Highlights of Changes: USP <795> Pharmaceutical Compounding Non-Sterile Preparations

On November 1, 2022, USP released the official revision of *USP <795> Pharmaceutical Compounding-Non-Sterile Preparations.* The finalization of the revised chapter changes the status of *USP <800> Hazardous Drugs - Handling in Healthcare Settings* and *USP <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging* chapter from informational to compendial. USP standards represent the minimum practice standards for the safe compounding of pharmaceutical compounds for patients. The expected date of compliance is November 1, 2023; noting, states may vary on expected compliance.

The following briefings highlights the key work that must be completed as part of a compliance program but should not be interpreted as an all-inclusive summary.

USP <795> Pharmaceutical Compounding – Non-Sterile Preparations Briefing

- Predecessor compendial chapter version: USP <795> v2014
- **Finalized and published November 1, 2022**
- **MUST** appears **184 times**, denoting **requirements**
- **SHOULD** appears **26 times**, denoting **recommendations**
- Noted major changes to USP <795> involve **Beyond Use Dates, Facilities, Cleaning, and Training**
- **18 noted** broad Standard Operating Procedures
- **2 Programs** defined and written: Training and Quality Assurance & Quality Control
- **Scope** of revised chapter does **not** include reconstitution to manufacturer directions; repackaging; splitting of tablets and administration of the product; **NOTE: state boards of pharmacy may include the listed exempted tasks as part of compliance.**

Compounded Non-sterile Preparation Categories and Beyond Use Dates (BUDs)

USP transitioned the categories for compounded non-sterile preparations from Simple, Moderate and Complex, and corresponding water content based assignment to water activity (aw). The aw represents the available water within a compound that can support microbial growth and degradation due to hydrolysis. USP <1112> Application of Water Activity Determination of Nonsterile Pharmaceutical Products goes into more detail on what is aw and how it is used to determine BUDs. Sites are not required to conduct their own for determination of aw, USP BUDs and an allowance of the use of comparable products listed in Table 3 and in USP <1112>. The following table are the BUD limits of the non-sterile compounded preparation in the absence of a USP monograph or stability studies.

Beyond Use Date Limits for Non-Sterile Compounded Preparations		
Preparation Characteristics	**Storage Conditions**	**BUD Limit**
Nonpreserved Aqueous Forms with aw >0.60	Refrigeration (2°C-8°C)	14 days
Preserved Aqueous Forms with aw >0.60	Controlled Room Temperature (20°C-25°C) Refrigeration (2°C-8°C)	35 days
Nonaqueous oral liquids with aw <0.60	Controlled Room Temperature (20°C-25°C) Refrigeration (2°C-8°C)	90 days
Other Nonaqueous Dosage Forms with aw <0.60	Controlled Room Temperature (20°C-25°C) Refrigeration (2°C-8°C)	180 days

Preparations with an aw >0.6, should incorporate an antimicrobial preservative if not contraindicated. If a preservative is contraindicated store in refrigeration.

Packaging and storage materials must maintain physical and chemical integrity and the stability of the product over the time of the BUD. Attributes for packaging is protection against damage and prevention of leakage, contamination, and degradation of the preparation.

BUDs may require shorter dating due to existing stability data and/or the expiration date of any of the components before assigned BUD. BUDs for non-sterile compounded pharmaceuticals must not exceed 180 days in absence of a USP-NF monograph, suitability testing and/or published stability information.

NOTE: adding flavoring agents to conventional manufacturer products is compounding and can impact the final preparation. USP has published an information document as a supplement to USP <795>. The informational document should minimize harm to patients that could result from "1) excessive microbial contamination, 2) variability from the intended strength of correct ingredients (e.g., ±10% of the labeled strength), 3) physical and chemical incompatibilities, 4) chemical and physical contaminants, and/or 5) use of ingredients of substandard quality. "

NOTE: reconstitution to manufacture specifications and repackaging or non-sterile preparations are out of scope for USP <795>. For repackaging of non-sterile products sites should refer to manufacturer instructions, USP <1178> Good Repackaging Practices, FDA Guidance for Industry document Expiration Dating of Unit-Dose Repackaged Solid Oral Dosage Form Drug Products August 2017, and state board of pharmacy statutes.

The Designated Non-Sterile Compounding Area and Equipment

Traditionally, non-sterile compounding areas are added to counter spaces near sinks or workstations with little thought to the cleaning and safety of compounding non-sterile preparations.

Sites **must** designate an area (NOTE: not a separate room) for non-sterile compounding and the area must be described in the SOPs. A visible perimeter should be present to define nonsterile compounding area. The designated area should not have carpet, be well lit (best practice: at least 100fc over critical work surfaces (USP <1066> Physical Environments That Promote Safe Medication Use)), clean, and designed to minimize cross-contamination and errors. Surfaces of fixtures and flooring in the designated compounding area should not be porous or particle generating and should be resistant to cleaning solution damage.

Temperature must be monitored at least daily or with a continuously monitoring device to ensure components, drugs and supplies are stored to manufacturer specifications.

A sink with hot and cold water must be readily available and the sink must be cleaned if dirty and cleared of contents prior to use for non-sterile compounding. Purified water or better quality of water must be used for compounding non-sterile compounded preparations. The plumbing should be free of defects, leaks and corrosion and in good working order.

Purified water, distilled water or reverse osmosis water must be used for rinsing equipment and utensils used for compounding. Equipment and supplies used for compounding must be stored off the floor.

A closed ventilated enclosure (CVE), biological safety cabinet (BSC) and/or a single-use containment glove bag system must be used when weighing, measuring, or manipulating components that could generate airborne particles. Sites should conduct a risk assessment to determine if these devices are needed to prevent exposure to personnel or contamination of the non-sterile compounding workspace or other preparations. CVEs and BSC used for non-sterile compounding must certified every 12 months or sooner to manufacturer standards and applicable state and federal requirements.

Storage of components and supplies used for non-sterile compounding should be in a manner to protect the integrity of the products. Storage areas for components of non-sterile preparations must be temperature monitored and documented daily.

Cleaning the Designated Non-sterile Compounding Area

USP 795 has now included a more robust cleaning requirements for the non-sterile compounding areas. Staff must be trained on cleaning and the cleaning must be documented. The following highlights the cleaning requirements.

Cleaning and Sanitizing the Designated Non-sterile Compounding Area	
Fixture	**Minimum Cleaning Frequency**
Equipment	• Post compounding and prior to the next preparation, equipment must be cleaned. • Purified Water, distilled water, or reverse osmosis water should be used for rinsing equipment. • Equipment must be stored in a manner that minimizes the risk of contamination
Work Surfaces	• At beginning and at the end of the compounding days • Between preparations • After spills or is surface suspected contamination
Containment Ventilated Equipment	• Beginning and end of each compounding day • Between preparations, clean and sanitize horizontal worksurface. • After spills, or if surface contamination is suspected
Biological Safety Cabinet	• Beginning and end of each compounding day • Between preparations, clean and sanitize horizontal worksurface. • After spills, or if surface contamination is suspected. • Under work surface cleaned and sanitized monthly
Sink(s)	• Cleaned prior compounding on compounding days. • Cleared of contents prior to use for non-sterile compounding
Floors	• Daily on days of compounding • After spills, or if surface contamination is suspected
Storage Shelving	• Every 3 months • After spills, or if contamination is suspected. • (BEST PRACTICE: clean storage bins and contents of bins)
Walls	• Visibly soiled • After spills, or if surface contamination is suspected
Ceilings	• Visibly soiled (BEST PRACTICE: monitor dust on air supply covers) • If surface contamination is suspected

Inspection of the compounding areas should incorporate a plan to address any insanitary conditions as defined by FDA as *'conditions that could cause a drug to become contaminated with filth or rendered injurious to health. The drug itself need not actually be contaminated. A drug that is actually contaminated with any filthy, putrid, or decomposed substance is deemed to be adulterated under section 501(a)(1) of the FD&C Act (21 U.S.C. 351(a)(1)).'*

The FDA published the final version of the *Insanitary Conditions at Compounding Facilities* in November 2020. Although this is a guidance document, some states have incorporated language into compounding statutes regarding 'insanitary conditions' potentially making guidance points regulatory. In addition, information from the guidance, should be reviewed for examples for remediation for best practice.

The scope of the guidance document does include non-sterile drugs, noting, it is possible for compounded, non-sterile drugs to become contaminated with microorganisms that may lead to patient harm. Compounded non-sterile aqueous solutions (ex. aw >0.60) are susceptible to microbial growth if contaminated. Insanitary conditions also include contamination such as non-viable 'filth' and the presence of unintended drug components; cross-contamination.

The following are a few examples of insanitary conditions listed within the guidance for sites to consider for inspection.

- Vermin, insects, rodents, other animals or evidence of presence in compounding area or adjacencies
    - Check light lenses, traps, corners of walls,
- Visible microbial contamination in compounding areas or adjacencies
- Foreign matter such as dust, rust, glass shavings, hair, paint chips, rubbish in compounding area
- Compounding drugs during construction to adjacent areas
- Standing water or evidence of leaks in the compounding area
    - Check stained ceiling tiles, stained flooring, drip residue on walls, dried water in light lenses.
- Handling bulk and active pharmaceutical ingredients without controls for cross-contamination
    - Check powder residue, spills and staining on equipment, surfaces, storage bins.
    - Compounding/mixing beta-lactam drugs without complete separation from other preparations
- Using components not of USP grade or cleared for human use (i.e., food grade)

Personnel Training and Evaluation

USP <795> requires a 'training program' for non-sterile compounding be written and implemented. Significant revisions are made to section 2. Personnel, Training and Evaluation.

Training program **must** be documented with demonstrative knowledge and competency of core skills and must be completed and passed prior to compounding. Unlike USP <797> there is no differentiation between compounding personnel and checking personnel training requirements.

Training and Evaluation Element	Process	Frequency
Review and comprehend requirements for USP <795>	Self-study & orientation	On hire & Every 12 Months
Review and comprehend Safety Data Sheets (SDS)	Self-study & orientation	
Review and comprehend Certificate of Analysis (COA), if required	Self-study & orientation	
Hand hygiene	Documented Observation	
Garbing (ex. gloves required for all compounding activities)	Documented Observation	
Cleaning and sanitization (ex. workspace, equipment, spills)	Documented Observation	
Handling & transporting components and compounded non-sterile preps	Documented Observation	

References

USP <795> Pharmaceutical Compounding- Non-Sterile Preparations now require a paid subscription to the USP Compounding Compendium

USP has published free references to assist with interpretation of new chapters.

1. NEW: USP <795> FAQs, November 1, 2022: https://go.usp.org/USP_GC_795_FAQs
2. NEW: USP BUD Scientific Rationale for the 2021 Proposed Revisions to <795> , September 2021: https://go.usp.org/l/323321/2021-08-31/5kmcjf/323321/1630438802OI493yjz/BUD_Scientific_Rationale_for_the_2021_Proposed_Revisions_to__795_.docx
3. NEW: <795>: Adding Flavor to Conventionally Manufactured Nonsterile Products: https://go.usp.org/795_Flavoring.pdf
4. US Department of Health and Human Services; Food and Drug Administration; CDER; Insanitary Conditions at Compounding Facilities, November 2020; https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

This guide is meant to present highlights of changes to USP <795> *Pharmaceutical Compounding- Non-Sterile Preparations* and is not meant to totally inclusive of all new and existing requirements and recommendations.