Broad Comparison of USP 795: Nonsterile Compounding

January 2014 version vs November 2022 version

(Implementation November 1, 2023)

January 25, 2023 Board of Pharmacy Meeting

Summary of 2022 Revision

- Easier to read
- More clear about documentation requirements
- Eliminated categories of compounding (simple, moderate, complex)
- Clearer definition of compounding: does not include reconstitution, repackaging or tablet splitting/crushing
- USP 800 incorporated for nonsterile compounding with hazardous drugs
- No section for pets, performance or food producing animals
  - The entire chapter applies to animals and humans

Summary of 2022 Revision

- Must have a designated person (DP)
- Training must be done initially and every 12 months
- Must wash hands and wear gloves to compound
- Recommend no carpet in the compounding area
- Sink must be emptied and clean
- Storage conditions meet the requirements of a compendial monograph, if applicable
- Minimum cleaning schedule clearly stated
- Evaluation to determine need for powder containment hood
- APIs must be from FDA registered facility

Summary of 2022 Revision

- Must have spill kit with policy and training
- Master Formulations – very similar
- Compound Records – very similar except no duplicate label required
- BUDs extended for some dosage forms but max for all dosage forms at 180 days
- SOPs more extensive
- Quality Assurance and Quality Control more robust including compliant and adverse event investigations
- Patient counseling not included

Scope

January 2014

- Applies to pharmacists and other healthcare professionals, and others engaged in the compounding of drug preparations

November 2022

- Applies to all persons who prepare CNSPs and all places where CNSPs are prepared

CNSPs: Compounded Non-Sterile Preparations

Scope

January 2014

- No mention of designated person (DP) several terms used to reference persons involved in CNSP
- 201 KAR 2:076 section 3
  - Requires PIC to be knowledgeable and oversee compounding

November 2022

- Requires a designated person (DP) to oversee USP 795
  - Oversees training program to ensure competency
  - Selects components
  - Monitors and observes compounding activities
    - Takes immediate corrective action if needed
  - Ensures that SOPs are fully implemented
  - Establishes, monitors and documents procedures for handling and storage of CNSPs and/or components of CNSPs
  - DP must be identified in the facility's SOPs

SOP: Standard Operating Procedures
CNSPs: Compounded Non-Sterile Preparations

Scope

January 2014

- Has 3 categories of nonsterile compounding
  - Simple
  - Moderate
  - Complex

November 2022

- No categories of nonsterile compounding

Training

January 2014

- Initially trained
- Recommended annually
- Ongoing to ensure accurate and adequate compounding

November 2022

- Initially trained
- Refresher training required every 12 months
- Ongoing by monitoring and observing to correct any issues at any time

Training

January 2014

- Training to include:
  - Knowledge of USP 795 and facility procedures
  - Demonstration of process
  - Documentation of training
  - Read and interpret SDS
  - Read and be familiar with procedures

November 2022

- Training to include 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 and Compounding Records)
  - Knowledge and understanding of USP 795
  - Understand and interpret SDS and COA
  - Read and understand procedures related to compounding duties

SDS: Safety Data Sheets
COA: Certificate of Analysis
CNSP: Compounded nonsterile preparation

Training

January 2014

- Compounder demonstrates procedures
- Compounder observes and guides employee throughout process
- Employee repeats procedure without assistance from but under the direct supervision of compounder
- Employee demonstrates a verbal and functional knowledge, then can compound without direct supervision

November 2022

- Personnel guided throughout process
- Personnel demonstrates competency under direct supervision
- Personnel may compound without direct supervision after independently demonstrating understanding and competency

Training

January 2014

- Does not address if only one compounder

November 2022

- If only one compounder in facility, that person must document:
  - Training obtained
  - Competency demonstrated

Personal Hygiene and Garbing

January 2014

- Potential contamination issues not addressed

November 2022

- Must notify DP of potential contamination issues:
  - Rashes
  - Recent tattoos
  - Oozing sores
  - Conjunctivitis
  - Active respiratory infection
- DP makes determination if person may compound

Personnel Preparation

January 2014

- Compounding personnel maintain good hygiene

November 2022

- Compounding personnel must remove:
  - Outer garments
  - Hand, wrist, other exposed jewelry
  - Earbuds or headphones
- DP may permit accommodations if quality of environment and CNSP will not be affected

DP: designated person
CNSPs: Compounded Non-Sterile Preparations

Hand Hygiene

January 2014

- Shall have access to:
  - A sink
  - Soap or detergent
  - Single use towels or
  - Air dryer

November 2022

- Before entering compounding area, personnel must:
  - Wash hands with soap and water for at least 30 seconds
  - Dry hands completely with disposable towels or wipers
  - Don gloves
  - Use of alcohol-based hand rub alone is not sufficient

Glove and Garb Requirements

January 2014

- Personnel wear clean clothing and Personal Protective Equipment (PPE) appropriate to the type of compounding (e.g. hair covers, gloves etc.)

November 2022

- Must wear gloves for all compounding
  - Recommended to wipe gloves or replace before beginning a CNSP that has different components
  - Must replace gloves if holes, punctures or tears are detected
- Recommend additional garb as deemed needed
  - Shoe covers
  - Head or hair covers
  - Facial hair covers
  - Face masks
  - Gowns

CNSPs: Compounded Non-Sterile Preparations

Building and Facilities: Compounding Space

January 2014

- Shall have adequate space
- Compounding environment is suitable
- Separate areas for sterile and nonsterile compounding
- Compounding done in clean and sanitized area dedicated to compounding

November 2022

- An area must be designated for nonsterile compounding
  - SOP to describe method of designation
  - Other activities cannot be occurring in this space at the same time as compounding
- Recommended no carpet in compounding area

SOP: standard operating procedure

Building and Facilities: Storage Area

January 2014

- Appropriate temperature and humidity monitoring

November 2022

- Must monitor temperatures by one of the following:
  - Manually – daily when facility is open
  - Electronically – continuously
- Documentation must be retrievable
- Must calibrate temperature monitoring devices every 12 months
- Storage conditions meet the requirements of a compendial monograph, if applicable

Buildings and Facilities: Water Source

January 2014

- Must have sink with hot and cold water easily accessible to compounding area
- 201 KAR 180 section 3 – Hot and cold water shall be readily accessible

November 2022

- Must have sink with hot and cold water easily accessible
- Sink must be emptied of all items unrelated to compounding when washing compounding equipment
- Must clean sink if visibly soiled before using to clean equipment for compounding

Cleaning and Sanitizing

January 2014

- Compounding is done in appropriately cleaned and sanitized area

November 2022

- Work surfaces
  - At the beginning and end of each shift
  - When spills or contamination occurs
  - Between compounding with different components
- Floors
  - Daily
  - When spills or contamination occurs
- Walls and Ceilings
  - When visibly soiled
  - When spills or contamination occurs
- Storage Shelving
  - Every 3 months
  - When spills or contamination occurs

- If not compounding daily, must clean before starting to compound

- No specific agents discussed

Equipment and Components: Equipment

January 2014

- Use of CVE, BSC, single use containment glove bags not specifically addressed

November 2022

- Must evaluate to determine need for using:
  - CVE– must be certified at least every 12 months
  - BSC – must be certified at least every 12 months
  - Single use containment glove bag

CVE: Containment Ventilated Enclosure
BSC: Biological Safety Cabinet

Equipment and Components: Equipment Cleaning

January 2014

- Equipment must be cleaned after use, properly maintained and used appropriately
- Stored to protect from contamination
- Inspected immediately before use

November 2022

- CVE and BSC must be cleaned:
  - At the beginning and end of each shift
  - After spills or contamination
  - Horizontal work surface
    - Between compounding CNSPs with different components
- BSC – clean and sanitize under the work surface at least monthly
- Other equipment must be cleaned:
  - Before first use and according to manufacturer
  - If nothing from manufacturer, between compounding with different components

CVE: Containment Ventilated Enclosure
BSC: Biological Safety Cabinet
CNSPs: Compounded Non-Sterile Preparations

Components: Selection

January 2014

- Active Pharmaceutical Ingredients (APIs) and all components
  - Recommended USP/NF source
  - First attempt to obtain from and FDA registered facility
  - COA consulted

November 2022

- Active Pharmaceutical Ingredients (APIs)
  - Must comply with USP/NF monograph, if there is one
  - Must have a COA
  - Must be from an FDA registered facility
- All components other than APIs
  - Should have a COA
  - Should be from an FDA registered facility

COA: Certificate of Analysis

Components: Receipt

January 2014

- Should obtain COA at time of receipt

November 2022

- Must review COA
- Must document:
  - Date of receipt
  - Quantity received
  - Supplier name
  - Lot number
  - Expiration date
  - Results of any testing

COA: Certificate of Analysis

Components: Containers

January 2014

- Allows transfer of components to other containers

November 2022

- Once component is removed from original container, recommended that any unused portion be discarded and not returned to original container
  - For example, excess from weighing

Components: Spill and Disposal

January 2014

- Spills not specifically addressed

November 2022

- Must maintain chemical hazard and disposal information (SDS) and update every 12 months
- Must have a spill kit in the compounding area
- Personnel must receive training in spill management at least every 12 months
- Training must be documented

SDS: Safety Data Sheets

Master Formulations

January 2014

- Very similar, more wordy

November 2022

- Very similar, more concise

Compounding Records

January 2014

- Very similar
  - Requires a duplicate label

November 2022

- Very similar
  - No duplicate label required

Preparation Approval

January 2014

- Compounder shall review each procedure in the process as part of the final approval
- Compounder shall observe finished preparation

November 2022

- After compounding and prior to dispensing CNSP must be visually inspected:
  - Physical appearance
    - Including certain characteristics
  - Labeling
  - Container closure integrity
- Must document checks

CNSPs: Compounded Non-Sterile Preparations

Labeling Definitions

January 2014

- No definition of labeling and label

November 2022

- 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 CNSP is enclosed

- Label – the part of the labeling on the immediate container

CNSPs: Compounded Non-Sterile Preparations

Labeling

January 2014

- Prescription container is labeled according to all state and federal laws
- Label shall include:
  - BUD
  - Storage information
  - Handling information
- KRS 217.065 – labeling requirements
- 201 KAR 2:076 Section 4 –compounding label requirements
- 201 KAR 2:311 Section 4 –veterinary office use

November 2022

- Label must contain:
  - Internal ID number
  - Active components(s) and their amount(s), activities, concentrations
  - Storage conditions, if other than room temperature
  - Beyond Use Date (BUD)
  - Dosage form
  - Total volume of each container

Labeling

January 2014

- Labeling should indicate that this is a compounded preparation

November 2022

- Recommend that label contains:
  - Route of administration
  - Indication that the preparation is compounded
  - Any applicable special handling instructions
  - Any applicable warning statements
  - Compounding facility name, contact information if CNSP leaves facility

CNSPs: Compounded Non-Sterile Preparations

Beyond Use Dates (BUDs)

January 2014

- Beyond Use Date – the date after which a compounded preparation should not be used
- Determined from the date the preparation is compounded

November 2022

- Beyond Use Date – the date or the hour and date, beyond which the preparation cannot be used and must be discarded

Beyond Use Dates (BUDs): Water Activity (a_w) November 2022

- November 2022 version takes into account the water activity (a_w) as described in USP 1112, *Application of Water Activity Determination to Nonsterile Pharmaceutical Products* in the determination of the BUD
- A_w aids in determining CNSP susceptibility to microbial contamination and degradation due to hydrolysis
- A_w is different from the water content, it may be considered as the available water to support microbial growth and hydrolytic reactions
- *CNSPs with* a_w ≥0.6 should have antimicrobial agent or be refrigerated

CNSPs: Compounded Non-Sterile Preparations

BUDs

January 2014

Formulation Type	BUD	Storage
Water-containing Oral Formulations	14 days	Refrigerator
Water-Containing Topical/Dermal and Mucosal Liquid and Semisolid Formulations	30 days	Controlled room temperature
Nonaqueous Formulations	6 months	Controlled room temperature

November 2022

Preparation	BUD	Storage
	Aqueous Dosage Forms $a_w \geq 0.6$	
Non-preserved aqueous dosage forms	14 days	Refrigerator
Preserved aqueous dosage forms	35 days	Controlled room temperature or refrigerator
	Nonaqueous Dosage Forms $a_w < 0.6$	
Oral liquids (nonaqueous)	90 days	Controlled room temperature or refrigerator
Other nonaqueous dosage forms	180 days	Controlled room temperature or refrigerator

Aqueous dosage forms: emulsions, gels, creams, solutions, sprays, or suspensions
Nonaqueous dosage forms: capsules, tablets, granules, powders, nonaqueous topicals, suppositories, troches or lozenges

Shorter BUDs

January 2014

- The BUD shall not be later than the expiration date on any component

November 2022

- The BUD of the CNSP must not exceed the shortest remaining expiration date of any of the components
- However, there are acceptable instances when the BUD of the final CNSP exceeds the BUD of the components
  - For example: pH-altering solutions

BUD: Beyond Use Date
CNSP: Compounded Non-Sterile Preparations

Extending BUDs

January 2014

- May use stability information to extend BUDs
  - USP-NF Monograph
  - Published peer-reviewed literature
  - Stability study
- Recommend susceptible CNSPs contain suitable antimicrobial agents

November 2022

- If there is a USP-NF monograph
  - The BUD must not exceed the BUD in the monograph
- CNSPs with stability information
  - BUD indicated by the stability study may be used
  - Maximum of 180 days
- Must be tested for antimicrobial effectiveness
  - Conducted or contracted testing for each formulation
  - Use results provided by a FDA-registered facility
  - Use results published in peer-reviewed literature
  - Bracketing study

BUD: Beyond Use Date
CNSP: Compounded Non-Sterile Preparations

Standard Operating Procedures (SOPs)

January 2014

- Recommend having written SOPs covering all significant procedures performed in compounding area
- Only minimal required SOPs
- 201 KAR 2:076 Section 1—Policy and Procedures

November 2022

- Must have SOPs on all aspects of compounding operation
- Personnel conducting or overseeing compounding must be trained in SOPs
- Designated Person must ensure follow-up occurs if problems, deviation or errors are identified

SOP: Standard Operating Procedure

Quality Assurance and Quality Control

January 2014

- Quality control
  - Checking documentation
  - Checking compounding process

November 2022

- Quality Assurance (QA)
  - System of procedures, activities and oversight that ensures that the compounding process consistently meets quality standards
- Quality Control (QC)
  - Sampling, testing and documentation of results that ensure that specifications have been met before release of CNSP

CNSP: Compounded Non-Sterile Preparation

QA and QC

January 2014

- No formalized program
- No required SOPs

November 2022

- Must have a formal QA and QC program that establishes a system of:
  - Adherence to procedures
  - Prevention and detection of errors and other quality problems
  - Evaluation of complaints and adverse events
  - Appropriate investigations and corrective actions
- Must have SOPs on QA and QC program
  - Reviewed every 12 months by the designated person
  - Results of review must be documented

SOP: Standard Operating Procedure
QA: Quality Assurance
QC: Quality Control

QA and QC: Recall

January 2014

- Recalls not specifically addressed

November 2022

- Facility must have procedures in place to:
  - Determine when recalls must be initiated
    - Notify prescriber
  - Recall any unused dispensed CNSPs and quarantine any stock
  - Investigate if other lots are affected and recall if necessary

- Must have SOP for recall that includes:
  - Procedures to determine severity and urgency
  - Procedure to determine distribution of CNSP
  - Procedure to identify patients who have received CNSP
  - Procedure for disposal and documentation of recalled CNSP
  - Procedure to investigate and document the reason for recall

SOP: Standard Operating Procedures
CNSPs: Compounded Non-Sterile Preparations

Complaint Handling and Adverse Events

January 2014

- Required to investigate and document any reported problem
- Required to take corrective action

November 2022

- DP must review all complaints
- If a quality issue, must investigate the cause and have corrective action
- Must keep readily retrievable record of each complaint
  - Name of complainant or some ID
  - Date complaint received
  - Nature of complaint
  - Response to complaint
  - Name/strength of CNSP and assigned ID (if known)
  - Findings of investigation
  - Follow-up
- Adverse events must be reported in accordance with SOPs and all laws/regulations
  - If likely to affect other patients, those patients and prescribers must be informed

DP: Designated Person

Packaging and Transport

January 2014

- Compounder ensures that containers and container closures used in packaging CNSPs meet USP requirements (USP 659)
- 201 KAR 2:076 Section 4(6)—Transportation and containers

November 2022

- Facility SOP must describe packaging of CNSPs
- Personnel selects and uses packaging materials to maintain the physical and chemical integrity and stability of the CNSPs
- If transporting CNSPs, facility must have SOP to describe:
  - Mode of transportation
  - Special handling instructions
  - Temperature monitoring devices, if needed

SOP: Standard Operating Procedure
CNSPs: Compounded Non-Sterile Preparations

Documentation

January 2014

- Not as clear as to required documentation
- No time frame for document retention
- 201 KAR 2:076 requires document retention for 5 years
  - Patient profile
  - Purchase records
  - Quality assurance records
  - Other records and reports as required by law

November 2022

- Must be readily retrievable for at least 2 years
- Must have documentation of:
  - Personnel training
  - Equipment records
  - COAs
  - Receipt of components
  - SOPs, MFRs, CRs
  - Release inspection and testing records
  - Complaints and Adverse Events
  - Corrective actions
  - Cleaning and sanitizing
  - Temperature logs
  - Accommodations to personnel
  - Any required routine review

COA: Certificate of Analysis
MFR: Master Formulation Record
SOP: Standard Operating Procedures
CR: Compounding Record

Patient Counseling

January 2014

- Required patient counseling

November 2022

- Patient counseling not addressed

Compounding for Animals

January 2014

- Section on compounding for animals
- Addresses pets, performance, and food producing animals

November 2022

- Introduction states USP 795 is the minimum standard for preparation of CNSPs for humans and animals

CNSPs: Compounded Non-Sterile Preparations

USP 795

- November 2022 version
  - Expected implementation is November 1, 2023
- 201 KAR 2:076 specifically references the Jan 1, 2014 version of USP 795
  - Waivers are allowed
  - No waivers requested (for 795) as of this date