



Compounding Committee: Drafted USP <795>

BY: SUPERVISING INSPECTORS CHRISTINE ACOSTA AND ANNA KALANTAR

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Compounding Committee

- ▶ The following presentation is board staff's summary of the USP's proposed Chapter 795, Pharmaceutical Compounding – Nonsterile Preparations. It is not comprehensive, nor is it a substitute for reading the proposed chapter. Persons who must comply with USP standards should review the proposed revisions to the chapter in its entirety. The proposed chapter is available at USP.org.
- ▶ This presentation has been modified to ensure compliance with ADA provisions



United States Pharmacopeia (USP)

2015-2020 Resolutions

- ▶ Resolution VII - Quality Standards for Compounded Medicines:
 - ▶ USP will continue working with stakeholders to develop and maintain practice and quality standards for sterile and non-sterile compounding.
 - ▶ USP will increase the availability of its compounding standards, expand stakeholder engagement and education, and promote adoption of these standards by compounding professionals and regulatory authorities.



United States Pharmacopeia (USP)

- ▶ General Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations
- ▶ General Chapter <797> Pharmaceutical Compounding – Sterile Preparations
- ▶ General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings
- ▶ General Chapter <825> Radiopharmaceuticals— Preparation, Compounding, Dispensing, and Repackaging



Milestones for revisions

- ▶ Public comment period March 30, 2018 through July 31, 2018
- ▶ Open microphone session April 20, 2018
- ▶ Intended publication date June 1, 2019
- ▶ Intended official date of December 1, 2019



General Chapter <795> *Pharmaceutical Compounding – Nonsterile Preparations*

- ▶ Open microphone on 4/20/18:
- ▶ Available at:
<https://www.usp.org/sites/default/files/usp/document/our-work/compounding/795-open-microphone-presentation.pdf>
- ▶ Web recording:
<https://www.hapyak.com/portal/viewer/9cf36d6ce9585fdcd a76c09851896b01>



USP <795> background

- ▶ **First Published in USP 24–NF 19** (2000) Revision from USP <1161> Pharmacy Compounding Practices
- ▶ **Subsequent Revisions Revised in USP 27–NF 22** (2004)
 - ▶ **Revised in USP 34–NF 29** (2011)
 - ▶ Incorporated USP <1075> Good Compounding Practices
- ▶ **Most Recent Revision Bulletin** (Official Jan 1, 2014)
 - ▶ Removed the reference to sterile preparations in the section on Beyond-Use Dates (BUDs)
 - ▶ Clarified that the BUDs in <795> are specific for nonsterile preparations and do not apply to sterile preparations



Overview of Major Changes

- ▶ **Purpose of Current Revision** To reflect new science and evidence based on updated guidance documents, best practices, and new learnings from investigations
 - ▶ To respond to stakeholder input received throughout the cycle
 - ▶ To clarify topics that are frequently queried and misconstrued
 - ▶ To align with published <800> and revision efforts for <797>
- ▶ **Current <795> Served as an Template for Revision**
 - ▶ Many sections were “summary” statements and were expanded to add clarity and additional information
 - ▶ Revision proposal was modeled after current revision efforts for <797>



Overview: sections

1. INTRODUCTION AND SCOPE
2. PERSONNEL QUALIFICATIONS—TRAINING, EVALUATION, AND REQUALIFICATION
3. PERSONAL HYGIENE AND GARBING
4. BUILDINGS AND FACILITIES
5. CLEANING AND SANITIZING
6. EQUIPMENT AND COMPONENTS
7. SOPs AND MASTER FORMULATION AND COMPOUNDING RECORDS
8. RELEASE TESTING
9. LABELING
10. ESTABLISHING BEYOND-USE DATES
11. QUALITY ASSURANCE AND QUALITY CONTROL
12. CNSP HANDLING, PACKAGING, STORAGE, AND TRANSPORT
13. COMPLAINT HANDLING AND ADVERSE EVENT REPORTING
14. DOCUMENTATION



Section 1. Introduction And Scope

- ▶ Scope Added information on types of **Compounded Nonsterile Preparations (CNSP)**
- ▶ Hazardous Drugs removed all information on handling of hazardous drugs and added references to General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings.
- ▶ Affected Personnel and Settings Added roles and responsibility of the designated person
 - ▶ **Designated person** = one or more individual responsible and accountable for the performance and operation of the facility and personnel



Section 1. Introduction And Scope

- ▶ **Compounding** is combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer package insert, or otherwise altering a drug or bulk drug substance to create a nonsterile medication.
- ▶ **Reconstituting** a conventionally manufactured nonsterile product in accordance with the directions contained in the approved labeling provided by the product's manufacturer is **not** considered compounding as long as the product is prepared for an individual patient and not stored for future use



Section 2. Personnel Qualifications— Training, Evaluation, And Requalification

- ▶ All personnel involved in the preparation and handling of CNSPs must be trained, must demonstrate competency, and must undergo annual refresher training.
- ▶ Before independently beginning to prepare CNSPs, personnel must complete training and be able to **demonstrate proficiency** in the theoretical principles and hands-on skills of nonsterile manipulations for the type of compounding they will be performing.



Section 2. Personnel Qualifications— Training, Evaluation, And Requalification

- ▶ Demonstrated proficiency steps:
 - ▶ **designated person** demonstrates procedures,
 - ▶ **designated person** observes and guide personnel throughout the training process.
 - ▶ personnel repeats the procedures independently, but under the direct supervision of the **designated person**.
 - ▶ personnel independently demonstrates understanding and competency to the **designated person** to perform the procedure.
- ▶ Only one person compounds: must document that they have obtained appropriate training outside of the facility and demonstrated competency.



Section 2. Personnel Qualifications— Training, Evaluation, And Requalification

- ▶ **Proficiency** must be demonstrated in at least the following core competencies:
 - ▶ Hand hygiene
 - ▶ Garbing
 - ▶ Cleaning and sanitizing
 - ▶ Component selection, handling, and transport
 - ▶ Performing calculations
 - ▶ Measuring and mixing
 - ▶ Use of equipment
 - ▶ Documentation of the compounding process (e.g., Master Formulation Records and Compounding Records)



Section 3. Personal Hygiene And Garbing

- ▶ Compounding personnel must maintain personal hygiene
- ▶ Before entering a designated compounding area, compounding staff must remove any items that are not easily cleanable and that might interfere with garbing. At a minimum, personnel must:
 - ▶ Remove personal outer garments
 - ▶ Remove all hand, wrist, and other exposed jewelry or piercing that can interfere with the effectiveness of the garb or hand hygiene
 - ▶ Remove headphones and earphones
 - ▶ Keep nails clean and neatly trimmed to minimize particle shedding and avoid glove punctures



Section 3. Personal Hygiene And Garbing

- ▶ Hand Hygiene is required

Box 3-1 within the proposed revised chapter provides hand hygiene procedures



Section 3. Personal Hygiene And Garbing

- ▶ Gloves are required for all compounding activities
- ▶ Garb must be used as appropriate.
 - ▶ Garb must be stored to prevent contamination (e.g., away from sinks to avoid splashing onto garb).
 - ▶ Visibly soiled garb or garb with tears or punctures must be changed immediately
 - ▶ May reuse gown for one shift if not soiled **and** retained in the compounding area.
 - ▶ Gloves, shoe covers, hair covers, facial hair covers, face masks, or head coverings, may **not** be reused and must be replaced with new ones



Section 4. Buildings And Facilities

- ▶ Designated compounding area is required:
 - ▶ Must be separated from areas **not** directly related to compounding.
 - ▶ Must be separated and distinct from the areas intended for sterile compounding
 - ▶ Areas used to compound hazardous CNSPs must **not** be used for compounding nonhazardous CNSPs.
 - ▶ Surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets must be cleanable and must be kept clean.
 - ▶ Carpet is not allowed in the compounding area.
 - ▶ Maintained in a clean, orderly, and sanitary condition, and in a good state of repair.



Section 4. Buildings And Facilities

- ▶ Facilities:
 - ▶ A source of hot and cold water and an easily accessible sink must be available for compounding.
 - ▶ The plumbing system must be free of defects.
 - ▶ All components, equipment, and containers must be stored off the floor and in a manner that will prevent contamination and permit inspection and cleaning of the compounding and storage area.



Section 5. Cleaning And Sanitizing

- ▶ **Cleaning:** The process of removing soil (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products
- ▶ **Sanitizing agent:** An agent for reducing, on inanimate surfaces, the number of all forms of microbial life including fungi, viruses, and bacteria.



Section 5. Cleaning And Sanitizing

- ▶ Cleaning and sanitizing of the surfaces in the nonsterile compounding areas must occur on a regular basis at the minimum frequencies specified in *Table 1 of the proposed revised chapter*.



Section 6. Equipment And Components

- ▶ Any weighing, measuring, or other manipulation of an API or added substance in powder form that can generate airborne contamination from drug particles must occur inside a **Containment ventilated enclosure (CVE)** (i.e., powder containment hood).
 - ▶ CVE must be cleaned
 - ▶ CVE must be certified annually, or ever 6 months if no equipped with an exhaust alarm.

Active pharmaceutical ingredient (API): Any substance or mixture of substances intended to be used in the compounding of a preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans and animals or affecting the structure and function of the body.



Section 6. Equipment And Components

- ▶ The CVE must be cleaned as described in *Table 2* of the proposed revised chapter.



Section 6. Equipment And Components

- ▶ Components:
 - ▶ Must use qualified vendors to purchase
 - ▶ APIs must be manufactured by an FDA-registered facility
 - ▶ API must be accompanied by a valid certificate of analysis (COA)
 - ▶ COA includes the specifications and test results and shows that the API meets an official USP–NF monograph, if one exists, and any additional specifications required to appropriately use the API in preparing the CNSP
 - ▶ Ingredients other than APIs should be obtained from an FDA-registered facility
 - ▶ Ingredients that lack vendor expiration must **not** be used after 1 year from the date of receipt.
 - ▶ must be handled and stored in accordance with the manufacturer's instructions or per applicable laws and regulations of the regulatory jurisdiction.



Section 7. SOPs and Master Formulation And Compounding Records.

- ▶ Must establish and follow written **standard operating procedures** (SOPs)
- ▶ Must develop SOPs on all aspects of the compounding operation.
- ▶ All personnel who conduct or oversee compounding activities must be trained in the SOPs and are responsible for ensuring that they are followed.



Section 7. SOPs and Master Formulation And Compounding Records.

- ▶ Master Formulation Record must be prepared for each unique formulation of a CNSP.
- ▶ Any changes or alterations to the Master Formulation Record must be performed only by the **designated person**, and all changes must be documented.

Box 7-1 provides the proposed requirements for the master formulation record



Section 7. SOPs and Master Formulation And Compounding Records.

- ▶ Compounding Record is required for each CNSP.
- ▶ Each Compounding Record must be reviewed for completeness before the CNSP is released.

Box 7-2 provides the proposed details that must be included as part of the compounding record



Section 8. Release Testing

- ▶ Visually inspection is require prior to the release of any CNSP:
 - ▶ physical appearance is as expected.
 - ▶ checked for certain characteristics (e.g., emulsions for phase separation)
 - ▶ CNSP and labeling match compounding records
 - ▶ inspection of container–closure integrity (e.g., checking for leakage, cracks in the container, or improper seals)
- ▶ All checks and inspections, and any other tests necessary to ensure the quality of the CNSP (e.g., pH, assays), must be detailed in the facility's SOPs and completed before release.



Section 9. Labeling

- ▶ **Label:** A display of written, printed, or graphic matter on the immediate container of any article.
 - ▶ Assigned internal identification number (e.g., prescription or lot number)
 - ▶ Chemical and/or generic name(s), or active ingredient(s), and amounts or concentrations
 - ▶ Dosage form
 - ▶ Total amount or volume
 - ▶ Storage conditions
 - ▶ BUD
 - ▶ Indication that the preparation is compounded



Section 9. Labeling

- ▶ **Labeling:** All labels and other written, printed, or graphic matter that are 1) on any article or any of its containers or wrappers, or 2) accompanying such an article.
 - ▶ Route of administration
 - ▶ Any special handling instructions
 - ▶ Any warning statements that are applicable
 - ▶ Name, address, and contact information of the compounding facility if the CNSP is to be sent outside of the facility or healthcare system in which it was compounded



Section 10. Establishing Beyond-Use Dates

- ▶ **Expiration Date** = applies to conventionally manufactured drug products
- ▶ **Beyond use date (BUD)** = the date or time beyond which a CNSP must be discarded (**not** used). The date or time is determined from the date or time when the preparation was compounded.
- ▶ Parameters to consider when establishing a BUD
 - ▶ Chemical and physical stability
 - ▶ Compatibility of container-closure system
 - ▶ Degradation of container-closure system
 - ▶ Potential for microbial proliferation



Section 10. Establishing Beyond-Use Dates

- ▶ Establishing a BUD:
 - ▶ The day that the preparation is compounded is considered day 1.
 - ▶ If there is a *USP–NF* compounded preparation monograph for the CNSP, the BUD specified in the monograph **must** be used, unless a shorter BUD is required.



Section 10. Establishing Beyond-Use Dates

- ▶ Maximum BUD by Type of Preparation in the **absence** of CNSP-Specific Stability Information.
- ▶ **Must** be in a packaged in tight, light-resistant containers.

Type of Preparation	BUDs	Storage Temperature
Solid dosage forms (Capsules, tablets, granules, powders)	180d	Controlled room temperature
Preserved aqueous dosage forms	30d	Controlled room temperature
Non-preserved aqueous dosage $A_w > 0.6$ (emulsions, gels, creams, solutions, sprays, or suspensions)	14d	Refrigerator
Nonaqueous dosage forms $A_w \leq 0.6$ (suppositories, ointments, fixed oils, or waxes)	90d	Controlled room temperature

A_w = water activity



Section 10. Establishing Beyond-Use Dates

- ▶ USP <1112> APPLICATION OF WATER ACTIVITY DETERMINATION TO NONSTERILE PHARMACEUTICAL PRODUCTS



Section 10. Establishing Beyond-Use Dates

- ▶ Extension of the BUD:
 - ▶ **Max 180 day** with a stability study (published or unpublished) using a stability-indicating assay for the specific API, CNSP, **and** container-closure that will be used
 - ▶ Aqueous CNSP must first be tested for antimicrobial effectiveness at the end of the proposed BUD
- ▶ Shorting of a BUD:
 - ▶ **cannot** be extended past the expiration date or BUD of any component in the CNSP
 - ▶ APIs or ingredients known to be susceptible to decomposition



Section 11. Quality Assurance and Quality Control

- ▶ **Quality assurance (QA):** A set of written processes that, at a minimum, verifies, monitors, and reviews the adequacy of the compounding process.
- ▶ **Quality control (QC):** The sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CNSP.
- ▶ Must have a formal, written QA and QC program that establishes a system of adherence to procedures, prevention and detection of errors and other quality problems, and appropriate corrective actions when needed.



Section 12. CNSP Handling, Packaging, Storage, And Transport

- ▶ Packaging materials:
 - ▶ Maintain the physical and chemical integrity and stability of the CNSPs.
 - ▶ Must protect CNSPs from damage, leakage, contamination, degradation, and adsorption, while simultaneously protecting transport personnel from exposure.
- ▶ Storage:
 - ▶ Controlled room temperature area must be either monitored manually at least once daily on days that compounding is performed or by a continuous temperature recording device to determine.
- ▶ Shipping and Transporting:
 - ▶ Must have written SOPs that describe appropriate shipping containers, insulating materials, and packaging materials based on the chemical and physical characteristics of the CNSP.



Section 13. Complaint Handling And Adverse Event Reporting

- ▶ Must develop and implement SOPs for complaint receipt, acknowledgment, and handling.
- ▶ **Designated person** must review all complaints to determine whether the complaint indicates a potential quality problem with the CNSP.
- ▶ **Designated person** must review all reports of potential adverse drug events (ADR) involving a CNSP.
- ▶ An investigation is required if the ADR or complaint show a possible quality problem with a CNSP.



Section 14. Documentation

- ▶ All facilities where CNSPs are prepared must have and maintain written or electronic documentation to demonstrate compliance with this chapter.
- ▶ Must include, but is not limited to, the following:
 - ▶ Personnel training, competency assessment, and qualification records including corrective actions for any failures
 - ▶ Equipment records (e.g., calibration, verification, and maintenance reports)
 - ▶ Receipt of components
 - ▶ SOPs, Master Formulation Records, and Compounding Records
 - ▶ Release testing, including corrective actions for any failures
 - ▶ Information related to complaints and adverse events including corrective actions taken
- ▶ Records must be legible and stored in a manner that prevents their deterioration and/or loss



References:

- ▶ <https://www.usp.org>
- ▶ <https://www.usp.org/compounding/general-chapter-795>
- ▶ <https://www.usp.org/sites/default/files/usp/document/our-work/compounding/795-open-microphone-presentation.pdf>
 - ▶ Web recording:
<https://www.hapyak.com/portal/viewer/9cf36d6ce9585fdcda76c09851896b01>
- ▶ <https://www.usp.org/frequently-asked-questions/compounding>
- ▶ https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/usp-nf-notices/m7808_pre-post.pdf

Questions?

