<795> Pharmaceutical Compounding—Nonsterile Preparations

Type of Posting	Revision Bulletin
Posting Date	22–Nov–2019
Official Date	01–Dec–2019
Expert Committee	Compounding
Reason for Revision	Compliance—Postponement

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, USP is postponing the official date of Pharmaceutical Compounding—Nonsterile Preparations <795>.

After publication of the revised <795> on June 1, 2019, USP received appeals on certain provisions in <795>. In accordance with USP's Bylaws, the responsible Expert Committees worked with a sense of urgency to consider the information raised in the appeals and issued decisions on the appeals. As part of the formal USP appeals process, stakeholders who submitted appeals to the compounding chapters had the opportunity to request further review by an appointed Panel, and USP has received three (3) such requests on <795>.

In light of these appeals, and in accordance with our Bylaws, USP is **postponing the official date of <795> until further notice**. In the interim, the currently official version of <795> (last revised in 2014) will remain official. The decisions on the appeals to <795> do not foreclose the possibility of future revisions to this chapter.

Should you have any questions, please contact Jeanne Sun, Senior Manager, Healthcare Quality and Safety (CompoundingSL@usp.org).

Change to read:

▲⟨795⟩ PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS

The official date for this chapter is postponed until further notice. When the official date is reestablished, the period allowed for implementation will not be less than six months.

1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed when preparing compounded nonsterile preparations (CNSPs) for humans and animals. For purposes of this chapter, nonsterile compounding is defined as combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug or bulk drug substance to create a nonsterile medication.

The requirements in this chapter must be followed to minimize harm, including death, to human and animal 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 inappropriate quality.

Handling of nonsterile hazardous drugs (HDs) must additionally comply with *Hazardous Drugs—Handling in Healthcare Settings* ⟨800⟩.

1.1 Scope

CNSPS SUBJECT TO THE REQUIREMENTS IN THIS CHAPTER

CNSPs that must comply with this chapter include but are not limited to the following dosage forms:

- Solid oral preparations
- Liquid oral preparations
- Rectal preparations
- Vaginal preparations
- Topical preparations (i.e., creams, gels, ointments)
- Nasal and sinus preparations intended for local application (i.e., nasal sprays and nasal irrigation)
- Otic preparations

PRACTICES NOT SUBJECT TO THE REQUIREMENTS IN THIS CHAPTER

The following practices are not considered compounding and are not required to meet the requirements of this chapter:
Administration: Preparation of a single dose for a single patient when administration will begin within 4 hours of beginning the preparation is not required to meet the standards in this chapter.
Nonsterile radiopharmaceuticals: Compounding of nonsterile radiopharmaceuticals is not required to meet the standards in this chapter and is subject to the requirements in *Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging* ⟨825⟩.
Reconstitution: Reconstitution of a conventionally manufactured nonsterile product in accordance with the directions contained in the manufacturer approved labeling is not required to meet the standards in this chapter.
Repackaging: Repackaging of conventionally manufactured drug products is not required to meet the standards in this chapter (see *Good Repackaging Practices* ⟨1178⟩).
Splitting tablets: Breaking or cutting a tablet into smaller portions is not required to meet the standards in this chapter.

PERSONNEL AND SETTINGS AFFECTED

This chapter applies to all persons who prepare CNSPs and all places where CNSPs are prepared. This includes but is not limited to pharmacists, technicians, nurses, physicians, veterinarians, dentists, naturopaths, and chiropractors, in all places including but not limited to pharmacies, hospitals and other healthcare institutions, patient treatment sites, and physicians' or veterinarians' practice sites.

The compounding facility's leadership and all personnel involved in preparing, storing, packaging, and transporting CNSPs are responsible for 1) ensuring that the applicable practices and quality standards in this chapter are continually and consistently applied to their operations, and 2) proactively identifying and remedying potential problems within their operations. Personnel engaged in the compounding of CNSPs must also comply with laws and regulations of the applicable regulatory jurisdiction.

The compounding facility must designate one or more individuals to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of CNSPs. The responsibilities of the designated person(s) include but are not limited to:

- Overseeing a training program to ensure competency of personnel involved in compounding, handling, and preparing of CNSPs
- Selecting components
- Monitoring and observing compounding activities and taking immediate corrective action if deficient practices are observed
- Ensuring that standard operating procedures (SOPs) are fully implemented. The designated person(s) must ensure that follow-up is carried out if problems, deviations, or errors are identified
- Establishing, monitoring, and documenting procedures for the handling and storage of CNSPs and/or components of CNSPs

The designated person(s) must be identified in an SOP. If the compounding facility has only one person responsible for all of the compounding in the facility, then that person is the designated person.

2. PERSONNEL TRAINING AND EVALUATION

All personnel involved in the preparation and handling of CNSPs must be initially trained, must demonstrate competency, and must undergo refresher training every 12 months. Training and competency of personnel must be documented as described in *15. Documentation*.

A designated person must oversee a training program that describes the required training, the frequency of training, and the process for evaluating the competency of personnel involved in nonsterile compounding and handling of CNSPs. This program must equip personnel with knowledge and training in the required skills necessary to perform their assigned tasks.

Before beginning to prepare CNSPs independently, all compounding personnel must complete training and be able to demonstrate proficiency in the principles and hands-on skills of nonsterile manipulations for the type of compounding they will be performing. Proficiency must be demonstrated every 12 months in at least the following core competencies:

- Hand hygiene
- Garbing
- Cleaning and sanitizing

- Handling and transporting components and CNSPs
- Measuring and mixing
- Proper use of equipment and devices selected to compound CNSPs
- Documentation of the compounding process (e.g., Master Formulation Records and Compounding Records)

Steps in the training procedure must include the following:

- Read and understand this chapter, other applicable standards, and other relevant literature
- Understand and interpret Safety Data Sheets (SDSs) and, if applicable, Certificates of Analysis (COA)
- Read and understand procedures related to their compounding duties

A designated person must oversee the training of personnel. Training and observation may be performed by the designated person(s) or an assigned trainer. Personnel must be observed and guided throughout the training process. The personnel will then be expected to repeat the procedures independently, but under the direct supervision of the designated person(s) and/or trainer. Personnel will be permitted to perform the procedure without direct supervision only after independently demonstrating understanding and competency. Upon completion of the training program, the designated person(s) and/or trainer must document that the personnel has been trained and successfully completed competency assessments (see *15. Documentation*).

In addition to the initial and annual competency training and evaluation described in this section, a designated person should monitor and observe compounding activities and must take immediate corrective action if deficient practices are observed. SOPs must describe procedures for the monitoring and observing of compounding activities and personnel.

If the facility has only one person in the compounding operation, that person must document that they have obtained training and demonstrated competency, and they must comply with the other requirements of this chapter.

3. PERSONAL HYGIENE AND GARBING

Individuals entering the compounding area must maintain personal hygiene. Individuals must evaluate whether they have a personal risk of potentially contaminating the compounding environment and CNSP (e.g., personnel with rashes, recent tattoos or oozing sores, conjunctivitis, or active respiratory infection). Individuals must report these conditions to the designated person(s). The designated person(s) is responsible for evaluating whether these individuals should be excluded from working in compounding areas before their conditions have resolved because of the risk of contaminating the CNSP and the environment.

3.1 Personnel Preparation

Personnel engaged in compounding must maintain hand hygiene and maintain cleanliness required for the type of compounding performed.

Before entering the compounding area, compounding personnel must remove any items that are not easily cleanable and that might interfere with garbing. At a minimum, personnel must:

- Remove personal outer garments (e.g., bandanas, coats, hats, jackets)
- Remove all hand, wrist, and other exposed jewelry, including piercings that could interfere with the effectiveness of garbing or hand hygiene (e.g., watches, rings that may tear gloves)
- Remove earbuds or headphones

The designated person(s) may permit accommodations as long as the quality of the environment and CNSP will not be affected.

3.2 Hand Hygiene

Personnel must perform hand hygiene when entering the compounding area to compound as described in *Box 3-1*. Alcohol hand sanitizers alone are not sufficient.

Box 3-1. Hand Hygiene Procedures

- Wash hands and forearms up to the elbows with soap and water for at least 30 seconds.
- Dry hands and forearms to the elbows completely with disposable towels or wipers.
- Allow hands and forearms to dry thoroughly before donning gloves.

To minimize the risk of cross-contaminating other CNSPs and contaminating other objects (e.g., pens and keyboards), gloves should be wiped or replaced before beginning a CNSP with different components.

All gloves must be inspected for holes, punctures, or tears and must be replaced immediately if such defects are detected.

3.3 Garb and Glove Requirements

Gloves must be worn for all compounding activities. Other garb (e.g., shoe covers, head and facial hair covers, face masks, gowns) should be worn as needed for the protection of personnel from chemical exposures and for prevention of preparation contamination and must be appropriate for the type of compounding performed. The garbing requirements and frequency of changing the garb must be determined by the facility and documented in the facility's SOPs.

Garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing). Visibly soiled garb or garb with tears or punctures must be changed immediately.

If gowns are worn, they may be re-used if not soiled. If used, gloves, shoe covers, hair covers, facial hair covers, face masks, or head coverings may not be re-used and must be replaced with new ones. If used, non-disposable garb, such as goggles, should be cleaned and sanitized with 70% isopropyl alcohol before re-use.

4. BUILDINGS AND FACILITIES

4.1 Compounding Space

Space must be specifically designated for nonsterile compounding. The method of designation (e.g., visible perimeter) must be described in the facility's SOP. Other activities must not be occurring in the space at the same time as compounding. The compounding space must be well-lighted and must be maintained in a clean, orderly, and sanitary condition, and in a good state of repair. Carpet is not allowed in the compounding space. Surfaces should be resistant to damage by cleaning and sanitizing agents.

The space must provide for the orderly placement of equipment and materials to prevent mix-ups among components, containers, labels, in-process materials, and finished CNSPs. The space should be designed, arranged, and used in a way that minimizes cross-contamination from non-compounding areas.

4.2 Storage Area

Compounding personnel must monitor temperatures in storage area(s) either manually at least once daily on days that the facility is open or by a continuous temperature recording device to determine whether the temperature remains within the appropriate range for the CNSPs or components. The results of the temperature readings must be documented on a temperature log or stored in the continuous temperature recording device, and must be retrievable. All temperature monitoring equipment must be calibrated or verified for accuracy as recommended by the manufacturer or every 12 months if not specified by the manufacturer.

The compounding facility must adhere to SOPs to detect and prevent temperature excursions within storage area(s). When it is known that a CNSP or component has been exposed to temperatures either below or above the storage temperature limits for the CNSP or component, personnel must determine whether the CNSP or component integrity or quality has been compromised and, if so, the CNSP or component must be discarded.

All CNSPs, components, equipment, and containers must be stored off the floor and in a manner that prevents contamination and permits inspection and cleaning of the storage area(s).

4.3 Water Sources

A source of hot and cold water and an easily accessible sink must be available for compounding. The sink must be emptied of all items unrelated to compounding and cleaned when visibly soiled before being used to clean any equipment used in nonsterile compounding. The plumbing system must be free of defects that may contribute to the contamination of any CNSP. *Purified Water* (see *Water for Pharmaceutical Purposes* ⟨1231⟩), distilled water, or reverse osmosis water should be used for rinsing equipment and utensils.

5. CLEANING AND SANITIZING

Cleaning and sanitizing of the surfaces in the nonsterile compounding area(s) must occur on a regular basis at the minimum frequencies specified in *Table 1* or, if compounding is not performed daily, cleaning and sanitizing must be completed before initiating compounding. Cleaning and sanitizing must be repeated when spills occur and when surfaces are visibly soiled.

Cleaning and sanitizing agents must be selected and used with consideration of compatibilities, effectiveness, and to minimize the potential to leave residues.

If cleaning and sanitizing are performed as separate steps, cleaning must be performed first.

Table 1. Minimum Frequency for Cleaning and Sanitizing Surfaces in Nonsterile Compounding Area(s)

Site	Minimum Frequency
Work surfaces	• At the beginning and end of each shift, after spills, and when surface contamination is known or suspected • Clean and sanitize the work surfaces between compounding CNSPs with different components
Floors	Daily, after spills, and when surface contamination (e.g., splashes) is known or suspected
Walls	Every 3 months, after spills, and when surface contamination (e.g., splashes) is known or suspected
Ceilings	When visibly soiled and when surface contamination is known or suspected
Storage shelving	Every 3 months, after spills, and when surface contamination (e.g., splashes) is known or suspected

6. EQUIPMENT AND COMPONENTS

6.1 Equipment

The equipment and supplies used for compounding a CNSP must be suitable for the specific compounding process. Equipment surfaces that contact components must not be reactive, additive, or sorptive, and must not alter the quality of the CNSPs. Disposable or dedicated equipment may be used to reduce the chance of bioburden and cross-contamination.

Equipment must be stored in a manner to minimize the risk of contamination and must be located to facilitate its use, maintenance, and cleaning. Equipment and devices used in the compounding or testing of compounded preparations must be inspected prior to use and, if appropriate, verified for accuracy as recommended by the manufacturer and at the frequency recommended by the manufacturer, or at least every 12 months, whichever is more frequent. After compounding, the equipment must be cleaned to prevent cross-contamination of the next preparation.

Weighing, measuring, or otherwise manipulating components that could generate airborne chemical particles [e.g., active pharmaceutical ingredients (APIs), added substances, conventionally manufactured products] must be assessed to determine if these activities must be performed in closed system processing device to reduce the potential exposure to personnel or contamination of the facility or CNSPs. Examples of closed system processing devices include containment ventilated enclosures (CVEs), biological safety cabinets (BSCs), or single-use containment glove bags. The process evaluation must be carried out in accordance with the facility SOP and the assessment must be documented.

If a BSC or CVE is used, it must be certified every 12 months according to requirements such as the current Controlled Environment Testing Association (CETA), NSF International, or American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) guidelines, or other laws and regulations of the applicable regulatory jurisdiction.

If a CVE or other non-disposable device is used, it must be cleaned as described in *Table 2*.

Table 2. Minimum Frequency for Cleaning and Sanitizing Equipment in Nonsterile Compounding Area(s)

Site	Minimum Frequency
CVE	• At the beginning and end of each shift, after spills, and when surface contamination is known or suspected • Clean and sanitize the horizontal work surface of the CVE between compounding CNSPs with different components
Other devices and equipment used in compounding operations	• Before first use and thereafter in accordance with the manufacturer's recommendations • If no recommendation is available, after compounding CNSPs with different components

6.2 Components

The compounding facility must have written SOPs for the selection and inventory control of all components from receipt to use in a CNSP.

SDSs must be readily accessible to all personnel working with APIs and added substances located in the compounding facility. Personnel must be instructed on how to retrieve and interpret needed information.

COMPONENT SELECTION

A designated person must be responsible for selecting components to be used in compounding.

APIs:

- Must comply with the criteria in the *USP–NF* monograph, if one exists
- Must have a COA that includes the specifications and test results and shows that the API meets the specifications
- In the United States, must be obtained from an FDA-registered facility
- Outside of the United States, must comply with laws and regulations of the applicable regulatory jurisdiction

All components other than APIs:

- Should be accompanied by a COA that verifies that the component meets the criteria in the *USP–NF* monograph, if one exists, and any additional specifications for the component
- In the United States, should be obtained from an FDA-registered facility
    - If it cannot be obtained from an FDA-registered facility, the designated person(s) must select a component that is suitable for the intended use
- Outside of the United States, must comply with laws and regulations of the applicable regulatory jurisdiction

COMPONENT RECEIPT

Upon receipt of components other than conventionally manufactured products, the COA must be reviewed to ensure that the component has met the acceptance criteria in a *USP-NF* monograph, if one exists. For components other than conventionally manufactured products, information including the receipt date, quantity received, supplier name, lot number, expiration date, and results of any in-house or third-party testing performed must be documented.

The date of receipt by the compounding facility must be clearly and indelibly marked on each component package that lacks a vendor expiration date. Packages of components (i.e., API and added substances) that lack a vendor's expiration date must not be used by the compounding facility after 3 years from the date of receipt. A shorter expiration date must be assigned

according to *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩, *9.3 Components, Component Receipt* if the same component container is also used in sterile compounding or if the ingredient is known to be susceptible to degradation.

For each use, the lot must be examined for evidence of deterioration and other aspects of unacceptable quality. Once removed from the original container, components not used in compounding (e.g., excess after weighing) should be discarded and not returned to the original container to minimize the risk of contaminating the original container.

Any component found to be of unacceptable quality must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal. Any other lots of that component from that vendor must be examined to determine whether the other lots have the same defect.

COMPONENT EVALUATION BEFORE USE

Before use, compounding personnel must visually re-inspect all components. Packages must be inspected to detect container breaks, looseness of the cap or closure, or deviation from the expected appearance or texture of the contents that might have occurred during storage.

Compounding personnel must ascertain before use that components are of the correct identity based on the labeling and have been stored under required conditions in the facility.

If the correct identity, strength, purity, and quality of components intended for preparation of CNSPs cannot be confirmed (e.g., containers with damaged or incomplete labeling), they must be immediately rejected. If they are not immediately discarded, they must be clearly labeled as rejected, and segregated to prevent their use before disposal.

COMPONENT HANDLING

All components must be handled in accordance with the manufacturer's instructions or per laws and regulations of the applicable regulatory jurisdiction. The handling must minimize the risk of contamination, mix-ups, and deterioration (e.g., loss of identity, strength, purity, and quality).

COMPONENT SPILL AND DISPOSAL

The facility must maintain chemical hazard and disposal information (e.g., SDSs) and must review and update its chemical hazard and disposal information every 12 months. The chemical hazard and disposal information (e.g., SDSs) must be made accessible to compounding personnel.

The facility must have an SOP for the management of nonhazardous component spills and disposal. If required by the SOP, these activities must be documented and corrective action taken.

The facility must have a readily accessible spill kit in the compounding area. The contents of the spill kit should be affixed to the packaging of the spill kit if not readily visible on the manufacturer's label.

All personnel who may be required to remediate a spill must receive training in spill management of chemicals used and stored at the compounding facility. Refresher training must be conducted every 12 months and documented for all personnel who may be required to clean up a spill.

Waste must be disposed of in accordance to laws and regulations of the applicable regulatory jurisdiction. The disposal of components must comply with laws and regulations of the applicable regulatory jurisdiction. For information on the handling of HDs, see ⟨800⟩.

7. MASTER FORMULATION AND COMPOUNDING RECORDS

7.1 Creating Master Formulation Records

A Master Formulation Record is a detailed record of procedures that describes how the CNSP is to be prepared. A Master Formulation Record must be created for each unique formulation of a CNSP. CNSPs are prepared according to the Master Formulation Record and the preparation information is documented on a Compounding Record (see *7.2 Creating Compounding Records*). Any changes or alterations to the Master Formulation Record must be approved and documented according to the facility's SOP. *Box 7-1* lists the information that must be included in a Master Formulation Record.

Box 7-1. Master Formulation Records

A Master Formulation Record must include at least the following information:

- Name, strength or activity, and dosage form of the CNSP
- Identities and amounts of all components
  - If applicable, relevant characteristics of components (e.g., particle size, salt form, purity grade, solubility)
- Container–closure system(s)
- Complete instructions for preparing the CNSP, including equipment, supplies, and a description of the compounding steps
- Physical description of the final CNSP
- Assigned beyond-use date (BUD) and storage requirements
- Reference source to support the assigned BUD and storage requirements
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of API
- Labeling requirements (e.g., shake well)
- Quality control (QC) procedures (e.g., pH testing, visual inspection) and expected results
- Other information needed to describe the compounding process and ensure repeatability (e.g., adjusting pH, temperature)

7.2 Creating Compounding Records

A Compounding Record documents the compounding of each CNSP. A Compounding Record must be created for all CNSPs. Each Compounding Record must be reviewed for completeness before the CNSP is released. The identifier of the person completing the review and the date of review must be documented on the Compounding Record. The Compounding Record must permit traceability of all components in the case of a recall or known quality issue. The Master Formulation Record can be used as the basis for preparing the Compounding Record. For example, a copy of the Master Formulation Record can be made that contains spaces to record the information needed to complete the Compounding Record. *Box 7-2* lists the information that must be included in a Compounding Record.

Box 7-2. Compounding Records

Compounding Records must include at least the following information:

- Name, strength or activity, and dosage form of the CNSP
- Date and time of preparation of the CNSP
- Assigned internal identification number (e.g., prescription, order, or lot number)
- A method to identify the individuals involved in the compounding process and verifying the final CNSP
- Name, vendor or manufacturer, lot number, and expiration date of each component
- Weight or measurement of each component
- Total quantity compounded
- Assigned BUD and storage requirements
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of API
- Physical description of the final CNSP
- Results of quality control procedures (e.g., pH testing, visual inspection)
- Master Formulation Record reference for the CNSP

8. RELEASE INSPECTIONS

At the completion of compounding and before release and dispensing, the CNSP must be visually inspected to determine whether the physical appearance is as expected. Inspections must also confirm that the CNSP and its labeling match the Compounding Record and the prescription or medication order. Some CNSPs, as noted in their Master Formulation Record, also must be visually checked for certain characteristics (e.g., emulsions must be checked for phase separation). All checks and inspections, and if required, any other tests necessary to ensure the quality of the CNSP must be detailed in the facility's Master Formulation Records. Checks and inspections must be documented. Additional quality assurance (QA) and quality control activities are described in *12. Quality Assurance and Quality Control*. Pre-release inspection also must include a visual inspection of container–closure integrity (e.g., checking for leakage, cracks in the container, or improper seals). CNSPs with observed defects must be immediately discarded, or marked and segregated from acceptable units in a manner that prevents them from being released or dispensed.

9. LABELING

The term labeling designates all labels and other written, printed, or graphic matter on the immediate container or on, or in, any package or wrapper in which the article is enclosed, except any outer shipping container. The term label designates the part of the labeling on the immediate container. See *Labeling* ⟨*7*⟩.

Every dispensed CNSP must be labeled with adequate, legible identifying information to prevent errors during storage, dispensing, and use. All labeling must be in compliance with laws and regulations of the applicable regulatory jurisdiction.

The label on each immediate container of the CNSP must, at a minimum, display the following information:

- Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
- Active component(s), and amounts, activities, or concentrations
- Dosage form
- Amount or volume in each container
- Storage conditions if other than controlled room temperature
- BUD

The labeling on the CNSP should display the following information:

- Route of administration
- Indication that the preparation is compounded
- 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

Labeling operations must be controlled to prevent labeling errors and CNSP mix-ups. A final check must be conducted to verify that the correct label has been affixed to the finished CNSP. All labels must also comply with laws and regulations of the applicable regulatory jurisdiction.

10. ESTABLISHING BEYOND-USE DATES

10.1 Terminology

Each CNSP label must state the date, or the hour and date, beyond which the preparation cannot be used and must be discarded (i.e., the BUD). BUDs for CNSPs are calculated in terms of hours, days, or months.

BUDs and expiration dates are not the same. An expiration date identifies the time during which a conventionally manufactured drug product, active ingredient, or added substance can be expected to meet the requirements of a compendial monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions. The expiration date limits the time during which a conventionally manufactured product, API, or added substance may be dispensed or used (see *Labeling* ⟨7⟩*, Labels and Labeling for Products in Other Categories, Expiration Date and Beyond-Use Date*). Expiration dates are assigned by manufacturers based on analytical and performance testing of the sterility, chemical and physical stability, and packaging integrity of the product. Expiration dates are specific for a particular formulation in its container and at stated exposure conditions of illumination and temperature.

10.2 Parameters to Consider in Establishing a BUD

BUDs for CNSPs should be established conservatively to ensure that the preparation maintains its required characteristics to minimize the risk of contamination or degradation.

When establishing a BUD for a CNSP, it is critical that personnel carefully consider the possible ways that the physical or chemical characteristics of the CNSP could change over time. The following factors must be considered:

- The chemical and physical stability properties of the API and any added substances in the preparation (e.g., if the API and added substances in the preparation are known to degrade over time and/or under certain storage conditions, which would reduce the strength of the preparation and/or produce harmful impurities)
- The compatibility of the container–closure system with the finished preparation (e.g., leachables, interactions, adsorption, and storage conditions)
- Degradation of the container–closure system, which can lead to a reduction in integrity of the CNSP
- The potential for microbial proliferation in the CNSP

10.3 Establishing a BUD for a CNSP

The BUDs indicate the days after the CNSP is prepared and beyond which the CNSP must not be used. The day that the preparation is compounded is considered Day 1. The BUDs in *Table 3* are based on the ability of the CNSP to maintain chemical and physical stability and to suppress microbial growth. *Table 3* represents the maximum BUDs for CNSPs that are packaged in tight, light-resistant containers unless conditions under *10.4 CNSPs Requiring Shorter BUDs* or *10.5 Extending BUDs for CNSPs* apply.

The aqueous and nonaqueous dosage forms in *Table 3* are defined based on the water activity (Aw) of the most similar drug product described in *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* ⟨1112⟩. In general, the use of Aw aids in assessing the susceptibility of CNSPs to microbial contamination and the potential for API degradation due to hydrolysis. Reduced Aw greatly assists in the prevention of microbial proliferation in conventionally manufactured products and is expected to convey the same benefit to CNSPs. The list of manufactured products in *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* ⟨1112⟩, *Table 2* is not exhaustive. However, it provides guidance on the Aw value of a particular CNSP and can assist personnel in determining the BUD by dosage form based on *Table 3*.

CNSPs with an Aw > 0.6 should contain suitable antimicrobial agents to protect against bacteria, yeast, and mold contamination from proliferation if inadvertently introduced during or after the compounding process. When antimicrobial preservatives are clinically contraindicated in a CNSP, storage of the preparation in a refrigerator is required if such storage does not change the physical or chemical properties of the CNSP (i.e., precipitation).

Table 3. Maximum BUD by Type of Preparation in the Absence of a *USP-NF* Compounded Preparation Monograph or CNSP-Specific Stability Information

Type of Preparation	BUDs (days)	Storage Temperature[a]
Non-preserved aqueous dosage forms[b]	14	Refrigerator
Preserved aqueous dosage forms[b]	35	Controlled room temperature or refrigerator
Nonaqueous dosage forms[c]	90	Controlled room temperature or refrigerator
Solid dosage forms[d]	180	Controlled room temperature or refrigerator

[a] See *Packaging and Storage Requirements* ⟨659⟩.
[b] An aqueous preparation is one that has an Aw of > 0.6 (e.g., emulsions, gels, creams, solutions, sprays, or suspensions).
[c] Any preparation other than solid dosage forms that have a reduced Aw of ≤0.6 (e.g., suppositories, ointments, fixed oils, or waxes).
[d] Capsules, tablets, granules, powders.

10.4 CNSPs Requiring Shorter BUDs

A shorter BUD must be established under the following circumstances:

- If the API or any other components in the CNSP have an expiration date that is earlier than the BUD that could be assigned from *Table 3*, the expiration date supersedes the BUD and must be the assigned shortest date
- If the CNSP includes components from conventionally manufactured product(s), the BUD of the CNSP must not exceed the shortest remaining expiration date of any of those conventionally manufactured product(s)
- If the CNSP includes components from other compounded preparations, the BUD of the final CNSP must not exceed the shortest remaining BUD of any of those compounded preparations
- If the formulation is known to require a shorter BUD

10.5 Extending BUDs for CNSPs

CNSPS WITH A *USP–NF* MONOGRAPH

If there is a *USP–NF* compounded preparation monograph for the CNSP, the BUD must not exceed the BUD specified in the monograph.

CNSPS WITH STABILITY INFORMATION

The BUDs specified in *Table 3* for aqueous dosage forms and nonaqueous dosage forms may be extended up to maximum of 180 days if there is a stability study (published or unpublished) using a stability-indicating assay for the API(s), CNSP, and type of container–closure that will be used.

If the BUD of the CNSP is extended beyond the BUDs in *Table 3*, an aqueous CNSP should be tested for antimicrobial effectiveness (see *Antimicrobial Effectiveness Testing* ⟨51⟩). The compounder may rely on 1) antimicrobial effectiveness testing that is conducted (or contracted for) once for each formulation in the particular container–closure system in which it will be packaged or 2) antimicrobial effectiveness testing results provided by an FDA-registered facility or published in peer-reviewed literature sources if the CNSP formulation (including any preservative) and container–closure system are exactly the same as those tested unless a bracketing study is performed. Antimicrobial effectiveness testing may be performed on a low concentration and a high concentration of the active ingredient in the formulation to establish preservative effectiveness across various strengths of the same formulation (e.g., bracketing). The concentration of all other ingredients (including preservatives) must be the same throughout the bracketing study.

11. SOPS

Facilities preparing CNSPs 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.

One or more person(s) must be designated to ensure that SOPs are fully implemented. The designated person(s) must ensure that follow-up occurs if problems, deviations, or errors are identified.

12. QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance and quality control programs are necessary to ensure that consistently high-quality CNSPs are prepared. QA is a system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards. QC is the sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CNSP. See *Quality Assurance in Pharmaceutical Compounding* ⟨1163⟩.

A facility's QA and QC programs must be formally established and documented in SOPs that ensure that all aspects of the preparation of CNSPs are conducted in accordance with this chapter and laws and regulations of the applicable regulatory jurisdiction. A designated person must ensure that the facility has formal, written QA and QC programs that establish a system of:

1. Adherence to procedures
2. Prevention and detection of errors and other quality problems
3. Evaluation of complaints and adverse events
4. Appropriate investigations and corrective actions

The SOPs must describe the roles, duties, and training of the personnel responsible for each aspect of the QA program. Designated person(s) responsible for the QA program must have the training, experience, responsibility, and authority to perform these duties. The overall QA and QC program must be reviewed at least once every 12 months by the designated person(s). The results of the review must be documented and appropriate action must be taken if needed.

13. CNSP PACKAGING AND TRANSPORTING

13.1 Packaging of CNSPs

SOPs must describe packaging of CNSPs. Personnel should select and use packaging materials that will maintain the physical and chemical integrity and stability of the CNSPs. Packaging materials must protect CNSPs from damage, leakage, contamination, and degradation, while simultaneously protecting personnel from exposure.

13.2 Transporting CNSPs

If transporting CNSPs, the facility must have written SOPs to describe the mode of transportation, any special handling instructions, and whether temperature monitoring devices are needed.

14. COMPLAINT HANDLING AND ADVERSE EVENT REPORTING

Compounding facilities must develop and implement SOPs for complaint and adverse event report receipt, acknowledgment, and handling and designate one or more person(s) to be responsible for handling them. Complaints may include concerns or reports on the quality and labeling of, or possible adverse reactions to, a specific CNSP.

14.1 Complaint Handling

The designated person(s) must ensure that all complaints are reviewed to determine whether the complaint indicates a potential quality problem with the CNSP. If it does, a thorough investigation into the cause of the problem must be initiated and completed. The investigation must consider whether the quality problem extends to other CNSPs. Corrective action, if necessary, must be implemented for all potentially affected CNSPs. Consider whether to initiate a recall of potentially affected CNSPs and whether to cease nonsterile compounding processes until all underlying problems have been identified and corrected.

A readily retrievable written or electronic record of each complaint must be kept by the facility, regardless of the source of the complaint (e.g., e-mail, telephone, mail). The record must contain the name of the complainant or unique identifier, the date the complaint was received, the nature of the complaint, and the response to the complaint. In addition, to the extent that the information is known, the following should be recorded: the name and strength of the CNSP, the prescription or medication order number, and the lot number, if one is assigned.

The record must also include the findings of any investigation and any follow-up. Records of complaints must be easily retrievable for review and evaluation for possible trends and must be retained in accordance with the record-keeping requirements in *15. Documentation*. A CNSP that is returned in connection with a complaint must be quarantined until it is destroyed after completion of the investigation and in accordance with laws and regulations of the applicable regulatory jurisdiction.

14.2 Adverse Event Reporting

The designated person(s) must ensure that reports of potential adverse events involving a CNSP are reviewed. If the investigation into an adverse event reveals a quality problem with a CNSP that is likely to affect other patients, those patients and prescribers potentially affected must be informed. The designated person(s) must review all adverse event reports as part of the QA and QC programs (see *12. Quality Assurance and Quality Control*). Adverse events must be reported in accordance with facility SOPs and all laws and regulations of the applicable regulatory jurisdiction. In addition, adverse events associated with a CNSP should be reported to the FDA through the MedWatch program for human drugs and through Form FDA 1932a for animal drugs.

15. DOCUMENTATION

All facilities where CNSPs are prepared must have and maintain written or electronic documentation to demonstrate compliance with the requirements in this chapter. This documentation must include, but is not limited to, the following:

- Personnel training, competency assessments, and corrective actions for any failures
- Equipment records (e.g., calibration, verification, and maintenance reports)
- COA
- Receipt of components
- SOPs, Master Formulation Records, and Compounding Records
- Release inspection and testing records
- Information related to complaints and adverse events including corrective actions taken
- Results of investigation and corrective actions

Documentation must comply with all laws and regulations of the applicable regulatory jurisdiction. Records must be legible and stored in a manner that prevents their deterioration and/or loss. All required compounding records for a particular CNSP (e.g., Master Formulation Record, Compounding Record, and release inspection and testing results) must be readily retrievable

for at least 3 years after preparation or as required by the laws and regulations of the applicable regulatory jurisdiction, whichever is longer.

GLOSSARY

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.

Added substances: Ingredients that are necessary to compound a preparation but are not intended or expected to cause a pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded preparation. The term is used synonymously with the terms inactive ingredients, excipients, and pharmaceutical ingredients.

Biological safety cabinet (BSC): A ventilated cabinet which may be used for compounding. These cabinets divided into three general classes (Class I, Class II, and Class III). Class II BSCs are further divided into types (Type A1, Type A2, Type B1, and Type B2).

Certificate of Analysis (COA): A report from the supplier of a component, container, or closure that accompanies the supplier's material and contains the specifications and results of all analyses and a description of the material.

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.

Component: Any ingredient used in the compounding of a preparation, including any active ingredient, added substance, or conventionally manufactured product.

Compounded nonsterile preparation (CNSP): A preparation intended to be nonsterile created by combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering of a drug or bulk drug substance.

Compounder: Personnel trained to compound preparations.

Compounding: The process of combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug or bulk drug substance to create a nonsterile medication.

Compounding area: A space that is specifically designated for nonsterile compounding. A visible perimeter should establish the boundaries of the nonsterile compounding area.

Container–closure system: Packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection.

Containment glove bag: A single-use disposable glove bag that is capable of containing airborne chemical particles.

Containment ventilated enclosure (CVE): A full or partial enclosure that uses ventilation principles to capture, contain, and remove airborne contaminants through high-efficiency particulate air (HEPA) filtration and to prevent their release into the work environment.

Conventionally manufactured product: A pharmaceutical dosage form, usually the subject of an FDA-approved application that is manufactured under current good manufacturing practice conditions.

Designated person(s): One or more individuals assigned to be responsible and accountable for the performance and operation of the facility and personnel for the preparation of CNSPs.

Hazardous drug (HD): Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low dose in humans or animals, genotoxicity, or new drugs that mimic existing HDs in structure or toxicity. See ⟨800⟩.

Label: A display of written, printed, or graphic matter on the immediate container of any article.

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.

Purified Water: The minimal quality of source water for the production of Purified Water is drinking water whose attributes are prescribed by the US Environmental Protection Agency (EPA), the EU, Japan, or the World Health Organization (WHO). This source water may be purified using unit operations that include deionization, distillation, ion exchange, reverse osmosis, filtration, or other suitable purification procedures. (See *Water for Pharmaceutical Purposes* ⟨1231⟩*, 3. Waters Used for Pharmaceutical Manufacturing and Testing Purposes, 3.1 Bulk Monographed Waters and Steam, 3.1.1 Purified Water*.)

Preservative: A substance added to inhibit microbial growth.

Quality assurance (QA): A system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards.

Quality control (QC): The sampling, testing, and documentation of results that, taken together, ensure that specifications have been met before release of the CNSP.

Reconstitution: The process of adding a diluent to a conventionally manufactured product to prepare a solution or suspension.

Release inspection and testing: Visual inspection and testing performed to ensure that a preparation meets appropriate quality characteristics.

Sanitizing agent: An agent for reducing, on inanimate surfaces, the number of all forms of microbial life including fungi, viruses, and bacteria.

Specification: The tests, analytical methods, and acceptance criteria to which an API or other components, CNSP, container–closure system, equipment, or other material used in compounding CNSPs must conform to be considered acceptable for its intended use.

Stability: The extent to which a product or preparation retains physical and chemical properties and characteristics within specified limits throughout its expiration or BUD.

APPENDIX

Acronyms

API(s)	Active pharmaceutical ingredient(s)
ASHRAE	American Society of Heating, Refrigerating, and Air-Conditioning Engineers
Aw	Water activity
BSC(s)	Biological safety cabinet(s)
BUD(s)	Beyond-use date(s)
CETA	Controlled Environment Testing Association
CNSP(s)	Compounded nonsterile preparation(s)
COA	Certificate(s) of Analysis
CVE	Containment ventilated enclosure
FDA	Food and Drug Administration
HD(s)	Hazardous drug(s)
QA	Quality assurance
QC	Quality control
SDS(s)	Safety Data Sheet(s)
SOP(s)	Standard operating procedure(s)▲ (Postponed on 1-Dec-2019)