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

Broad Comparison of USP 797: Sterile Compounding

JUNE 2008 VERSION VERSUS NOVEMBER 2022 VERSION

JANUARY 25, 2023 BOARD OF PHARMACY MEETING

Summary of Revision

- Easier to read
- More clear about documentation requirements and processes
- Have designated person (DP)
- No risk categories – low, medium, and high
- Now Category 1, Category 2, Category 3 compounded sterile preparations (CSP)
- USP 800 incorporated for sterile compounding with hazardous drugs
- Radiopharmaceuticals have own chapter, USP 825
- No appendices with sample forms
- Training is completed:
  - Every 6 months for Category 1 & 2
  - Every 3 months for Category 3

Summary of Revision

- Blood-derived and other biological materials must be clearly separated from other compounding activities and equipment, SOPs to address cross contamination
- CAI and CACI in SCA may only be used for Category 1 CSPs
  - 12 hour BUD room temperature or 24 hour BUD refrigerated
- CAI and CACI in classified compounding suite may have longer BUDs
- Pharmaceutical Isolator (not a CAI or CACI) addressed
- ISO 8 environment required to have 20 Air Changes Per Hour (ACPH)
- Sink may be outside ante room in a clean space
- Surface sampling must be completed
  - Monthly for Category 1 & 2
  - Weekly for Category 3
- Air sampling must be completed
  - Every 6 months for Category 1 & 2
  - Monthly for Category 3

CAI: Compounding Aseptic Isolator
CACI: Compounding Aseptic Containment Isolator
BUD: Beyond Use Date

Summary of Revision

- Must attempt to analyze growth to the genus only if out of limits
- Cleaning and disinfecting more clearly defined
  - Sterile cleaning agents and wipes required in PEC
- Requires use of sporicidal agent:
  - Monthly for Category 1 & 2
  - Weekly for Category 3
- Requires Master Formulations for batches and any CSP from non-sterile components
- Requires Compounding Records
- BUDs changed with some extended but a max regardless of stability
- Single Dose Vials may be used up to 12 hours as long as storage requirements are maintained

PEC: Primary Engineering Control
CSP: Compounded Sterile Preparation
BUD: Beyond Use Date

Scope

June 2008

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

November 2022

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

CSP: Compounded Sterile Preparation

Designated Person

June 2008

- No mention of designated person (DP)
- 201 KAR 2:076 Section 3
  - Requires PIC to be knowledgeable and oversee compounding

November 2022

- Requires designated person(s) (DP) to be responsible and accountable for the performance and operation of the facility and personnel in the preparation of CPSs and for all other functions described in USP 797

Scope: Types of Compounded Sterile Preparations Clarified

June 2008

- Irrigations for wounds and body cavities

November 2022

- Irrigations for internal body cavities
  - Any space that does not normally communicate with the environment outside of the body such as the bladder cavity or peritoneal cavity
  - Irrigations for the mouth, rectal cavity, sinus cavity are not required to be sterile

Preparation Per Approved Labeling

June 2008

- CSPs include:
  - Manufactured sterile products that are either prepared strictly according to the instructions appearing in manufacturers' approved labeling (product package inserts) or prepared differently than published in such labeling.

November 2022

- Preparing a conventionally manufactured sterile product in accordance with the directions in the manufacturer's approved labeling is out of scope of this chapter only if:
  - The product is prepared as a single dose for an individual patient, and
  - The approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time.

CSP: Compounded Sterile Preparation

Proprietary Bag and Vial System

June 2008

- Follow manufacturer's instructions for handling and storing systems

November 2022

- Docking and activation of system for immediate administration
  - Not considered compounding
- Docking for future activation and administration
  - Is considered compounding
- Use manufacturer beyond use date

Immediate Use

June 2008

- For emergency or immediate administration
- CSP involves not more than 3 different sterile products
- Compounding is continuous and takes no more than 1 hour
- Administration begins not later than 1 hour following the start of the preparation

November 2022

- For direct and immediate administration
- CSP involves not more than 3 different sterile products
- Administration begins within 4 hours of start of preparation

CSP: Compounded Sterile Preparation

CSP Categories

June 2008

- Risk levels (low, medium, high) assigned according to the potential for microbial, chemical and physical contamination

November 2022

- Categories 1, 2 & 3 determined based on:
  - The state of environmental control during compounding
  - Probability for microbial growth
  - Time period within CSPs must be used

CSP: Compounded Sterile Preparation

CSP Categories

June 2008

- Low Risk with 12 hour BUD
- Low Risk
- Medium Risk
- High Risk

November 2022

- Category 1
  - 12 hour BUD room temperature, or
  - 24 hour BUD refrigerated
  - Compounded in Segregated Compounding Area (SCA)
- Category 2
  - Have a BUD longer than Category 1 CSPs
  - Compounded in clean room suite
- Category 3
  - Have a BUD longer than Category 2 CSPs
  - Increased training for personnel
  - Sterile garb
  - Increased use of sporicidal disinfectants
  - Increased frequency of environmental monitoring and stability determination
  - Compounded in clean room suite

BUD: Beyond Use Date
CSP: Compounded Sterile Preparation

Training

June 2008

- Every 12 months
  - Cleaning and disinfecting observed procedures
  - Didactic exam

November 2022

- DP responsible for training program
- Non-compounding supervisory personnel and compounding personnel -- every 12 months:
  - Cleaning and disinfecting observed
  - Written or electronic exam

DP: Designated Person

Observed Competency

June 2008

- Low and Medium Risk – every 12 months
  - Hand hygiene and garbing
  - Aseptic technique
  - Media fill test (MFT)
  - Gloved fingertip test (GFT)
- High risk – every 6 months
  - Same as above

November 2022

- Category 1 and 2 CSPs compounding personnel – every 6 months
  - Hand hygiene and garbing
  - Aseptic technique
  - Media fill test (MFT) & surface sampling
  - Gloved fingertip test (GFT)
- Category 3 CSPs compounding personnel – every 3 months
  - Hand hygiene and garbing
  - Media fill test (MFT) & surface sampling
  - Gloved fingertip test (GFT)
- Non-compounding supervisory personnel addressed in chapter

CSP: Compounded Sterile Preparation

Personal Hygiene

June 2008

- Cannot compound if have:
  - Rashes
  - Oozing sores
  - Conjunctivitis
  - Sun burn
  - Respiratory infection

November 2022

- Must inform DP if have:
  - Rashes
  - Oozing sores
  - Conjunctivitis
  - Recent tattoos
  - Respiratory infection
- DP determines if person can compound and maintain state of control

DP: Designated Person

Personnel Preparation

June 2008

- Must remove:
  - Outer garments
  - Cosmetics
  - Hand, wrist, exposed jewelry
  - Nails – neat and trimmed

November 2022

- Must remove:
  - Outer garments
  - Cosmetics
  - Hand, wrist, exposed jewelry
  - No ear buds or headphones
  - No electronic devices not necessary for compounding
  - Wipe eyeglasses, if worn
  - Nails – clean and trimmed
    - No polish, artificial nails, extenders
- DP may make accommodations if maintain state of control

DP: Designated Person

Hand Hygiene

June 2008

- Recommend to not use brush
- May use single towels or air dryer
- Remove debris from under nails
- Use alcohol based, waterless surgical scrub with persistent activity

November 2022

- Must **not** use brushes
- Must **not** use air dryer
- Must use closed system (non-refillable) soap container
- Clean underneath fingernails
- Use alcohol based hand rub before donning sterile gloves

Gloves & Garb

June 2008

- Not specifically stated to don sterile gloves over RABS gloves
- Apply sIPA 70% regularly and each time reentering ISO 5

November 2022

- Donning and doffing garb should not occur in same area at the same time
  - Sterile gloves not donned or doffed in ISO 5
- Sterile gloves must be donned over isolator gloves
- Apply sIPA 70%:
  - Regularly
  - When touch nonsterile surface
- Category 3
  - All low-lint outer garb must be sterile including use of sterile sleeves over gauntlet sleeves for RABS
  - No exposed skin in buffer room (e.g. face and neck must be covered)

RABS: Restricted Access Barrier System (includes compounding aseptic isolators and compounding aseptic containment isolators)
sIPA: sterile isopropyl alcohol

Types of Primary Engineering Controls and Placement

June 2008

- Integrated Vertical Laminar Flow Zone (IVLFZ) not specifically addressed

November 2022

- Laminar Airflow Work Bench (LAWF)
- Biological Safety Cabinet (BSC)
- Integrated Vertical Laminar Flow Zone (IVLFZ)
  - Per USP 797 – it is difficult to achieve and maintain unidirectional airflow in IVLFZs

Types of Primary Engineering Controls and Placement

June 2008

- Compounding Aseptic Isolator (CAI) and Compounding Aseptic Containment Isolator (CACI)
  - May be in non-classified area for all types of compounding

November 2022

- Restricted-Access Barrier System (RABS)
  - Compounding Aseptic Isolator (CAI)
  - Compounding Aseptic Containment Isolator (CACI)
- For Category 2 and 3 – must be in clean room suite with buffer and ante rooms

Types of Primary Engineering Controls and Placement

June 2008

- Pharmaceutical Isolator – not addressed

November 2022

- Pharmaceutical Isolator (not a CAI or CACI) comprised of:
  - Controlled workspace
  - Transfer device
  - Access device
  - Integral decontamination system
- For Category 2 and 3 – may be in ISO 8 environment
  - Do not need ante room

CAI: Compounding Aseptic Isolator
CACI: Compounding Aseptic Containment Isolator

Segregated Compounding Area

June 2008

- RABS able to maintaining ISO 5 in a non-classified area
- Low Risk 12 hour BUD

November 2022

- Category 1
- The area within 1 meter of PEC should be dedicated only for sterile compounding

RABS: Restricted Access Barrier System
BUD: Beyond Use Date
PEC: Primary Engineering Control

Clean Room Suite Design

June 2008

- Allows for HEPA filters upstream
- Must have line of demarcation in ante room
- Recommended air returns be mounted low on wall

November 2022

- HEPA filters must be in ceiling of buffer and ante rooms
- Must have line of demarcation in ante room OR have clean and dirty ante rooms
- Air returns in cleanroom suite must be low on wall unless visual smoke study demonstrates an absence of stagnant airflow

HEPA: Hight Efficiency Particulate Air

Air Exchange Requirements

June 2008

- Recommended ISO 8 environments have 20 ACPH

November 2022

- Required ISO 8 environments have 20 ACPH
- At least 15 ACPH must come from the HEPA filters in ceiling

ACPH: Air Exchanges Per Hour
HEPA: Hight Efficiency Particulate Air

Water Sources

June 2008

- Sink must be on clean side of ante room
- Low risk 12 hour BUD – sink should be separated from immediate area of PEC

November 2022

- Allows sink to be inside or outside of ante room
- If outside ante room, must be in a clean space
- SCA- sink must be placed not closer than 1 meter to the PEC

BUD: Beyond Use Date
PEC: Primary Engineering Control
SCA: Segregated Compounding Area

Certification

June 2008

- Number of people in the room during certification not specifically addressed

November 2022

- Certification must record number of people in each PEC and SEC during particle counts and smoke testing

PEC: Primary Engineering Control
SEC: Secondary Engineering Control

Viable Air Sampling

June 2008

- Viable air sampling performed:
  - Every 6 months
- Fungal sampling required for high risk compounding only
- May sample 400 to 1000 L of air
  - Exception: ISO 5 must be 1000 L
- Must analyze all growth down to the genus

November 2022

- Viable air sampling performed:
  - Every 6 months for Category 1 & 2
  - Monthly for Category 3
- Fungal sampling required for all compounding
- Must sample 1000 L of air at all locations
- Must attempt to analyze growth down to genus if exceed action levels

Surface Sampling

June 2008

- Surface sampling performed periodically
  - Typically every 6 months
- Must analyze all growth down to the genus

November 2022

- Surface sampling performed:
  - Category 1 & 2 - monthly
  - Category 3 - weekly
    - And after compounding batches
- Completed in conjunction with media fill test
- Must attempt to analyze growth down to genus if exceed action levels

Cleaning and Disinfecting

June 2008

- Cleaning and disinfecting used interchangeably
- Sporicidal agent not required
- Agent in PEC is not required to be sterile

November 2022

- Defines cleaning and disinfecting
- Requires use of sporicidal agent:
  - Category 1 & 2 - monthly
  - Category 3 – weekly
- In PEC, cleaning, disinfecting, and sporicidal agents must be sterile

IPA: Isopropyl Alcohol
PEC: Primary Engineering Control

Introducing Items into the SEC and PEC

June 2008

- Allows items to be sprayed or wiped prior to introduction into clean side of ante room
- Allows items to be sprayed or wiped prior to introduction into the PEC

November 2022

- Requires items to be wiped with low lint wiper by a gloved person prior to introduction into clean side of ante room
- Requires items to be wiped with sterile low lint wipe prior to introduction into PEC

PEC: Primary Engineering Control
SEC: Secondary Engineering Control

Component Selection

June 2008

- Allows for more discretion in obtaining APIs

November 2022

- Active Pharmaceutical Ingredients (APIs)
  - Must comply with USP-NF monograph, if one exists
  - Must have a COA
  - Must be from FDA registered facility
- Other Components
  - Must comply with USP-NF monograph, if one exists
  - Must have documentation (e.g. COA, labeling)
  - Must be from FDA registered facility

APIs: Active Pharmaceutical Ingredients
COA: Certificate of Analysis

Component Storage

June 2008

- Must monitor temperature of component storage area
- Must monitor humidity of component storage area

November 2022

- Must monitor temperature of component storage area with one of the following:
  - Manually – daily when facility is open
  - Electronically – continuously
- Temperature log must be readily retrievable
- Storage conditions meet the requirements of a compendial monograph, if applicable

Sterilization and Depyrogenation

June 2008

- CSPs not sterilized within 12 hours at cold temperature or 6 hours room temperature must be sterility tested
- Endotoxin Challenge Vials (ECV) must be use – frequency not defined

November 2022

- Injectables must be sterilized within 6 hours of completing preparation
- For filter sterilization, cannot use filters labeled, "For Laboratory Use Only"
- Endotoxin Challenge Vials (ECV) must be used per the facility's SOP

CSP: Compounded Sterile Preparation
SOP: Standard Operating Procedure

Master Formulation

June 2008

- Master Formulation not specifically addressed

November 2022

- Master Formulation required for:
  - CSPs for more than 1 patient
  - CSPs involving nonsterile ingredients

CSP: Compounded Sterile Preparation

Master Formulation Requirements

- Name, strength or activity, and dosage form of the CSP
- Identities and amounts of all ingredients
- Type and size of container–closure system(s)
- Complete instructions for preparing the CSP, including equipment, supplies, a description of the compounding steps, and any special precautions
- Physical description of the final CSP
- BUD and storage requirements
- Reference source to support the stability of the CSP
- Quality control (QC) procedures (e.g., pH testing, filter integrity testing)
- Other information as needed to describe the compounding process and ensure repeatability (e.g., adjusting pH and tonicity, sterilization method (e.g., steam, dry heat, irradiation, or filter)

CSP: Compounded Sterile Preparation
BUD: Beyond Use Date

Compounding Records

June 2008

- Compound Records (CR) vaguely addressed

November 2022

- Compound Records (CR) required for all CSPs

CSP: Compounded Sterile Preparation

Compounding Records Requirements

- Name, strength or activity, and dosage form of the CSP
- Date and time of preparation of the CSP
- 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 CSP
- Name of each component
- Vendor, lot number, and expiration date for each component for CSPs prepared for more than 1 patient and for CSPs prepared from nonsterile ingredient(s)
- Weight or volume of each component
- Strength or activity of each component
- Total quantity compounded
- Final yield (e.g. quantity, containers, number of units)
- Assigned BUD and storage requirements
- Results of Quality Control (QC) procedures (e.g., visual inspection, filter integrity testing, pH testing)
- Master Formulation Record reference for the CSP, if applicable
- Calculations made to determine and verify quantities and/or concentrations of components, if applicable

Visual Inspection of CSP

June 2008

- Must use light and dark background to visually check CSP

November 2022

- Must visually check CSP

CSP: Compounded Sterile Preparation

Labeling

June 2008

- Labeling and label not defined
- 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

- Labeling – all labels and other written, printed, graphic matter on immediate container or, on or in, any package wrapper in which CSP is enclosed
- Label – the part of the labeling on the immediate container

Beyond Use Date: November 2022 Version

- Must also consider chemical and physical stability properties of the drug and/or its formulation
- Aseptic processing
  - Compounding with only sterile ingredients, or
  - Compounding with nonsterile ingredients, followed by sterilization by filtration
    - Note: sterilization by filtration is not a form of terminal sterilization
- Terminal sterilization
  - Compounding with sterile and/or nonsterile starting ingredients and subsequent sterilization with a process to achieve a Probability of a Nonsterile Unit (PNSU) of 10^{-6}
    - Examples: dry heat sterilization, steam sterilization, irradiation
  - Is the preferred method of sterilization, unless contraindicated

Beyond Use Date

June 2008

- Low Risk in Segregated Compounding Area (SCA)
  - 12 hours

November 2022

- Category 1
  - Compounded in SCA
  - 12 hours room temperature
  - 24 hours refrigerated

SCA: Segregated Compounding Area

Beyond Use Date

June 2008

Risk	Sterility Testing	Controlled Room Temp (20°-25°)	Refrigerator (2°-8°)	Freezer (-25° to -10°)
Low	No	48 hours	14 days	45 days
	Yes	BUD limited by stability of CSP		
Medium	No	30 hours	9 days	45 days
	Yes	BUD limited by stability of CSP		
High	No	24 hours	3 days	45 days
	Yes	BUD limited by stability of CSP		

November 2022

Category 2 CSPs				
Preparation Characteristics		Storage Conditions		
Compounding Method	Sterility Testing Performed and Passed	Controlled Room Temp (20°-25°)	Refrigerator (2°-8°)	Freezer (-25° to -10°)
Aseptically processed CSPs	No	1 nonsterile component: 1 day	1 nonsterile component: 4 days	1 nonsterile component: 45 days
		Sterile only components: 4 days	Sterile only components: 10 days	Sterile only components: 45 days
	Yes	30 days	45 days	60 days
Terminally sterilized CSPs	No	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

Beyond Use Date for Category 3

Category 3 CSPs			
Preparation	Storage Conditions		
Compounding Method	Controlled Room Temp (20°-25°)	Refrigerator (2°-8°)	Freezer (-25° to -10°)
Aseptically processed, sterility tested and passed all applicable tests	60 days	90 days	120 days
Terminally sterilized, sterility tested and passed all applicable tests	90 days	120 days	180 days

Sterility Testing

June 2008

- Must sterility test:
  - Extend BUD for any risk level
  - High Risk batches of 25 units or more or not immediately sterilized
- Must follow USP 71 for quantities to be sterility tested
  - Minimum to send for sterility testing is 4

November 2022

- Must sterility test:
  - Category 2 where the BUD requires sterility testing
  - All Category 3 CSP
- For batch quantities of 40 CSPs or more, must follow USP 71 for quantities to be sterility tested
- For batch quantities of 1 to 39 CSPs, test 10% rounded up to nearest whole number
- Maximum batch size for all CSPs requiring sterility testing is limited to 250 final yield units

BUD: Beyond Use Date
CSP: Compounded Sterile Preparation

Bacterial Endotoxin Testing

June 2008

- Required for high risk CSPs compounded in groups of more than 25 single dose packages or in multiple dose packages used for multiple patients

November 2022

- Required: Category 2 CSPs compounded from nonsterile components with a BUD requiring sterility testing
  - Recommended: Category 2 CSPs compounded from nonsterile components with a BUD not requiring sterility testing
- Required: Category 3 CSPs compounded from nonsterile component

BUD: Beyond Use Date
CSP: Compounded Sterile Preparation

Compounded Multiple Dose Vials

June 2008

- Silent on antimicrobial effectiveness testing

November 2022

- Must be prepared as Category 2 or Category 3 CSP
- Must perform antimicrobial effectiveness testing for aqueous multiple-dose CSP
  - May perform testing, required once for used container closure system
  - May rely on data from FDA registered facility using same formulation and container closure system
  - May rely on data from peer review literature using same formulation and container closure system
  - May bracket test using lowest and highest concentrations

CSP: Compounded Sterile Preparation

Single Dose Vials

June 2008

- SDV punctured in ISO 5
- Stored in ISO 5
- May be used up to 6 hours

November 2022

- SDV punctured in ISO 5
- May be used up to 12 hours as long as storage requirements are maintained

SDV: Single Dose Vial

Pharmacy Bulk Packaging

June 2008

- Pharmacy Bulk Packaging treated like a single dose vial
- Stored in ISO 5 up to 6 hours, then discarded

November 2022

- Pharmacy Bulk Packaging must be used per manufacturer's labeling

Use of Compounded Single Dose CSPs and Stock Solution CSPs

June 2008

- Not clearly addressed

November 2022

- When compounded single dose (SD) CSPs or stock solution (SS) CSPs are used to compound additional CSPs
  - Original SD or SS CSPs must be entered/punctured in ISO 5 or better
  - Must be stored under conditions upon which BUD is based
    - Room temperature, refrigerated
  - SD or SS CSP may be used up to 12 hours or its BUD, whichever is shorter
  - Remainder discarded

CSP: Compounded Sterile Preparation
SD: Single Dose
SS: Stock Solution
BUD: Beyond Use Date

Standard Operating Procedures

June 2008

- Does not address the frequency of review of SOPs
- 201 KAR 2:076 Section 1—Policy and Procedures annual review

November 2022

- SOPs must be reviewed every 12 months and documented review by the designated person
- Recommended that all personnel involved in the processes and procedures document and acknowledge the communication of any revisions

SOP: Standard Operating Procedure

Quality Assurance and Quality Control

June 2008

- Has a Quality Assurance requirement

November 2022

- Quality Assurance (QA)
  - System of procedures, activities and oversight that ensures the compounding process consistently meets quality standards
- Quality Control (QC)
  - Sampling, testing and documentation of results that, taken together, ensure that specifications have been met before releasing the CSP
- DP must ensure facility has formal, written QA and QC programs that establish 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

DP: Designated Person
QA: Quality Assurance
QC: Quality Control
CSP: Compounded Sterile Preparation

Complaint Handling and Adverse Events

June 2008

- Complaint Handling and Adverse Events are not specifically addressed

November 2022

- DP must review all complaints
- If quality issue, must investigate and have corrective action
- Must keep readily retrievable record of all complaints, include
  - Name of complaint (or some ID)
  - Date complaint received
  - Nature of complaint
  - Response to complaint
  - Findings of any investigation
  - Follow-up

DP: Designated Person

Compounding Allergenic Extracts

June 2008

- Allergen Extracts as CSPs Section
  - Exempts Allergen CSPs from personnel, environmental, and storage requirements of Chapter if certain criteria are met

November 2022

- Compounding Allergenic Extracts Section
  - Requirements for:
    - Personnel qualifications
    - Hand hygiene and garbing
    - Facilities
    - Cleaning and disinfecting
    - BUDs – up to 1 year
    - Labeling
    - Shipping and transporting
    - Documentation including compounding record

CSP: Compounded Sterile Preparation
BUD: Beyond Use Date

USP 797

- November 2022 version - expected implementation November 1, 2023

- 201 KAR 2:076 specifically references the November 1, 2008 version of USP 797
  - Permit specific waivers are subject to board approval
  - Waivers currently granted:
    - Sterility requirements for inhalation preparation
    - Single dose vial storage
    - Multiple waivers granted for hazardous drug compounding requirements under USP 797 - pharmacies following USP 800 requirements
      - Containment segregated compounding areas
      - Assessment of risk for hazardous drugs