## 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) ► Requires designated person to oversee USP 797 ► 201 KAR 2:076 Section 3 ► Requires PIC to be knowledgeable and oversee compounding

## Scope: Types of Compounded Sterile Preparations (CSPs) Clarified June 2008 Irrigations for wounds and body cavities 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

- 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

- 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 June 2019 ▶ Every 12 months: ► Every 12 months ▶ Cleaning and disinfecting ▶ Cleaning ► Calculations, measuring, mixing ▶ Didactic exam Use of equipment Documentation of compounding ▶ Principles of HEPA in ISO 5 Proper use of PEC Principles of movement of materials and people Written or electronic exam



### Personal Hygiene June 2008 June 2019 ▶ Cannot compound if have: Must inform DP if have: Rashes Rashes Oozing sores Oozing sores ▶ Conjunctivitis ▶ Conjunctivitis ▶ Sun burn Recent tattoos Respiratory infection Respiratory infection ▶ DP determines if person can compound and 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 (nonrefillable) 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

- 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)

- 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

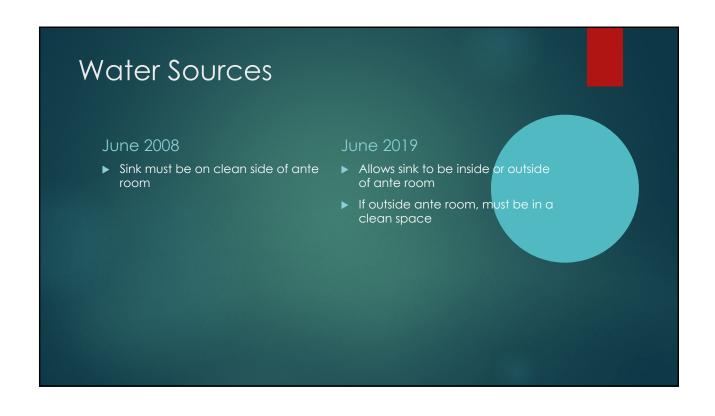
## Types of Primary Engineering Controls (PECs) and Placement

### June 2008

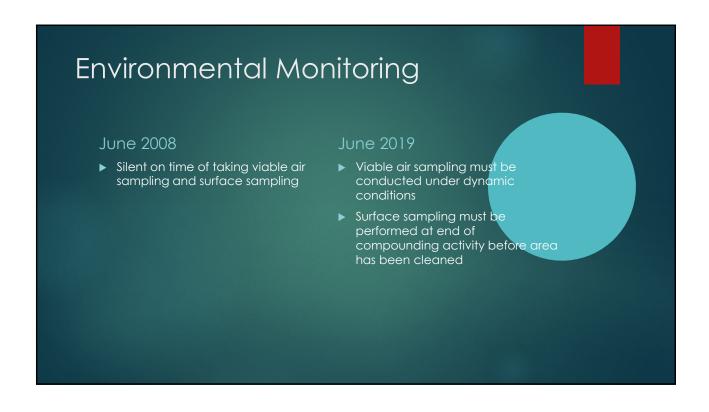
Pharmaceutical Compounder (PC) – not addressed

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



## 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



### 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

- 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

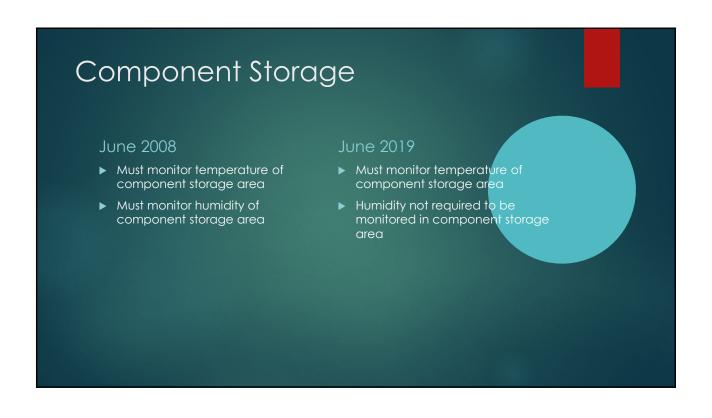
## Introducing Items into the SEC and PEC

### June 2008

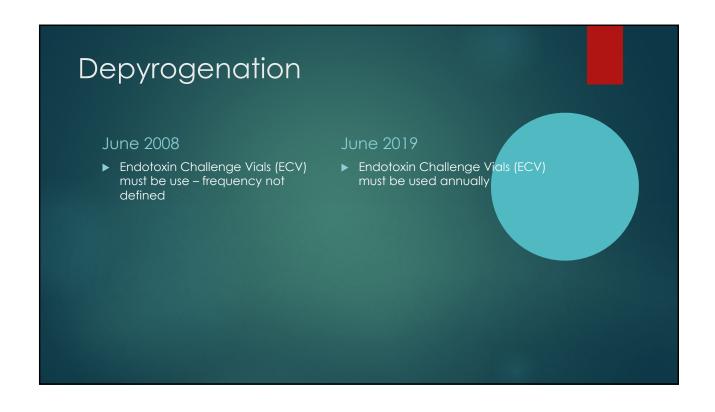
- Allows items to be sprayed or wiped prior to introduction into clean side of ante room
- Allows items to be sprayed or wiped prior to introduction into the PEC

- 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

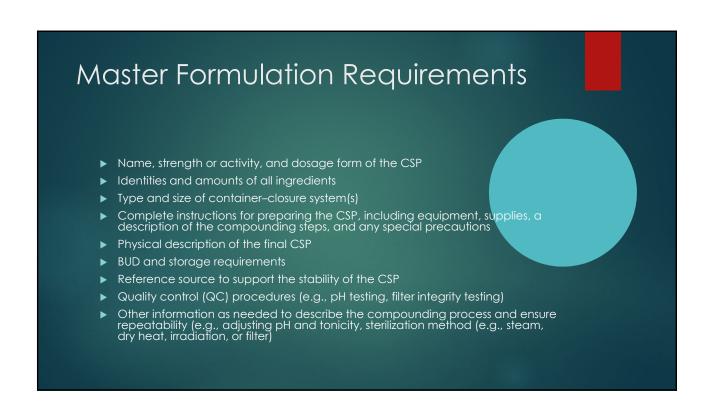
## June 2008 Allows for more discretion in obtaining APIs June 2019 Active Pharmaceutical Ingredients (APIs) Must be from FDA registered facility Other Components Should be from FDA registered facility



# 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"



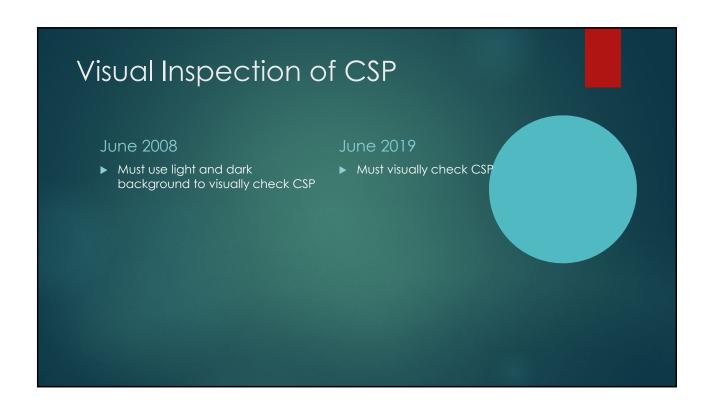
## Master Formulation June 2008 Master Formulation (MF) not specifically addressed June 2019 Master Formulation required for CSPs for more than 1 patient or involving nonsterile ingredients

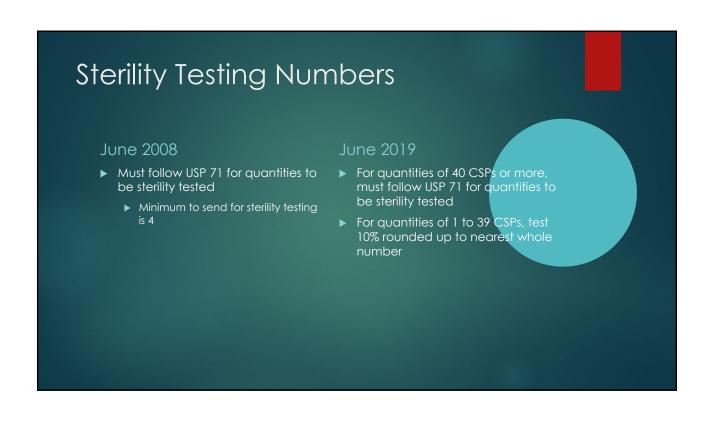


## Compounding Records (CR) June 2008 Compound Records (CR) vaguely addressed June 2019 Compound Records (CR) required for all CSPs

### 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





### **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

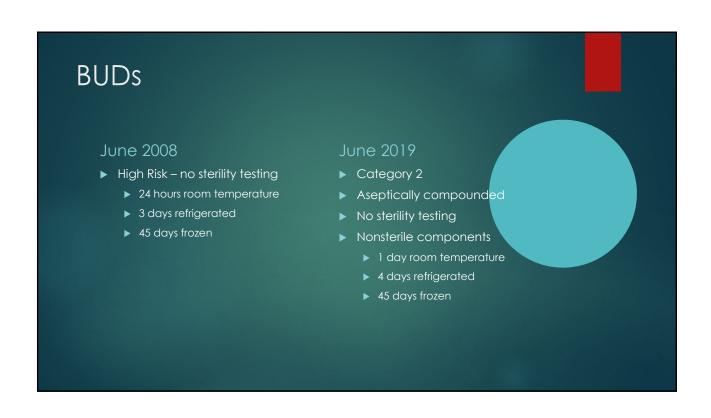
- ► Labeling all labels and other written, printed, graphic matter on immediate container or, on or in, any package wrapper in which CNSP is enclosed
- Label the part of the labeling on the immediate container

## 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

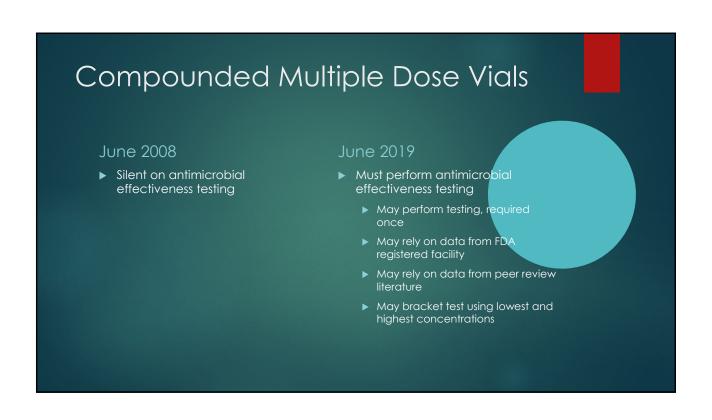
### **BUDs** June 2008 June 2019 ► Low Risk – no sterility testing ▶ Category 2 ▶ 48 hours room temperature Aseptically compounded ▶ 14 days refrigerated No sterility testing ▶ 45 days frozen ► All sterile ingredients ► Medium Risk – no sterility testing 4 days room temperature ▶ 30 hours room temperature ▶ 10 days refrigerated 9 days refrigerated ▶ 45 days frozen ▶ 45 days frozen











## 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



## 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

- ▶ 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