It is noted that, in some instances, articles may have a recommended storage condition below −20° (−4° F). In such cases, the temperature of the storage location should be controlled to ±10° of the recommended storage condition.

Leadership

Facilities must always have documented arrangements for procedures for public health emergencies or natural disasters, including stewardship strategies and leadership arrangements. <797> requires that the compounding facility must designate one or more individuals [i.e., the designated person(s)] to be responsible and accountable for the performance and operation of the facility and personnel in the preparation of CSPs and for performing other functions. In a state of public health emergency or natural disaster, the designated person(s) (or their designate) is responsible for ensuring SOPs and emergency protocols are followed. If the designated person(s) cannot be reached, a new appropriately-trained designated person(s) must be appointed.

Training

All personnel who compound or have direct oversight of compounding personnel must be initially trained and qualified by demonstrating knowledge and competency in compounding CSPs according to the requirements in <797> before being allowed to perform their job functions independently.

The designated person(s) is responsible for ensuring that tasks are assigned based on level of training and competency, and that the person's skills are appropriate for the assigned task.

Personnel who only prepare immediate-use CSPs are not required to perform media-fill testing per <797>, but the facility's SOPs must determine how their competency will be evaluated. When specific conditions in <797> are met, compounding of CSPs for direct and immediate administration is not subject to the requirements for Category 1, Category 2, or Category 3 CSPs. Personnel must be trained and demonstrate competency in aseptic processes as they relate to assigned tasks and the facility's SOPs. The competency should include appropriate preparation (e.g., hand washing, cleaning the area that will be used) and technique that is evaluated and approved by a qualified individual.

Considerations for Certification and Recertification

- Primary and secondary engineering controls must not be used without initial (i.e., startup) certification.
- Understanding resource constraints during public health emergencies and natural disasters, regulators may allow delaying recertification in some instances.
    - Consider increased environmental monitoring and applying shorter BUDs if certification is delayed.

Cleaning and Disinfecting

Standards for cleaning, disinfecting, and applying sporicidal disinfectants and sterile 70% isopropyl alcohol (IPA) that help ensure quality CSPs must be maintained.

- Follow facility policies and procedures for environmental cleaning and disinfection consistently and correctly.
- Routinely clean and disinfect frequently touched surfaces and objects.
- For areas outside the PEC, use soap and water or detergent prior to applying an Environmental Protection Agency (EPA)-registered disinfectant (or equivalent).
    - Follow manufacturer-recommended contact times.
- Dispose of cleaning supplies according to facility procedures.

Regulatory Considerations and Additional Resources

USP will continue to monitor public health emergencies and natural disasters and will update this section with relevant guidance documents and resources accordingly. USP recommends that compounders also check with state boards and other regulatory bodies to determine the existence of waivers or interim requirements. Additionally, any adverse events potentially associated with the quality of CSPs must be reported in accordance with <797> *Section* 18.3 *Adverse Event Reporting*.

- ASA: Hurricane Helen Baxter Shortages
- ASHP: Small- and Large-Volume Fluid Shortages – Suggestions for Management and Conservation
- ASPEN Resources for IV Fluid Shortages
- EDSA Supply Chain Disruption Report
- FDA Drug Shortages
- FDA's Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act Guidance for Industry
- FDA Temporary Policies for Compounding Certain Parenteral Drug Products
- Hurricane Helene: Baxter's manufacturing recovery in North Carolina | FDA
- Insanitary Conditions at Compounding Facilities Guidance for Industry
- ISMP Safe Practice Guidelines for IV Push Medications
- NHIA Response to Manufacturing Disruption of IV Solutions Due To Hurricane Helen