Broad Comparison of USP 795: Nonsterile Compounding

JANUARY 2014 VERSION VERSUS JUNE 2019 VERSION

SEPTEMBER 25, 2019 BOARD OF PHARMACY MEETING

Summary

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

Summary

- Must have a designated person
- Training must be done initially and every 12 months
- Must wash hands and wear gloves to compound
- No carpet in designated compounding area
- Must keep sink clean
- No humidity monitoring required
- Descriptive cleaning schedule
- Evaluation to determine need for powder containment hood, etc.
- APIs must be from FDA registered facility

Summary

- 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 complaint and adverse event investigations
- Patient counseling not included

Scope

January 2014

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

June 2019

- Requires designated person (DP) to oversee USP 795

Scope

January 2014

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

June 2019

- No categories of nonsterile compounding

Training

January 2014

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

June 2019

- 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 included:
  - Knowledge of USP 795 and facility procedures
  - Demonstration of process
  - Documentation of training

June 2019

- Training defined to include:
  - Hand hygiene
  - Garbing
  - Cleaning & sanitizing
  - Handling & transporting
  - Measuring & Mixing
  - Proper use of equipment
  - Documentation of compounding procedures

Training

January 2014

- Training to include:
  - Reading and be familiar with USP 795 and other relevant publications
  - Read and interpret SDS
  - Read and be familiar with procedures

June 2019

- Training to include:
  - Read and understand USP 795 and other relevant literature
  - Understand and interpret SDS and COA, if needed
  - Read and understand pertinent procedures

Training

January 2014

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

June 2019

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

Training

January 2014

- Does not address if only one compounder

June 2019

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

Personal Hygiene and Garbing

January 2014

- Potential contamination issues not addressed
  - Rashes
  - Sunburns
  - Tattoos
  - Respiratory infections

June 2019

- Must notify DP of potential contamination issues
  - Rashes
  - Sunburns
  - Tattoos
  - Respiratory infections
- DP makes determination if person may compound

Personnel Preparation

January 2014

- Compounding personnel maintain good hygiene

June 2019

- Compounding personnel MUST remove:
  - Outer garments
  - Hand & wrist jewelry and piercings if interfere with garbing
  - Ear buds & head phones
- DP may make allowances if state of control is maintained

Hand Hygiene

January 2014

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

June 2019

- Before entering compounding area, personnel MUST:
  - Wash hands and forearms up to elbows for at least 30 seconds with soap and water
  - Dry with single use/disposable towels or wipers
  - Allow hands to dry before donning gloves

Hand Hygiene

January 2014

- Hand hygiene is not specifically addressed

June 2019

- During compounding, personnel:
  - SHOULD wipe or change gloves between compounding with different components
  - MUST change gloves if ripped, torn, punctured, etc.

Glove and Garb Requirements

January 2014

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

June 2019

- MUST wear gloves for all compounding
- MAY wear other garb as deemed needed
  - Gowns
  - Shoe covers
  - Head covers
  - Face masks
  - Eye covers

Buildings and Facilities: Compounding Space

January 2014

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

June 2019

- Space specifically designated for compounding
  - SOP to describe method of designation (i.e. visible perimeter)
  - Other activities cannot be occurring in this space at the same time as compounding
- No carpet

Buildings and Facilities: Storage Area

January 2014

- Appropriate temperature and humidity monitoring

June 2019

- Must monitor temperatures
  - Manually - daily
  - Continuously electronically
- Documentation must be retrievable
- Must calibrate temperature monitoring devices every 12 months
- Components must be stored in appropriate conditions
  - Temperature, humidity, lighting

Buildings and Facilities: Water Source

January 2014

- Must have sink with hot and cold water easily accessible to compounding area

June 2019

- Must have sink with hot and cold water easily accessible to compounding area
- Sink must be emptied of all items not related to compounding when washing equipment
- Must clean sink when visibly soiled before using to clean equipment for compounding

Cleaning and Sanitizing

January 2014

- Compounding is done in appropriately cleaned and sanitized area

June 2019

- Work surfaces
  - At beginning and end of each shift
  - When spills, contamination occurs
  - Between compounding with different components
- Floors
  - Daily
  - After spills, contamination
- Walls
  - Every 3 months
  - After spills, contamination

Cleaning and Sanitizing

January 2014

- Compounding is done in appropriately cleaned and sanitized area

June 2019

- Ceilings
  - When visibly soiled and if known contamination happened
- Storage Shelving
  - Every 3 months
  - After spills, contamination
- If not compounding daily, must clean before starting to compound
- No specific agents discussed

Equipment and Components: Equipment

January 2014

- Use of Containment Ventilated Enclosures (CVE), Biological Safety Cabinets (BSC), single use containment glove bags not specifically addressed

June 2019

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

Equipment and Components: Equipment Cleaning

January 2014

- Equipment must be cleaned after use

June 2019

- CVE, BSC must be cleaned:
  - Beginning and end of shift
  - Spills, contamination
  - Horizontal work surface
    - Between compounding with different components
- Other Equipment must be cleaned:
  - Before use and according to manufacturer
  - If nothing from manufacturer, between compounding with different components

Components: Selection

January 2014

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

June 2019

- Active Pharmaceutical Ingredients (APIs)
  - Must comply with USP/NF monograph, if there is one
  - Must have a Certificate of Analysis (COA)
  - Must be from FDA registered facility

Components: Selection

January 2014

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

June 2019

- All components other than APIs
  - Should have a COA
  - Should be from an FDA registered facility

Components: Receipt

January 2014

- Should obtain COA at time of receipt

June 2019

- For non-manufactured, must review COA
- Must document
  - Date of receipt
  - Quantity received
  - Supplier name
  - Lot number
  - Expiration date
  - Results of any testing

Components: Receipt

January 2014

- Allows transfer of components to other containers

June 2019

- Once component is removed from original container, SHOULD be discard
  - For example, excess from weighing

Components: Evaluation Before Use and Handling

January 2014

- Shall be stored appropriately

June 2019

- Components must be evaluated before use
- Components must be handled properly

Components: Spill and Disposal

January 2014

- Spills not specifically addressed

June 2019

- Must maintain chemical hazard and disposal information (SDS) and update every 12 months
- Must have a spill kit accessible to compounding area
- Must train personnel in use of spill kit
  - Refresher training every 12 months

Master Formulations

January 2014

- Very similar, more wordy

June 2019

- Very similar, more concise

Compounding Records

January 2014

- Very similar
  - Requires duplicate label

June 2019

- Very similar
  - No duplicate label required

Release Inspections

January 2014

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

June 2019

- Prior to releasing, dispensing CNSP, must visually inspect:
  - Physical appearance
    - Including certain characteristics
  - Labeling
  - Container closure
- Must document checks

Labeling

January 2014

- No definition of labeling and label

June 2019

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

Labeling

January 2014

- Prescription container is labeled according to all state and federal laws
- Label SHALL include:
  - BUD
  - Storage information
  - Handling information
- KRS 215.065 – labeling requirements

June 2019

- Label MUST contain:
  - Internal id number
  - Active component(s) and their amounts, activities, concentrations
  - Dosage form
  - Amount or volume of each container
  - Storage conditions, if other than room temperature
  - Beyond Use Date (BUD)
- KRS 215.065 – labeling requirements

Labeling

January 2014

- Labeling SHOULD indicate that this is a compounded preparation

June 2019

- Labeling SHOULD contain:
  - Route of administration
  - Indication prep is compounded
  - Any special handling instructions
  - Any warning statements
  - Name, address, contact info of compounding facility if CNSP leaves facility

Beyond Use Dates (BUDs): Water Activity (Aw) June 2019

- June 2019 version takes into account water activity (Aw) as described in USP 1112, *Application of Water Activity Determination to Nonsterile Pharmaceutical Products*
  - This is the Aw of manufactured products
- Aw aids in determining CNSP susceptibility to microbial contamination and degradation due to hydrolysis
- CNSPs with Aw > 0.6 SHOULD have antimicrobial agent or be refrigerated

Beyond Use Dates (BUDs)

January 2014

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

June 2019

- Beyond Use Date (BUD) – the number of days after which a CNSP is prepared and beyond which it cannot be used
- The day of compounding is Day 1

Beyond Use Dates (BUDs)

January 2014

- Water containing oral formulations
  - 14 days refrigerated
- Water containing topical/dermal and mucosal liquid and semi-solid formulations
  - 30 days

June 2019

- Non-preserved aqueous dosage forms
  - Aw > 0.6
    - Emulsions
    - Creams
    - Gels
    - Solutions
    - Sprays
    - Suspension
- 14 days refrigerated

BUDs

January 2014

- Water containing oral formulations
  - 14 days refrigerated
- Water containing topical/dermal and mucosal liquid and semi-solid formulations
  - 30 days

June 2019

- Preserved aqueous dosage forms
  - Aw > 0.6
    - Emulsions
    - Creams
    - Gels
    - Solutions
    - Sprays
    - Suspension
- 35 days controlled room temperature or refrigerated

BUDs

January 2014

- Nonaqueous formulations
  - 6 months

June 2019

- Non-aqueous dosage forms
  - Non-solid dosage form with reduced Aw ≤ 0.6
    - Suppositories
    - Ointments
    - Fixed oils
    - Waxes
- 90 days controlled room temperature or refrigerated

BUDs

January 2014

- Nonaqueous formulations
  - 6 months

June 2019

- Solid dosage forms
  - Capsules
  - Tablets
  - Granules
  - Powders
- 180 days controlled room temperature or refrigerated

Shorter BUDs

January 2014

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

June 2019

- Must use a shorter BUD if any of the components used have an earlier BUD/expiration date than the BUD per USP 795

Extending BUDs

January 2014

- May use stability information to extend BUDs

June 2019

- If there is a USP/NF monograph
  - May use BUD of monograph
- CNSPs with stability information
  - Maximum of 180 days
  - Stability study using stability indicating assays for:
    - API
    - CNSP
    - Container closure
  - May be published or unpublished

Extending BUDs

January 2014

- Susceptible CNSPs SHOULD contain suitable antimicrobial agents

June 2019

- If extending BUD for aqueous dosage forms SHOULD:
  - Test for microbial effectiveness

Standard Operating Procedures (SOPs)

January 2014

- SHOULD have written SOPs covering all significant procedures performed in compounding area
- Only minimal required SOPs

June 2019

- Must have SOPs on all aspects of compounding operation
- Personnel conducting or overseeing compounding must be trained in SOPs
- Personnel responsible for ensuring SOPs followed

Quality Assurance and Quality Control

January 2014

- Quality Control
  - Checking documentation
  - Checking compounding process

June 2019

- 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 CNSP

QA and QC

January 2014

- No formalized program

June 2019

- Must have a formal QA and QC program that establishes system of:
  - Adherence to procedures
  - Prevention & detection of errors and other quality issues
  - Evaluation of complaints and adverse events
  - Appropriate investigations and corrective actions

QA and QC

January 2014

- No required SOPs
- No formalized program

June 2019

- Must have SOPs on QA and QC program
  - Reviewed every 12 months
  - Documented reviewed every 12 months
- DP in charge of program

Complaint Handling and Adverse Events

January 2014

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

June 2019

- 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

Complaint Handling and Adverse Events

January 2014

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

June 2019

- Adverse Event (AE)
  - DP must review all AE to determine if quality issue
  - SHOULD report to MedWatch or Form FDA 1932a (animals)

Documentation

January 2014

- Not as clear as to required documentation

June 2019

- Must have documentation of:
  - Training
  - Equipment records
  - COAs
  - Receipt of components
  - SOPs, MFs, CRs
  - Release inspection and testing
  - Complaints and AE
  - Results of investigations
  - Corrective actions

Documentation

January 2014

- 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

June 2019

- Documentation relating to CNSP, must be readily retrievable for 3 years
  - MF, CR, release information
- 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

Patient Counseling

January 2014

- Required patient counseling

June 2019

- Patient counseling not addressed

Compounding for Animals

January 2014

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

June 2019

- Introduction states USP 795 is the minimum standard for compounding for humans and animals

USP 795

- June 2019 version - expected compliance Federally has been delayed to an unknown time
  - Previously was December 1, 2019
- 201 KAR 2:076 specifically references the January 1, 2014 version of USP 795
  - Waivers are allowed
  - No waivers requested as of this date