Broad Comparison of USP 797: Sterile Compounding

JUNE 2008 VERSION VERSUS JUNE 2019 VERSION

SEPTEMBER 25, 2019 BOARD OF PHARMACY MEETING

Summary

- Easier to read
- More clear about documentation requirements and processes
- Have designated person (DP)
- No risk categories – was low, medium, and high
- Now Category 1 or Category 2 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 done every 6 months

Summary

- 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 compounding suite may have longer BUDs
- Pharmaceutical Compounders (PC) in SCA may only be used for Category 1 CSPs
  - 12 hour BUD room temperature or 24 hour BUD refrigerated
- PC in ISO 8 room may have longer BUDs
  - Anteroom not required
- ISO 8 environment required to have 20 Air Changes Per Hour (ACPH)
- Sink may be outside ante room in a clean space

Summary

- Surface sampling must be done monthly
- Must attempt to analyze growth to the genus only if out of limits
- Cleaning and disinfecting more clearly defined
- Requires use of sporicidal agent monthly
- Requires Master Formulations, exception CSP for 1 person
- 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

Designated Person (DP)

June 2008

- 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 797

Scope: Types of Compounded Sterile Preparations (CSPs) Clarified

June 2008

- Irrigations for wounds and body cavities

June 2019

- 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.

June 2019

- 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.

Proprietary Bag and Vial System

June 2008

- Follow manufacturer's instructions for handling and storing systems

June 2019

- 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 (BUD)

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

June 2019

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

CSP Categories

June 2008

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

June 2019

- 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

Training

June 2008

- Every 12 months
  - Cleaning
  - Didactic exam

June 2019

- Every 12 months:
  - Cleaning and disinfecting
  - Calculations, measuring, mixing
  - Use of equipment
  - Documentation of compounding process
  - Principles of HEPA in ISO 5
  - Proper use of PEC
  - Principles of movement of materials and people
  - Written or electronic exam

Training

June 2008

- Low and Medium Risk – 12 months
  - Hand hygiene and garbing
  - Observed aseptic technique
  - Media fill test (MFT)
  - Gloved fingertip test (GFT)
    - Initially, 3 times, 0 growth
    - After MFT, up to 3 growths
- High risk – 6 months
  - Same as above

June 2019

- Compounding personnel – 6 months
  - Hand hygiene and garbing
  - Observed aseptic technique
  - Media fill test (MFT
  - Gloved fingertip test (GFT)
    - Initially, 3 times, 0 growth
    - After MFT, up to 3 growths

Personal Hygiene

June 2008

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

June 2019

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

Personnel Preparation

June 2008

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

June 2019

- 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

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

June 2019

- Must not use brushes
- Must not use air dryer
- Must use closed system (non-refillable) soap container
- Remove visible debris with nail pick
- Use alcohol based hand rub before donning sterile gloves
- Sterile gloves not donned or doffed in ISO 5

Gloves

June 2008

- Not specifically stated to don sterile gloves over isolator gloves
- Apply sIPA 70% each time leave ISO 5

June 2019

- States sterile gloves must be donned over isolator gloves
- Apply sIPA 70%:
  - Regularly
  - When touch nonsterile surface

Types of Secondary Engineering Controls (SECs) and Design

June 2008

- Allows for HEPA filters upstream
- Must have line of demarcation (LOD) in ante room

June 2019

- HEPA filters must be in ceiling of buffer and ante rooms
- Must have LOD in ante room OR have clean and dirty ante rooms

Types of Primary Engineering Controls (PECs) and Placement

June 2008

- No mention of Integrated Vertical Laminar Flow Zone (IVLFZ)

June 2019

- Laminar Airflow Work Bench (LAWF)
- Integrated Vertical Laminar Flow Zone (IVLFZ)
  - Per USP 795 – it is difficult to achieve and maintain unidirectional airflow in IVLFZs
- Biological Safety Cabinet (BSC)

Types of Primary Engineering Controls (PECs) 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

June 2019

- Restricted-Access Barrier System (RABS)
  - Compounding Aseptic Isolator (CAI)
  - Compounding Aseptic Containment Isolator (CACI)
- For Category 1 – may be in SCA
- For Category 2 – must be in clean room suite with buffer and ante rooms

Types of Primary Engineering Controls (PECs) and Placement

June 2008

- Pharmaceutical Compounder (PC) – not addressed

June 2019

- Pharmaceutical Compounders (PC)
- For Category 1 – may be in SCA
- For Category 2 – must be in ISO 8 environment
  - Do not need ante room

Air Exchange Requirements (ACPH)

June 2008

- Recommended ISO 8 environments have 20 ACPH

June 2019

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

Water Sources

June 2008

- Sink must be on clean side of ante room

June 2019

- Allows sink to be inside or outside of ante room
- If outside ante room, must be in a clean space

Certification

June 2008

- Certification report not required to record number of people in each PEC and SEC during particle counts and smoke testing

June 2019

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

Environmental Monitoring

June 2008

- Silent on time of taking viable air sampling and surface sampling

June 2019

- Viable air sampling must be conducted under dynamic conditions
- Surface sampling must be performed at end of compounding activity before area has been cleaned

Viable Air Sampling

June 2008

- 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

June 2019

- 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

June 2019

- Surface sampling performed monthly
- Performed at the end of compounding prior to cleaning
- 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

June 2019

- Defines cleaning and disinfecting
- Requires use of sporicidal agent monthly

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

June 2019

- 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 low lint wiper prior to introduction into PEC

Component Selection

June 2008

- Allows for more discretion in obtaining APIs

June 2019

- Active Pharmaceutical Ingredients (APIs)
  - Must be from FDA registered facility
- Other Components
  - Should be from FDA registered facility

Component Storage

June 2008

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

June 2019

- Must monitor temperature of component storage area
- Humidity not required to be monitored in component storage area

Sterilization

June 2008

- CSPs not sterilized within 12 hours at cold temperature or 6 hours room temperature must be sterility tested

June 2019

- Injectables must be sterilized within 6 hours of completing preparation
- For filter sterilization, cannot use filters labeled, "For Laboratory Use Only"

Depyrogenation

June 2008

- Endotoxin Challenge Vials (ECV) must be use – frequency not defined

June 2019

- Endotoxin Challenge Vials (ECV) must be used annually

Master Formulation

June 2008

- Master Formulation (MF) not specifically addressed

June 2019

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

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)

Compounding Records (CR)

June 2008

- Compound Records (CR) vaguely addressed

June 2019

- Compound Records (CR) required for all CSPs

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
- Assigned BUD and storage requirements
- Results of 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

June 2019

- Must visually check CSP

Sterility Testing Numbers

June 2008

- Must follow USP 71 for quantities to be sterility tested
  - Minimum to send for sterility testing is 4

June 2019

- For quantities of 40 CSPs or more, must follow USP 71 for quantities to be sterility tested
- For quantities of 1 to 39 CSPs, test 10% rounded up to nearest whole number

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

June 2019

- Category 2 CSPs compounded from nonsterile components with a BUD requiring sterility testing MUST be endotoxin tested
- Category 2 CSPs compounded from nonsterile components with a BUD not requiring sterility testing SHOULD be endotoxin tested

Labeling

June 2008

- Labeling and label not defined

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

Beyond Use Date (BUD): Definitions from June 2019 Version

- 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

BUDs

June 2008

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

June 2019

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

BUDs

June 2008

- Low Risk – no sterility testing
  - 48 hours room temperature
  - 14 days refrigerated
  - 45 days frozen
- Medium Risk – no sterility testing
  - 30 hours room temperature
  - 9 days refrigerated
  - 45 days frozen

June 2019

- Category 2
- Aseptically compounded
- No sterility testing
- All sterile ingredients
  - 4 days room temperature
  - 10 days refrigerated
  - 45 days frozen

BUDs

June 2008

- High Risk – no sterility testing
  - 24 hours room temperature
  - 3 days refrigerated
  - 45 days frozen

June 2019

- Category 2
- Aseptically compounded
- No sterility testing
- Nonsterile components
  - 1 day room temperature
  - 4 days refrigerated
  - 45 days frozen

BUDs

June 2008

- Low, Medium, High Risk
- Sterility tested
- BUD is limited by stability of CSP

June 2019

- Category 2
- Aseptically Compounded
- Sterility tested
- Sterile and/or nonsterile starting ingredients
  - 30 days room temperature
  - 45 days refrigerated
  - 60 days frozen

BUDs

June 2008

- High Risk – no sterility testing
  - 24 hours room temperature
  - 3 days refrigerated
  - 45 days frozen

June 2019

- Category 2
- Terminally sterilized
- No sterility testing
  - 14 days room temperature
  - 28 days refrigerated
  - 45 days frozen

BUDs

June 2008

- High Risk
- Sterility tested
- BUD is limited by stability of CSP

June 2019

- Category 2
- Terminally Sterilized
- Sterility tested
  - 45 days room temperature
  - 60 refrigerated
  - 90 frozen

Compounded Multiple Dose Vials

June 2008

- Silent on antimicrobial effectiveness testing

June 2019

- Must perform antimicrobial effectiveness testing
  - May perform testing, required once
  - May rely on data from FDA registered facility
  - May rely on data from peer review literature
  - May bracket test using lowest and highest concentrations

Single Dose Vials (SDV)

June 2008

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

June 2010

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

Pharmacy Bulk Packaging

June 2008

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

June 2019

- 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

June 2019

- 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
  - Reminder discarded

Standard Operating Procedures (SOPs)

June 2008

- Does not address the frequency of review of SOPs

June 2019

- SOPs must be reviewed every 12 months and documented review

Quality Assurance and Quality Control

June 2008

- Has a Quality Assurance requirement

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

Complaint Handling and Adverse Events

June 2008

- Complaint Handling and Adverse Events are not specifically addressed

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

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

June 2019

- Compounding Allergenic Extracts Section
  - Not Category 1 or 2 CSPs
  - Requirements for:
    - Personnel qualifications
    - Hand hygiene and garbing
    - Facilities
    - Cleaning and disinfecting
    - BUDs – up to 1 year
    - Labeling
    - Shipping and transporting
    - Documentation including CR

USP 797

- 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 June 1, 2008 version of USP 797
  - Waivers are allowed
    - Waiver granted for inhalation being a clean preparation but not sterile
    - Waiver granted to follow SDV
    - Waiver to nuclear pharmacy to open syringes outside ISO 5