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⟨795⟩ PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS

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▲1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed for the preparation of 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 product or bulk drug substance to create a nonsterile preparation.

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

1.1.1 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, and ointments)
- Nasal and sinus preparations intended for local application (i.e., nasal sprays and nasal irrigation)
- Otic preparations (excluding use in perforated eardrums)

1.1.2 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. Handling of nonsterile HDs should additionally comply with ⟨800⟩. Refer to facility SOPs for additional safe practices (e.g., labeling).

- *Nonsterile radiopharmaceuticals:* Compounding of nonsterile radiopharmaceuticals 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
- *Repackaging:* Repackaging of conventionally manufactured drug products (see *Good Repackaging Practices* ⟨1178⟩ for recommendations)
- *Splitting tablets:* Breaking or cutting a tablet into smaller portions
- *Administration:* Preparation of a single dose for a single patient when administration will begin within 4 h. This includes crushing a tablet(s) or opening a capsule(s) to mix with food or liquids to facilitate patient dosing.

1.1.3 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, dispensing, 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 and dispensing of CNSPs must also comply with laws and regulations of the applicable regulatory jurisdiction.

1.1.4 Oversight by designated person(s): 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 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 the facility's SOPs. If the compounding facility has only one person responsible for all compounding in the facility, then that person is the designated person.

2. PERSONNEL TRAINING AND EVALUATION

All personnel who compound or have direct oversight of compounding CNSPs must be initially trained and qualified by demonstrating knowledge and competency according to the requirements in this section (*2. Personnel Training and Evaluation*) before being allowed to perform their job functions independently.

Designated person(s) are responsible for creating and implementing a training program that describes the required training, the frequency of training, and the process for evaluating the competency of personnel. This program must equip personnel with knowledge and training in the required skills necessary to perform their assigned tasks. Personnel who compound or have direct oversight of compounding personnel must complete training initially and at least every 12 months in appropriate compounding principles and practices as described in this section. Other personnel, who do not compound and only perform functions such as in-process checks, final verification, or dispensing of CNSPs, must undergo training as required by the facility's SOPs.

Training and competency of personnel must be documented as described in *14. Documentation*.

Before beginning to compound CNSPs independently or have direct oversight of compounding personnel, personnel must complete training and be able to demonstrate knowledge of principles and competency of skills for performing nonsterile manipulations as applicable to their assigned tasks. Knowledge and competency must be demonstrated initially and at least 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., *7. Master Formulation and Compounding Records*)

Steps in the training procedure must include the following:

- Understand the requirements in this chapter
- Understand and interpret safety data sheets (SDSs) and, if applicable, certificates of analysis (COA)
- Read and understand procedures related to their compounding duties

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 while under the direct supervision of the designated person(s) and/or assigned 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 assigned trainer must document that personnel have been trained and successfully completed competency assessments (see *14. Documentation*).

In addition to the initial and annual competency training and evaluation described in this section, the designated person(s) should monitor and observe compounding activities and must take immediate corrective action if deficient practices are observed. Facility SOPs must describe procedures for monitoring and observing 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 appropriate 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, oozing sores, conjunctivitis, or active respiratory infection). Individuals must report these conditions to the designated person(s). Because of the risk of contaminating the CNSP and the environment, the designated person(s) is responsible for evaluating whether these individuals should be excluded from working in compounding areas until their conditions have resolved.

3.1 Personnel Preparation

Personnel engaged in compounding must maintain appropriate hand hygiene and maintain appropriate 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, and 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 or rings that may tear gloves)
- Remove earbuds or headphones

The designated person(s) may permit accommodations provided that the quality of the environment and CNSP will not be affected. All accommodations should be documented.

3.2 Hand Hygiene

Personnel must perform procedures necessary for appropriate hand hygiene when entering the compounding area to compound as described in *Box 1*.

The use of alcohol-based hand rub alone is not sufficient.

Box 1. Hand Hygiene Procedures

- Wash hands with soap and water for at least 30 s
- Dry hands completely with disposable towels or wipers
- Don 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 that has 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 or hair covers, facial hair covers, face masks, and gowns) must be appropriate for the type of compounding performed and should be worn as needed for the protection of personnel from chemical exposures and for prevention of CNSP contamination. Garbing requirements and frequency of changing garb must be determined by the facility and documented in the facility's SOPs.

Garb must be replaced immediately if it becomes visibly soiled or if its integrity is compromised. All gloves must be inspected for holes, punctures, or tears and must be replaced immediately if such defects are detected. Garb must be stored in a manner that minimizes contamination (e.g., away from sinks to avoid splashing).

Garb should be removed when leaving the compounding area. When personnel exit the compounding area, garb, except for gowns, should be discarded. Disposable garb must not be laundered. If gowns are worn, they may be reused if not damaged or soiled. If gowns are to be reused, they must remain in the compounding area, and should only be reused during the same shift. The facility's SOPs must describe cleaning and sanitization procedures for reusing goggles, respirators, and other reusable equipment.

If compounding an HD, appropriate personal protective equipment (PPE) must be worn and disposed of in accordance with ⟨800⟩.

4. BUILDINGS AND FACILITIES

4.1 Compounding Area

An area must be designated for nonsterile compounding. The method of designation must be described in the facility's SOPs. Other activities must not be occurring in the compounding area at the same time as compounding. The compounding area must be well lit and must be maintained in a clean, orderly, sanitary condition and in a good state of repair. There should not be carpet in the compounding area.

The compounding area 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 area should be designed, arranged, and used in a way that minimizes cross contamination from noncompounding areas.

4.2 Storage Area

Compounding personnel must monitor temperatures in the storage area(s) either manually at least once daily on days that the facility is open, or continuously with a temperature recording device to ensure the temperature remains within the appropriate range for the CNSPs and 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 reduce the risk of temperature excursions within the 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 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. The sink must be emptied of all items unrelated to compounding and must be cleaned if 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⟩, 3.1.1 Purified Water), distilled water, or reverse osmosis water should be used for rinsing equipment and utensils.

5. CLEANING AND SANITIZING

Cleaning and sanitizing 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. Applicable cleaning and sanitizing must be documented daily on days when compounding occurs.

Surfaces should be resistant to damage by cleaning and sanitizing agents. Floors in the compounding area should be easily cleanable and should not be porous or particle generating.

Cleaning and sanitizing agents must be selected and used with consideration of compatibilities, effectiveness, and minimal 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 in Nonsterile Compounding Area(s)—Surfaces

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

6. EQUIPMENT AND COMPONENTS

6.1 Equipment

The equipment and components 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 CNSP. Disposable or dedicated equipment may be used to reduce the chance of bioburden and cross contamination.

Equipment must be stored in a manner that minimizes the risk of contamination and must be located to facilitate equipment 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 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, and conventionally manufactured products) must be evaluated to determine if these activities must be performed in a 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), and single-use containment glove bags. The process evaluation must be carried out in accordance with the facility's SOPs, and the assessment must be documented.

If a CVE or BSC is used, it must be certified at least every 12 months according to manufacturer specifications or other laws and regulations of the applicable regulatory jurisdiction.

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

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

Site	Minimum Frequency
CVE	• At the beginning and end of each shift on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspected • Clean and sanitize the horizontal work surface of the CVE between compounding CNSPs with different components
BSC	• At the beginning and end of each shift on days when compounding occurs, after spills, and when surface contamination (e.g., from splashes) is known or suspected • Clean and sanitize the horizontal work surface of the BSC between compounding CNSPs with different components • Clean and sanitize under the work surface at least monthly
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, between 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 components located in the compounding facility. Personnel must be instructed on how to retrieve and interpret needed information.

6.2.1 Component selection: Designated person(s) 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 specifications (e.g., compendial requirements for quality) and test results for the component that show the API meets expected quality
- In the United States, must be manufactured by an FDA-registered facility
- Outside of the United States, must comply with the 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 manufactured by an FDA-registered facility (If a component 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 the laws and regulations of the applicable regulatory jurisdiction

Water:

- *Purified Water* or better quality, e.g., *Sterile Water for Irrigation*, must be used for compounding nonsterile drug preparations when formulations indicate the inclusion of water

6.2.2 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 an appropriate *USP–NF* monograph, if one exists. The following information must be documented (see *14. Documentation*) according to the facility's SOPs: receipt date, quantity received, supplier name, lot number, expiration date, and results of any in-house or third-party testing performed.

For all components that lack a vendor expiration date, the date of receipt by the compounding facility must be clearly and indelibly marked on each packaging system. Packaging systems 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⟩, 9.3.2 Component receipt* if the same component container is also used in sterile compounding or if the ingredient is known to be susceptible to degradation.

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 the same vendor must be examined to determine whether the other lots have the same defect.

6.2.3 Component evaluation before use: Before use, compounding personnel must visually re-inspect all components. Each packaging system must be inspected to detect any container breakage, 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 identity, strength, purity, and quality of components intended for preparation of CNSPs cannot be verified (e.g., containers with damaged or incomplete labeling), the components must be immediately rejected. 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.

6.2.4 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, or quality). For each use, the lot must be examined for evidence of deterioration and other aspects of unacceptable quality. Once removed from the original container, any component 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.

6.2.5 Component spill and disposal: The facility must maintain current chemical hazard and disposal information (e.g., SDSs). Such information must be made accessible to compounding personnel.

The management and documentation of nonhazardous component spills and disposal must be described in the facility's SOPs.

The facility must have a readily accessible spill kit in the compounding area.

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. Training must be conducted at least every 12 months and documented for all personnel who may be required to clean up a spill.

Waste of any component must be disposed of in accordance 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 (MFR) is a detailed record of procedures that describes how the CNSP is to be prepared. An MFR must be created for each unique formulation of a CNSP. CNSPs are prepared according to the MFR, and the details of each preparation are documented on a compounding record (see *7.2 Creating Compounding Records*). Any changes or alterations to the MFR must be approved and documented according to the facility's SOP. See *Box 2* for information that must be included in an MFR.

Box 2. Master Formulation Record

An MFR 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 description of compounding steps
- Physical description of the final CNSP
- Beyond-use date (BUD) and storage requirements
- Reference source to support the assigned BUD
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of the API(s)
- 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 (CR) documents the compounding of each CNSP. A CR must be created for all CNSPs. Each CR must be reviewed for completeness before the CNSP is released. The name or other unique identifier of the person completing the review and the date of the review must be documented on the CR. The CR must permit traceability of all components in the case of a recall or known quality issue. The MFR can be used as the basis for preparing the CR. For example, a duplicate can be made of the MFR with blank fields for recording the information necessary to complete the CR. See *Box 3* for information that must be included in a CR.

Box 3. Compounding Record

A CR must include at least the following information:

- Name, strength or activity, and dosage form of the CNSP
- Date—or 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 individuals verifying the final CNSP
- Name, vendor or manufacturer, lot number, and expiration date of each component

- Weight or measurement of each component
- Total quantity of the CNSP compounded
- Assigned beyond-use date (BUD) and storage requirements
- If applicable, calculations to determine and verify quantities and/or concentrations of components and strength or activity of the API(s)
- Physical description of the final CNSP
- Results of quality control procedures (e.g., pH testing and visual inspection)
- MFR reference for the CNSP

8. RELEASE INSPECTIONS AND TESTING

All release inspections must be included in the facility's documentation (see *7. Master Formulation and Compounding Records* and *11. SOPs*). All checks, inspections, and any other required tests to ensure the quality of the CNSP must be detailed in the facility's MFR.

8.1 Visual Inspection

At the completion of compounding, before releasing and dispensing, the CNSP must be visually inspected to determine whether the physical appearance of the CNSP is as expected (e.g., color, texture, physical uniformity). Some CNSPs, as noted in their MFR, also must be visually checked for certain characteristics (e.g., emulsions must be checked for phase separation). The CNSP must be visually inspected to confirm that the CNSP and its labeling match the CR and the prescription or medication order. The inspection also must include a visual inspection of container closure integrity (e.g., checking for leakage, cracks in the container, or improper seals).

When a CNSP will not be released or dispensed on the day of preparation, a visual inspection must be conducted immediately before it is released or dispensed to make sure that the CNSP does not exhibit any defects (e.g., leakage) that could develop during storage. Any CNSP found to be of unacceptable quality (e.g., observed defects) must be promptly rejected, clearly labeled as rejected, and segregated from active stock to prevent use before appropriate disposal.

9. LABELING

Every CNSP must be labeled with appropriate, legible identifying information to prevent errors during storage, dispensing, and use. The term *labeling* designates all labels and other written, printed, or graphic matter on the immediate container or on or inside any packaging system 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⟩*.)

All labeling must be in compliance with laws and regulations of the applicable regulatory jurisdiction.

The label on each container of the prepared CNSP must, at a minimum, display prominently and legibly the following information:

- Assigned internal identification number (e.g., barcode, prescription, order, or lot number)
- Active ingredient(s), and their amount(s), activity(ies), or concentration(s)
- Storage conditions if other than controlled room temperature
- BUD
- Dosage form
- Total amount or volume if it is not obvious from the container

The labeling on the dispensed CNSP should display the following information:

- Route of administration
- Indication that the preparation is compounded
- Any applicable special handling instructions
- Any applicable warning statements
- Compounding facility name, and contact information if the CNSP is to be sent outside of the facility or healthcare system in which it was compounded

Labeling procedures must be followed as described in the facility's SOPs to prevent labeling errors and CNSP mix-ups.

The label of the CNSP must be verified to ensure that it conforms with the following:

1. Prescription or medication order;
2. MFR (see *7.1 Creating Master Formulation Records*); and
3. CR (see *7.2 Creating Compounding Records*).

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 product, API, 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 prescribed storage conditions. The expiration date limits the time during which a

conventionally manufactured product, API, or added substance may be dispensed or used (see ⟨7⟩, *Labels and Labeling for Products in Other Categories, Expiration Date and Beyond-Use Date*).

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, compounders must consider parameters that may affect quality, including but not limited to the following:

- 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 rapidly degrade over time and/or under certain storage conditions, reduce the strength of the preparation, or produce harmful impurities)
- 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
- Potential for microbial proliferation in the CNSP
- Significant deviations from essential compounding steps and procedures; changes to essential compounding steps may have an impact on the stability of the formulation

10.3 Establishing a BUD for a CNSP

The BUDs in *Table 4* are based on the ability of the CNSP to maintain chemical and physical stability and to suppress microbial growth. These BUDs represent the limit for CNSPs that are packaged in tight, light-resistant containers unless conditions in *10.4 CNSPs Requiring Shorter BUDs* or *10.5 Extending BUDs for CNSPs* apply.

The aqueous and nonaqueous dosage forms in *Table 4* are defined based on the water activity (a_w) of the most similar drug preparations described in *Table 3* or *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* ⟨1112⟩. In general, the use of a_w aids in assessing the susceptibility of CNSPs to microbial contamination and the potential for API degradation due to hydrolysis. The a_w is different from the water content and may be considered as the available water to support microbial growth and hydrolytic reactions. Nonaqueous dosage forms will not support spore germination or microbial growth due to their low a_w. Reduced a_w greatly assists in the prevention of microbial proliferation in conventionally manufactured products and is expected to convey the same benefit to CNSPs.

Compounders are not required to measure a_w for CNSPs. While the manufactured products in ⟨1112⟩, *Table 2* and compounded preparations in *Table 3* below are not exhaustive, they provide examples of dosage forms that have an $a_w < 0.6$ and those that have an $a_w \geq 0.6$ and can assist personnel in determining the BUD by dosage form using *Table 4*.

When preparing CNSPs, raw materials and equipment contribute a bioburden to the final preparation. CNSPs with an $a_w \geq 0.6$, and a BUD within the limits of *Table 4*, should contain suitable antimicrobial agents to protect against the proliferation of bacteria, yeast, and mold contamination that may be inadvertently introduced anytime during the compounding process or throughout the BUD under appropriate handling and storage conditions. All CNSPs with an extended BUD must follow *10.5 Extending BUDs for CNSPs*. Careful consideration should be taken when selecting a preservative to ensure microbiological effectiveness and stability. When antimicrobial preservatives are 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. Water Activity of Common Compounded Nonsterile Dosage Forms[a]

Nonaqueous Dosage Forms: $a_w < 0.6$			Aqueous Dosage Forms: $a_w \geq 0.6$		
Dosage Form	**Description**	**a_w**	**Dosage Form**	**Description**	**a_w**
Animal treat	Animal treat (oil flavor)	0.507	Animal treat	Animal treat with 15%–18% aqueous flavor	0.716
Capsule (oil filled)	Olive oil encapsulated	0.468	Cream	Cream vehicle (oil in water emulsion, petrolatum free)	0.968
Capsule (powder filled)	Powder base encapsulated	0.435	Cream	Emollient cream (petrolatum and mineral oil)	0.984
Gel (glycol based)	Propylene glycol, ethoxy diglycol,	0.056	Cream	Cream (oil in water emulsion with	0.989

Nonaqueous Dosage Forms: a_w < 0.6			Aqueous Dosage Forms: a_w ≥ 0.6		
Dosage Form	**Description**	**a_w**	**Dosage Form**	**Description**	**a_w**
	hydroxypropyl cellulose gel			natural oils)	
Lollipop (sorbitol based)	Sorbitol-based lollipop	0.460	Foam	Foaming surfactant solution	0.983
Ointment	Hydrophilic petrolatum	0.396	Gel (water based)	Alcohol-free aqueous gel	0.990
Ointment	Polyethylene and mineral oil gel base	0.459	Gel (water based)	Hydroxypropyl methylcellulose (HPMC) gel	1.000
Oral solution (glycol based)	20% Polyethylene glycol and 80% propylene glycol	0.009	Lotion	Lotion (oil in water emulsion)	0.986
Oral solution (oil based)	Medium chain triglycerides oil	0.338	Nasal spray	Nasal spray	0.991
Oral suspension (fixed oil)	Fixed oil with thickener	0.403	Oral solution (water based)	Low-sucrose syrup vehicle	0.906
Powder for inhalation	Encapsulated powder for inhalation	0.402	Oral solution (water based)	90% Water and 10% glycerin	0.958
Stick	Lip balm	0.181	Oral suspension (water based)	Oral suspension base	0.992
Suppository	Polyethylene glycol base	0.374	Rinse	Polymer gel with 30% water	0.960
Suppository	Fatty acid base	0.385	Shampoo	Shampoo	0.976
Tablet (compressed)	Compressed tablet	0.465	Simple syrup	Simple syrup	0.831
Tablet (triturate)	Tablet triturate (lactose and/or sucrose)	0.427	—	—	—
Troche or lozenge (gelatin based)	Gelatin troche or lozenge with NMT 3% aqueous flavor	0.332	—	—	—
Troche or lozenge (glycol based)	Polyethylene glycol troche or lozenge with NMT 3% aqueous flavor	0.571	—	—	—

[a] The measured a_w values in *Table 3* for the different dosage forms are intended to be representative examples. The descriptions listed are details about the tested formulation and are provided to assist personnel in determining whether their CNSPs are aqueous or nonaqueous.

Table 4. BUD Limit by Type of Preparation in the Absence of a *USP–NF* Compounded Preparation Monograph or CNSP-Specific Stability Information[a]

Type of Preparation	BUD (days)	Storage Temperature[b]
Aqueous Dosage Forms (a_w ≥ 0.60)		
Nonpreserved aqueous dosage forms[c]	14	Refrigerator
Preserved aqueous dosage forms[c]	35	Controlled room temperature or refrigerator
Nonaqueous Dosage Forms (a_w < 0.60)		
Oral liquids (nonaqueous)[d]	90	Controlled room temperature or refrigerator
Other nonaqueous dosage forms[e]	180	Controlled room temperature or refrigerator

[a] A shorter BUD must be assigned when the physical and chemical stability of the CNSP is less than the BUD limit stated in the table (see *10.4 CNSPs Requiring Shorter BUDs*).

[b] See *Packaging and Storage Requirements ⟨659⟩*.

[c] An aqueous preparation is one that has an a_w ≥ 0.6 (e.g., emulsions, gels, creams, solutions, sprays, or suspensions).

[d] A nonaqueous oral liquid is one that has an a_w < 0.6.

[e] Other nonaqueous dosage forms that have an a_w < 0.6 (e.g., capsules, tablets, granules, powders, nonaqueous topicals, suppositories, and troches or lozenges).

10.4 CNSPs Requiring Shorter BUDs

The BUDs in *Table 4* are the BUD limits for CNSPs in the absence of specific stability information. This does not absolve the designated person(s) from performing due diligence to determine if there is existing stability data that would require a shorter BUD.

Additionally,

- The BUD of the CNSP must not exceed the shortest remaining expiration date of any of the commercially available starting components.
- For CNSPs prepared from one or more compounded components, the BUD should generally not exceed the shortest BUD of any of the individual compounded components. However, there may be acceptable instances when the BUD of the final CNSP exceeds the BUD assigned to compounded components (e.g., pH-altering solutions). If the assigned BUD of the final CNSP exceeds the BUD of the compounded components, the physical, chemical, and microbiological quality of the final CNSP must not be negatively impacted.

10.5 Extending BUDs for CNSPs

- *CNSPs with a USP–NF monograph:* When compounding from a *USP–NF* compounded preparation monograph for the CNSP, the BUD must not exceed the BUD specified in the monograph.
- *CNSPs with stability information:* If there is a stability study using a stability-indicating analytical method for the API(s), CNSP formulation, and material of composition of the container closure that will be used, then the BUD indicated by the study may be used in lieu of the BUDs specified in *Table 4* for aqueous and nonaqueous dosage forms, up to a maximum of 180 days.

If the BUD of the CNSP is extended beyond the BUDs in *Table 4*, an aqueous CNSP must be tested for antimicrobial effectiveness (see *Antimicrobial Effectiveness Testing ⟨51⟩*). The designated person(s) may rely on antimicrobial effectiveness testing that is conducted (or contracted for) once for each formulation in the particular container closure system—including materials of composition of the container closure system—in which it will be packaged. Alternatively, the designated person(s) may rely on antimicrobial effectiveness testing results provided by an FDA-registered facility or published in peer-reviewed literature as long as the CNSP formulation (including any preservative) and container closure materials of composition are the same as those tested (unless a bracketing study is performed). When a bracketing study is performed, antimicrobial effectiveness testing may be performed on a low concentration and on 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 fall within the bracketed range.

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 facility's SOPs and be responsible for ensuring that they are followed.

One or more person(s) must be designated to ensure that the facility's 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 (QA) is a system of procedures, activities, and oversight that ensures that the compounding process consistently meets quality standards. Quality control (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 the facility's SOPs that ensure that all aspects of the preparation of CNSPs are conducted in accordance with the requirements in this chapter (⟨795⟩) and the laws and regulations of the applicable regulatory jurisdiction. Designated person(s) 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, and
4. Appropriate investigations and corrective actions.

The facility's 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.

12.1 Notification About and Recall of Dispensed CNSPs

The facility must have procedures in place to

- Determine when recalls must be initiated, which should include procedures to immediately notify the prescriber of a failure of specifications with the potential to cause patient harm (e.g., strength, purity, or other quality attributes)
- Recall any unused dispensed CNSPs and quarantine any stock remaining in the pharmacy
- Investigate if other lots are affected and recall if necessary

An SOP for recall of dispensed CNSPs must contain

- Procedures to determine the severity of the problem and the urgency for implementation and completion of the recall
- Procedures to determine the distribution of any affected CNSP, including the data and quantity of distribution
- Procedures to identify patients who have received the CNSP
- Procedures for disposal and documentation of the recalled CNSP
- Procedures to investigate and document the reason for recall

The nonsterile compounding facility must document the implementation of the recall procedures. The recall must be reported to appropriate regulatory bodies as required by the laws and regulations of the applicable regulatory jurisdiction.

12.2 Complaint Handling

Compounding facilities must develop and implement SOPs for handling complaints. Complaints may include but are not limited to concerns or reports on the quality, labeling, or possible adverse reactions related to a specific CNSP.

A designated person(s) must review all complaints 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., email, telephone, or mail). The record must contain the name of the complainant or other 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 and the assigned internal identification number (e.g., prescription, order, or lot number).

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 *14. 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.

12.3 Adverse Event Reporting

Adverse events potentially associated with the quality of CNSPs must be reported in accordance with the facility's SOPs and all laws and regulations of the applicable regulatory jurisdiction. 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.

13. CNSP PACKAGING AND TRANSPORTING

13.1 Packaging of CNSPs

The facility's 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 of 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. 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 qualification records including corrective actions for any failures
- Equipment records (e.g., calibration, verification, and maintenance reports)
- COAs and all documentation required for components not conventionally manufactured
- Receipt of components
- SOPs, MFRs, and CRs
- Release inspection and testing records
- Information related to complaints and adverse events including corrective actions taken
- Results of investigations and corrective actions
- Records of cleaning and sanitizing the designated compounding area
- Temperature logs
- Accommodations to personnel compounding CNSPs
- Any required routine review (e.g., yearly review of QA and QC programs, yearly review of chemical hazard and disposal information)

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 CRs for a particular CNSP (e.g., MFR, CR, and release inspection and testing results) must be readily retrievable for at least 2 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 or animals or affecting the structure and function of the body. Also referred to as *Bulk drug substance*. A conventionally manufactured drug product is not an API but is typically manufactured from an API(s).

Added substance: An ingredient that is necessary to compound a preparation but is 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 inactive ingredient, excipient, and pharmaceutical ingredient.

Administration: The preparation of a nonsterile pharmacologic or other therapeutic agent for ingesting, inserting, applying, or otherwise providing a nonsterile medication in its final form to a single patient. This includes crushing a tablet(s) or opening a capsule(s) to mix with food or liquids to facilitate patient dosing.

Alcohol-based hand rub: An alcohol-containing preparation (liquid, gel, or foam) designed for application to the hands of healthcare personnel to inactivate microorganisms and/or temporarily suppress their growth. Such preparations may contain one or more types of alcohol, other active ingredients, excipients, and humectants.

Assigned trainer: One or more individuals assigned by the designated person(s) to be responsible and accountable for directly providing the training, observation, and/or evaluation of personnel for the preparation of CNSPs.

Beyond-use date (BUD): The date, or hour and date, after which a CNSP must not be used, stored, or transported. The date is determined from the date or time the preparation is compounded.

Biological safety cabinet (BSC): A ventilated cabinet that may be used for compounding. These cabinets are 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, Type B2, and Type C1).

Bulk drug substance: See the entry for *Active pharmaceutical ingredient*.

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 substances (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products.

Cleaning agent: An agent, usually containing a surfactant, used for the removal of substances (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Closed-system processing device: A device designed to reduce the potential exposure to personnel or contamination of the facility or CNSPs. Examples include CVEs, BSCs, or single-use containment glove bags.

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

Compounded nonsterile preparation (CNSP): A preparation not intended to be sterile that is created by combining, admixing, diluting, pooling, reconstituting other than as provided in the manufacturer's labeling, or otherwise altering a drug product or bulk drug substance.

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

Compounding area: An area that is specifically designated for nonsterile compounding.
Compounding personnel: Personnel trained to compound or oversee compounding of preparations.
Compounding record (CR): Documents the compounding of each CNSP.
Container closure system: Packaging system components that together contain and protect the dosage form. This includes primary packaging system components and secondary packaging system 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 application approved by the applicable national regulatory agency, 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 as related to the preparation of CNSPs.
FDA: US Food and Drug Administration.
Formulation: The specific qualitative and quantitative composition of the final CNSP.
Hazardous drug (HD): Any drug identified by at least one of the following 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: The part of the labeling on the immediate container.
Labeling: All labels and other written, printed, or graphic matter on the immediate container or on or inside any packaging system or wrapper in which the article is enclosed, except for any outer shipping container.
Master formulation record (MFR): A detailed record of procedures that describes how the CNSP is to be prepared.
Monograph: A quality documentary standard within *USP–NF* that articulates the quality expectations for a medicine including for its identity, strength, purity, and performance. It also describes the tests to validate that a medicine and its ingredients meet these criteria.
Oversight: The review, monitoring, and supervision of actions taken by personnel; bearing responsibility for those actions; and being available if and when needed for consultation even if not physically present.
Preservative: A substance added to inhibit microbial growth.
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 European Union, 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 ⟨1231⟩, *3.1.1 Purified Water*.)
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 for 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 microorganisms (e.g., 70% isopropyl alcohol).
SDS: Safety data sheet.
SOP: Standard operating procedure.
Specification: The tests, analytical methods, and acceptance criteria to which any components, CNSP, container closure system, equipment, or other material used in the compounding of 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.
Verify: To confirm that a method, process, system, or equipment will perform as expected under the conditions of actual use.
Water activity (a_w): A measure of the fraction of total water that is unbound and freely available to participate in chemical, biochemical, or physicochemical reactions or provide an environment that can support microbial growth. Note that a_w is not water content.▲ (Official 1-Nov-2023)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<795> PHARMACEUTICAL COMPOUNDING--NONSTERILE PREPARATIONS	Selma Mitiche Associate Scientific Liaison	CMP2020 Compounding 2020

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