Understanding the new USP 797 Guidelines: Meaningful Changes

DIANEYSIS AVENDANO PHARMD., CPH., BCPS. BCSCP

ILEANA SOTO PHARMD., BCSCP

ACPE Accreditation
Request for Continuing Education

- Following the webinar attendees will receive a link to evaluate the presentation (SurveyMonkey link) . The evaluation will be used as verification of attendance and for CE purposes.
- **The link to the evaluation will be active until July 5th at noon. PLEASE complete by the deadline.**
- Allow 1-2 weeks following the deadline for CE reporting to CE Broker and CPE Monitor.
- Contact fshp@fshp.org if you do not receive aa link to the evaluation.

Presenters' Biographies

Ileana Soto Pharm.D., BCSCP is a Compounding Pharmacy Supervisor at Memorial Miramar Hospital in Florida. She earned her Doctor of Pharmacy degree from University of Arkansas for Medical Sciences and is a board-certified Sterile Compounding Pharmacist.

https://urldefense.com/v3/__http://linkedin.com/in/ileana-soto-b2a43129__;!!LqvVzw!RETEHYLnCm8Pva3D1i7y051q7ZCT0qcBbyWStxrRMTSnbSrd5BaUN0jVGnXuVxi0eSw1enARpP6wDw$

Dianeysis H. Avendano Pharm.D., BCSP, BCSCP is a Clinical Manager of Pharmacy at Memorial Miramar Hospital in Florida. She earned her Doctor of Pharmacy degree from NSU College of Pharmacy, where she now serves as an affiliate professor. Dr. Avendano is board certified in pharmacotherapy and sterile compounding, she served as one of nine inaugural members for the Board of Pharmacy Specialties Council on Compounded Sterile Preparations and is now a sterile compounding item writer for the Board of Pharmaceutical Specialties. Dr. Avendano specializes in implementing safe sterile compounding practices and helping hospitals and pharmacies obtain compliance with compounding regulations such as those in USP chapters <795>, <797> and <800>. http://linkedin.com/in/dianeysis-avendano-ab703460

Disclosures

The speaker reports no relevant financial or nonfinancial relationships, interests or affiliations to the materials and products discussed in this presentation

The changes mentioned in this presentation are not all inclusive.

Meaningful represents the presenters' opinion.

Refer to USP 797 for all the changes

OBJECTIVES

- Illustrate the history behind the revisions to United States Pharmacopeia compounding chapters
- Describe the major changes between the 2008 and the 2022 versions of USP <797> (effective November 1st, 2023)
- Provide examples of implementation strategies that meet the compliance requirements of the revised 2023 version of USP <797>
- Describe the responsibilities of designated person and compounding personnel
- Explain the role of the pharmacist in oversight and compliance with sterile compounding practices

TERMINOLOGY

BSC: Biological Safety Cabinet

BUD: Beyond Use Date

CAI: Compounding Aseptic Isolator

CACI: Compounding Aseptic Containment Isolator

CFU: Colony Forming Unit

CNSP: Compounded Nonsterile Preparation

CSP: Compounded Sterile Preparation

COA: Certificate of Analysis

SDS: Safety Data Sheet

CSTD: Close System Transfer Device

HEPA: High Efficiency Particulate Air

ISO: International Organization for Standardization

IPA: Isopropyl Alcohol

LAFW: Laminar Air Flow Workbench

PEC: Primary Engineering Control

PPE: Personal Protective Equipment

PNSU: Probability of Non Sterile Unit

QA: Quality Assurance

SCA: Segregated Compounding Area

USP: United States Pharmacopeia

The United States Pharmacopeia (USP) and It's History

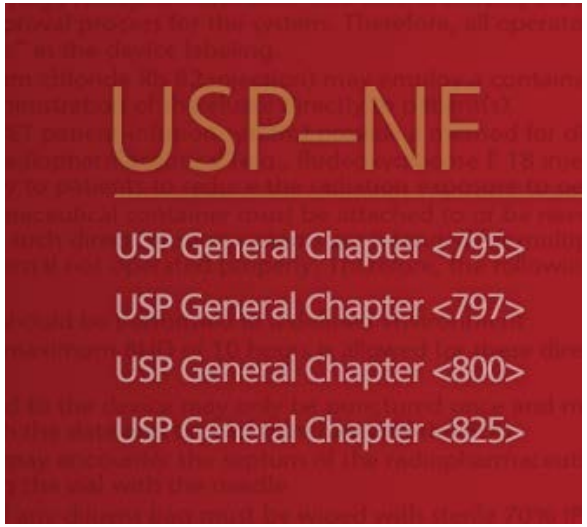
Blum K. Happy 200th Birthday USP. Pharmacy Practice News. Vol.47 No. 4 April 2020

- 1848 Drug Information Act
  - "Good Enough For America"
- Official compendia of the United States
  - United States Pharmacopeia (USP)
  - National Formulary (NF)
- Private, Non-governmental
- No enforcement authority

USP –NF Monographs A Recipe Book

- Delineate compounding requirements
- Compliance with the monograph is required and apply to any compounded article marketed in USA
- Standardization is the goal

USP Compounding Chapters



- USP general chapters below <1000> : Applicable and compendially required if:
  - Referenced in a monograph
  - Referenced in another chapter below <1000>
  - Referenced in general notices
- USP general chapters between <1000> - <1999>: For informational purposes
- FDA: Federal Food, Drug, and Cosmetic Act (FDCA)
  - Adulteration and misbranding provisions of the FDCA
- Florida DOH/BOP: Administrative Code rule 64B16-27-797

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/questions-and-answers-current-good-manufacturing-practices-general-provisions

Why Is It Important?

1990: Contaminated non-sterile cardioplegia solution compounded in a Nebraska hospital causes patients to contract a bacterial infection. Four died

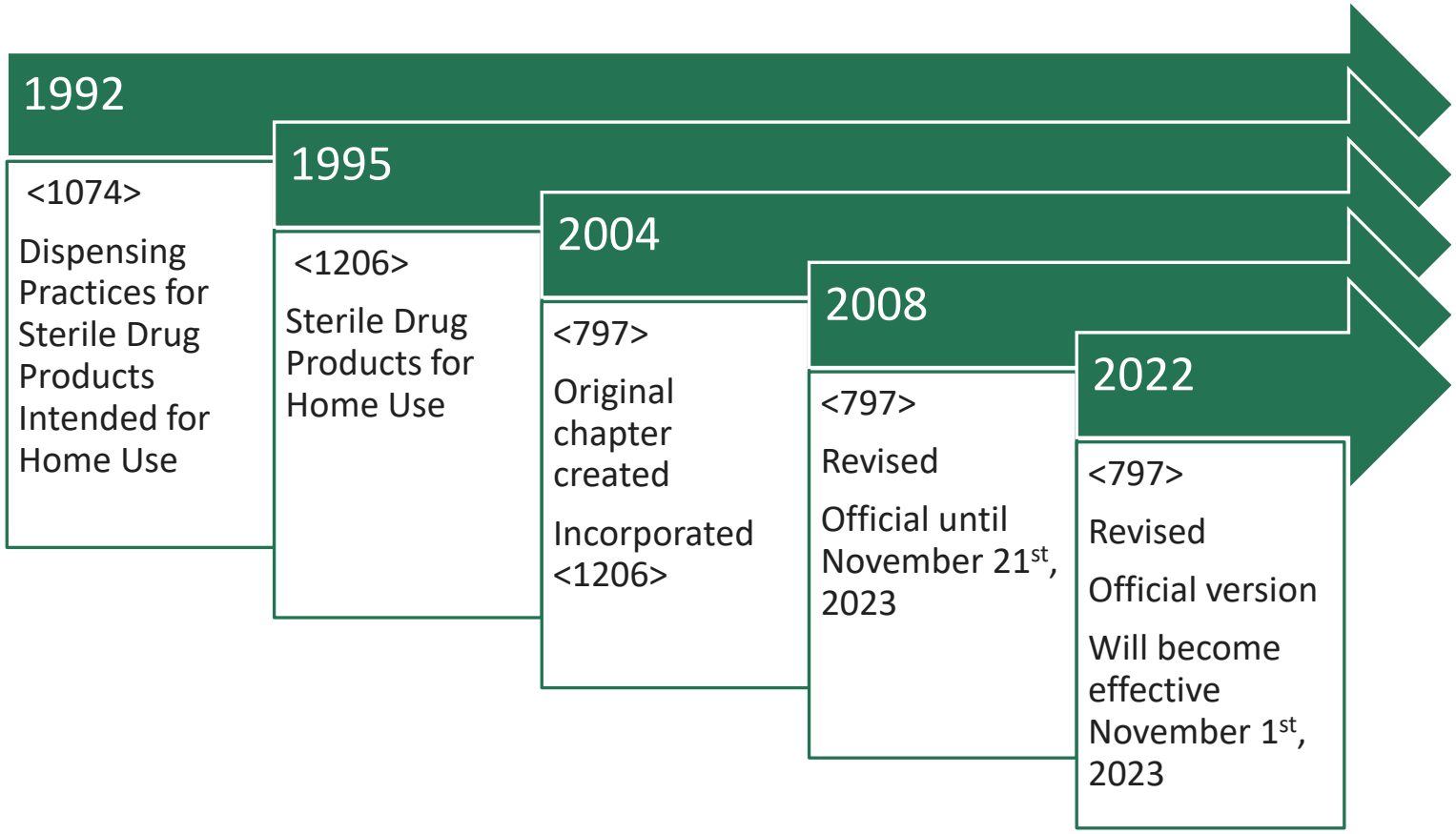
1998: Poor employee hand hygiene and garbing practices associated with contaminated pre-filled syringes causing Enterobacter cloacae bloodstream infections in 10 children in California

2012: 384 patients contracted fungal meningitis and spinal infections from contaminated methylprednisolone acetate injections compounded by New England Compounding Pharmacy, which lacked compliance with USP 797 and operated more like a manufacturer

https://www.youtube.com/watch?v=7U9fnDYec-k&feature=youtu.be
https://www.wcvb.com/article/necc-owner-to-be-sentenced-nearly-5-years-after-meningitis-outbreak/10220558#

ISMP: Sterile Compounding Tragedy is a Symptom of a Broken System on Many Levels | Institute For Safe Medication Practices (ismp.org) October 18 2012. Accessed 6.01.2023

USP 797


1992
<1074>
Dispensing Practices for Sterile Drug Products Intended for Home Use
1995
<1206>
Sterile Drug Products for Home Use
2004
<797>
Original chapter created
Incorporated <1206>
2008
<797>
Revised
Official until November 21st, 2023
2022
<797>
Revised
Official version
Will become effective November 1st, 2023

MEANINGFUL CHANGES

The changes mentioned in this presentation are not all inclusive. Meaningful represents the presenters' opinion.

Refer to USP 797 for all the changes

Scope of USP 797

- **Alternative technologies**: Deemed not inferior and not used to alter BUD or compounding environment
- Applies to CSPs made for humans or **animals**
- Clarification of irrigations for **internal** body cavities
  - Pulmonary inhalation, baths/soaks for live organs/tissues
- **Docking and activation** of proprietary bag and vial systems for **future activation** considered compounding
- **Repackaging** of a conventionally manufacturer sterile product considered compounding

Assessment question #1

A patient visits an urgent care center and is diagnosed with community acquired pneumonia. The physician prescribes Azithromycin 500mg IVPG one time over 1 hour.

The nurse prepares one dose, following the products labeling recommendations which include reconstitution and further dilution in normal saline prior to administration, concentration and storage requirements.

Is this considered compounding per the scope of the revised 2022 USP 797?

- A) YES
- B) NO

Azithromycin Package Insert

Preparation of the solution for intravenous administration is as follows:
Reconstitution

Prepare the initial solution of ZITHROMAX® (azithromycin for injection) by adding 4.8 mL of Sterile Water For Injection to the 500 mg vial and shaking the vial until all of the drug is dissolved. Since ZITHROMAX® (azithromycin for injection) is supplied under vacuum, it is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact amount of 4.8 mL of Sterile Water is dispensed. Each mL of reconstituted solution contains 100 mg azithromycin. Reconstituted solution is stable for 24 hours when stored below 30°C or 86°F.

Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.

Dilute this solution further prior to administration as instructed below.

Dilute this solution further prior to administration as instructed below.

Dilution

To provide azithromycin over a concentration range of 1.0-2.0 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin solution into the appropriate amount of any of the diluents listed below:

Normal Saline (0.9% sodium chloride)

Final Infusion Solution Concentration (mg/mL)	Amount of Diluent (mL)
1.0 mg/mL	500 mL
2.0 mg/mL	250 mL

Baxter
Manufactured for
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
by: Pfizer Inc, NY, NY 10017

For Product Inquiry 1 800 ANA DRUG
(1-800-262-3784)

LAB-0301-4.0
Revised August 2007

ZITHROMAX® (azithromycin for injection) should not be given as a bolus or as an intramuscular injection.

Other intravenous substances, additives, or medications should not be added to ZITHROMAX® (azithromycin for injection), or infused simultaneously through the same intravenous line.

Storage

When diluted according to the instructions (1.0 mg/mL to 2.0 mg/mL), ZITHROMAX® (azithromycin for injection) is stable for 24 hours at or below room temperature (30°C or 86°F), or for 7 days if stored under refrigeration (5°C or 41°F).

https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050733s018lbl.pdf (accessed 5.11.2023)

Preparation Per Approved Labeling OUT OF SCOPE FOR 797

2008: CSP INCLUDES

- Manufactured sterile products prepared strictly according to the instructions appearing in manufacturers' approved labeling:
  - Considered compounding
  - Labeling may not include all environmental quality, storage times, microbiological contamination studies to determine BUD

2022: CSP OUT OF SCOPE FOR 797

Preparation per approved labeling not considered compounding as long as

- Single dose for one individual patient
- Labeling must describe diluent, resultant strength, container closure system, and storage time

Azithromycin Package Insert

Preparation of the solution for intravenous administration is as follows:
Reconstitution

Prepare the initial solution of ZITHROMAX® (azithromycin for injection) by adding 4.8 mL of Sterile Water For Injection to the 500 mg vial and shaking the vial until all of the drug is dissolved. Since ZITHROMAX® (azithromycin for injection) is supplied under vacuum, it is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact amount of 4.8 mL of Sterile Water is dispensed. Each mL of reconstituted solution contains 100 mg azithromycin. Reconstituted solution is stable for 24 hours when stored below 30°C or 86°F.

Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.

Dilute this solution further prior to administration as instructed below.

Dilute this solution further prior to administration as instructed below.

Dilution

To provide azithromycin over a concentration range of 1.0-2.0 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin solution into the appropriate amount of any of the diluents listed below:

Normal Saline (0.9% sodium chloride)

Final Infusion Solution Concentration (mg/mL)	Amount of Diluent (mL)
1.0 mg/mL	500 mL
2.0 mg/mL	250 mL

Baxter
Manufactured for
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
by: Pfizer Inc, NY, NY 10017

For Product Inquiry 1 800 ANA DRUG
(1-800-262-3784)

LAB-0301-4.0
Revised August 2007

ZITHROMAX® (azithromycin for injection) should not be given as a bolus or as an intramuscular injection.

Other intravenous substances, additives, or medications should not be added to ZITHROMAX® (azithromycin for injection), or infused simultaneously through the same intravenous line.

Storage

When diluted according to the instructions (1.0 mg/mL to 2.0 mg/mL), ZITHROMAX® (azithromycin for injection) is stable for 24 hours at or below room temperature (30°C or 86°F), or for 7 days if stored under refrigeration (5°C or 41°F).

https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050733s018lbl.pdf (accessed 5.11.2023)

Assessment question #1

A patient visits an urgent care center and is diagnosed with community acquired pneumonia. The physician prescribes Azithromycin 500mg IVPG one time over 1 hour.

The nurse prepares one dose, following the products labeling recommendations which include reconstitution and further dilution in normal saline prior to administration, concentration and storage requirements.

Is this considered compounding per the scope of the revised 2022 USP 797?

- A) YES
- **B) NO**

Immediate Use CSPs

Immediate Use CSP 2008	Immediate Use CSP 2022
Emergency situations	
Low Risk level preparations • Simple transfer of no more than three commercially manufactured packages • No more than two entries into any one container	Prepared from not more than three different sterile products *(not packages)* • Preparation follows physical/chemical compatibility
Sterile Non-hazardous	Sterile Hazardous preparations must additionally comply with **USP 800**
Continuous compounding process not exceeding 1 hour, and administration begins within 1 hour of the start of the preparation	Administration begins within **4 hours** from start of preparation
	Written SOPs on aseptic process
	Personnel trained to demonstrate competency on aseptic technique • Frequency not specified

Note: Compounders can prepare multiple doses intended for use in one or more patients in a single batch if conditions in section 1.3 are met. It also requires a compounding record

Categories of CSPs

2008

LOW RISK COMPOUNDING
- BUD 48hr RT/ 14 days R. / 45 days F.
- Simple aseptic manipulations using not more than 3 packages and no more than 2 entries into one container

LOW RISK COMPOUNDING WITH 12 HOURS BUD
- PEC in a segregated compounding room

MEDIUM RISK COMPOUNDING
- BUD 30hr RT/ 10 days R. / 45 days F.
- Complex aseptic manipulations for multiple patients or to one patient on multiple occasions

HIGH RISK COMPOUNDING
- BUD 24hr RT/ 3 days R. / 45 days F.
- Non-sterile ingredients
- Poor quality ingredients, environmental controls or garbing requirements, etc.

2022

CATEGORY 1 CSPs	• **Prepared in a PEC located in an unclassified segregated compounding room** • **BUD up to 12hr RT / up to 24hr R.**
CATEGORY 2 CSPs	• **Prepared in a cleanroom suite** • **BUD > 12hr RT/ 24hr R** • **Refer to table 13 for maximum BUDs**
CATEGORY 3 CSPs	• **Prepared in a cleanroom suite** • **Sterility testing required & endotoxin when applicable** • **More requirements for personnel qualifications, sterile garb, sporicidal disinfectants & frequency of environmental monitoring** • **BUD > Category 2 CSPs** • **Refer to table 14 for maximum allowed BUDs**

RT: Controlled Room Temperature / R: Cold Temperature / F: Frozen solid state between -25 and -10 degrees Celsius

Designated Person

- One or More individual
- Responsible and accountable for:
  - Operations
  - Training and competency of personnel
  - SOPs appropriate and implemented
  - Corrective actions taken if problems, deviations, failures, or errors identified
  - Quality assurance and control program
  - Overall performance of compounding facility

Personnel Training and Competency Evaluation

Training and Testing / Hand Hygiene/Gloved Fingertips / Media-Fill Sampling

ILEANA SOTO

Assessment question

A pharmacy technician at XYZ Universal Hospital compounds category 2 CSPs.

How often is this technician's ongoing Garbing Competency

(including GFT) and Media Fill with Post-GFT and Surface

Sampling done?

- A) at least every 3 months
- B) at least every 6 months
- C) at least every 12 months

Personnel Training and Evaluation
Who *must* be trained

- Designated person
- All compounding personnel
- Personnel with direct oversight of compounders
- Personnel compounding immediate use CSPs
- Personnel who perform restocking and cleaning in the cleanroom suite

Training Program- Core skills

USP <797> 2008	USP <797> 2022
Personnel who prepare CSPs Initially – Before any compounding personnel begins to prepare CSPs Annually – Low/Medium risk level compounding Semiannually – High risk level compounding	

Designated person	initially and every 12 months
compounding personnel	initially and every 12 months
Personnel with direct oversight of compounders	initially and every 12 months
Personnel compounding immediate use CSPs	as determined by facility's SOP
Personnel who perform restocking and cleaning in the cleanroom suite	as determined by facility's SOP

Training Program –Observation & Sampling

	USP <797> 2008	USP <797> 2022	
Visual Observation of Hand Hygiene and Garbing with Gloved Fingertip and Thumb (GFT) Sampling	Initially – Before any compounding personnel begins to prepare CSPs		Initially for all personnel
	Low- and medium-risk level: at least annually	Compounding personnel	Category 1 and 2 at least every 6 months Category 3 at least every 3 months
	High-risk level: at least semi-annually	Designated person	At least every 12 months
Media Fill with Post GFT and Surface Sampling	Initially – Before any compounding personnel begins to prepare CSPs	Personnel with direct oversight of compounders	At least every 12 months
	Low- and medium-risk level: at least annually	Personnel compounding immediate use CSPs	as determined by facility's SOP
	High-risk level: at least semi-annually	Personnel who perform restocking and cleaning in the cleanroom suite	as determined by facility's SOP

Personnel Training and Evaluation

HAND HYGIENE ORDER AND GARBING	
USP <797> 2008	**USP <797> 2022**
• Garbing order from dirtiest to cleanest • Starting with donning of dedicated shoes or shoe covers, head and facial hair covers (e.g., beard covers in addition to face masks), and face masks/eye shields	• Garbing order must be donned and doffed in a manner that reduces the risk of contamination • The required garbing order must be determined by the facility and documented in the facility's SOPs
• Hands and forearms to the elbows to be dried using electronic hand dryers or lint-free disposal towels	• Hand dryers must not be used • Soap containers must disposable and not be refilled. • They need to be replaced with a new container

Assessment question

A pharmacy technician at XYZ Universal Hospital compounds category 2 CSPs.

How often is this technicians ongoing Garbing Competency

(including GFT) and Media Fill with Post-GFT and Surface

Sampling done?

A) at least every 3 months

B) at least every 6 months

C) at least every 12 months

Personnel Protective Equipment

ILEANA SOTO

Personnel Protective Equipment

	USP<797> 2008	USP<797> 2022
Minimum Garbing requirements (gown with sleeves, shoe covers, head covers, facial hair covers, and face masks/eye shields)	Non shedding	• Low-lint garb • If using a RABS (i.e., a CAI or CACI) ✓ Disposable gloves should be worn inside the gloves attached to the RABS sleeves ✓ Sterile gloves must be worn over the gloves attached to the RABS sleeve • For Category 3: All low-lint outer garb must be sterile

Personnel Protective Equipment

Reused Gowns	
USP <797> 2008	**USP <797> 2022**
Gowns are allowed to be reused on the same workday	**For Category 1 and Category 2** • Gowns may be reused within the same shift by the same person if the gown is maintained in a classified area in a manner that prevents contamination **For Category 3** • Disposable gowns cannot be reused • Laundered gowns must be re-sterilized and laundered again be reuse

Facility and Engineering Control

DIANEYSIS AVENDANO

Cleanroom Suite

ISO 7 Anteroom Servicing both ISO 7 buffer sterile room and ISO 7 hazardous buffer sterile room

Example of insanity condition: “Material flow directly between an unclassified area and a room in which sterile compounding is conducted (e.g., unclassified pass-through)*”

FDA Draft Guidance: Insanitary Conditions at Compounding Facilities Docket ID: FDA-2016-D-2268 accessed 6.21.2023

Cleanroom Suite

- ✓ ISO Class 7 Buffer room / ISO Class 7 or 8 Ante-area
- ✓ Categories 2 or 3 CSPs
- ✓ Air supplied to the cleanroom suite **MUST** be introduced through HEPA
  - HEPA Filters that are located the ceiling
  - Same 2008/2022
- ✓ Air returns in the cleanroom suite **MUST** be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow
  - 2008: Ceiling mounted returns not recommended

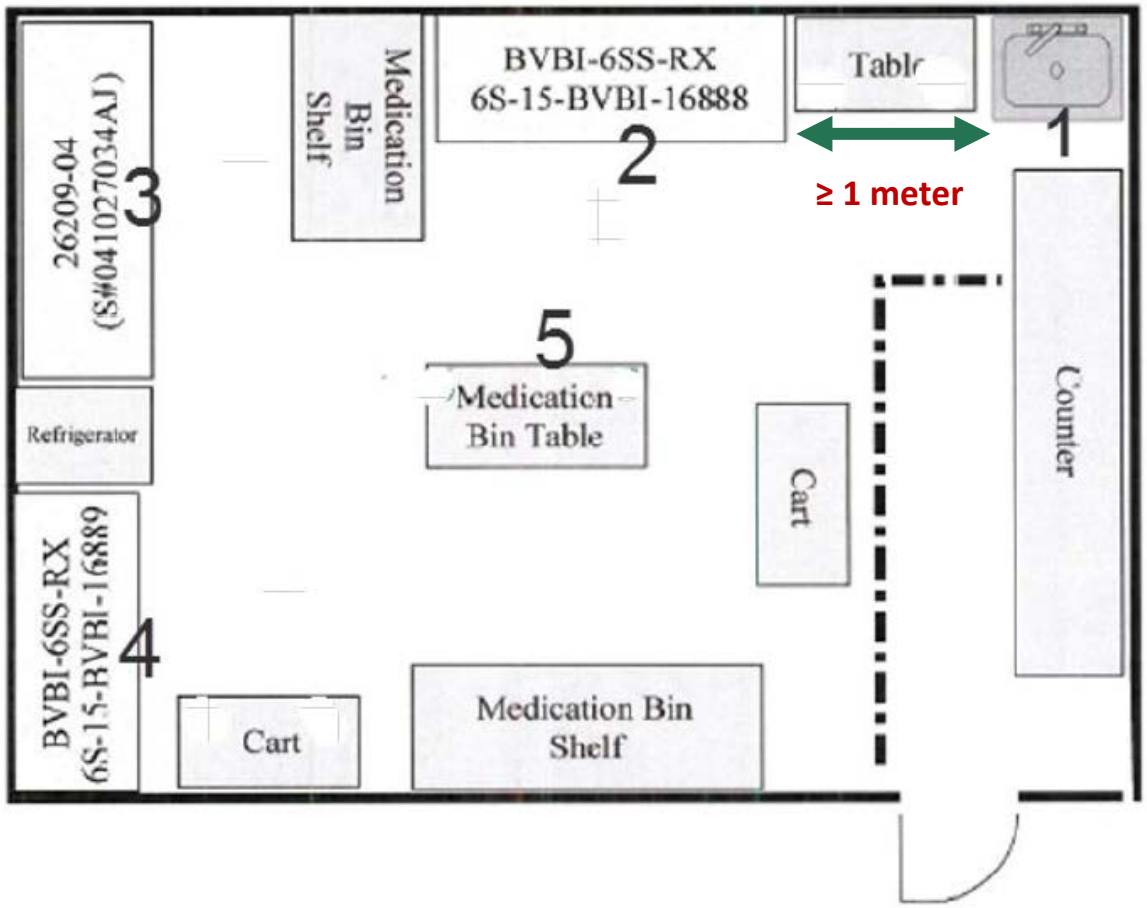
Cleanroom Suite

- ✓ The anteroom **MUST** have a line of demarcation
- ✓ Access doors ***SHOULD*** be hands-free
- ✓ Tacky mats **MUST** not be placed within ISO-Classified areas
- ✓ Ceilings/Walls/Floors/Doors/Shelving/Work Surfaces/Counters/Cabinets
  - **MUST BE** smooth, impervious, free from cracks and crevices, and non-shedding
  - Penetrations through ceiling or walls **MUST** be sealed
- ✓ SINK: Inside or outside ante-area, clean side or dirty side of ante-area

Segregated Compounding Area (SCA)

- ✓ Unclassified area (no buffer room or anteroom)
- ✓ Only for Category 1 CSPs compounding
- ✓ Area within 1 meter of the PEC ***SHOULD*** be dedicated only for sterile compounding
- ✓ Sink inside or near SCA
  - **MUST be** located at least 1 meter away from PEC
- ✓ Ceilings/Walls/Floors/Doors/Shelving/Work Surfaces/Counters/Cabinets:
  - **SHOULD BE** smooth, impervious, free from cracks and crevices, and non-shedding

Segregated Compounding Room

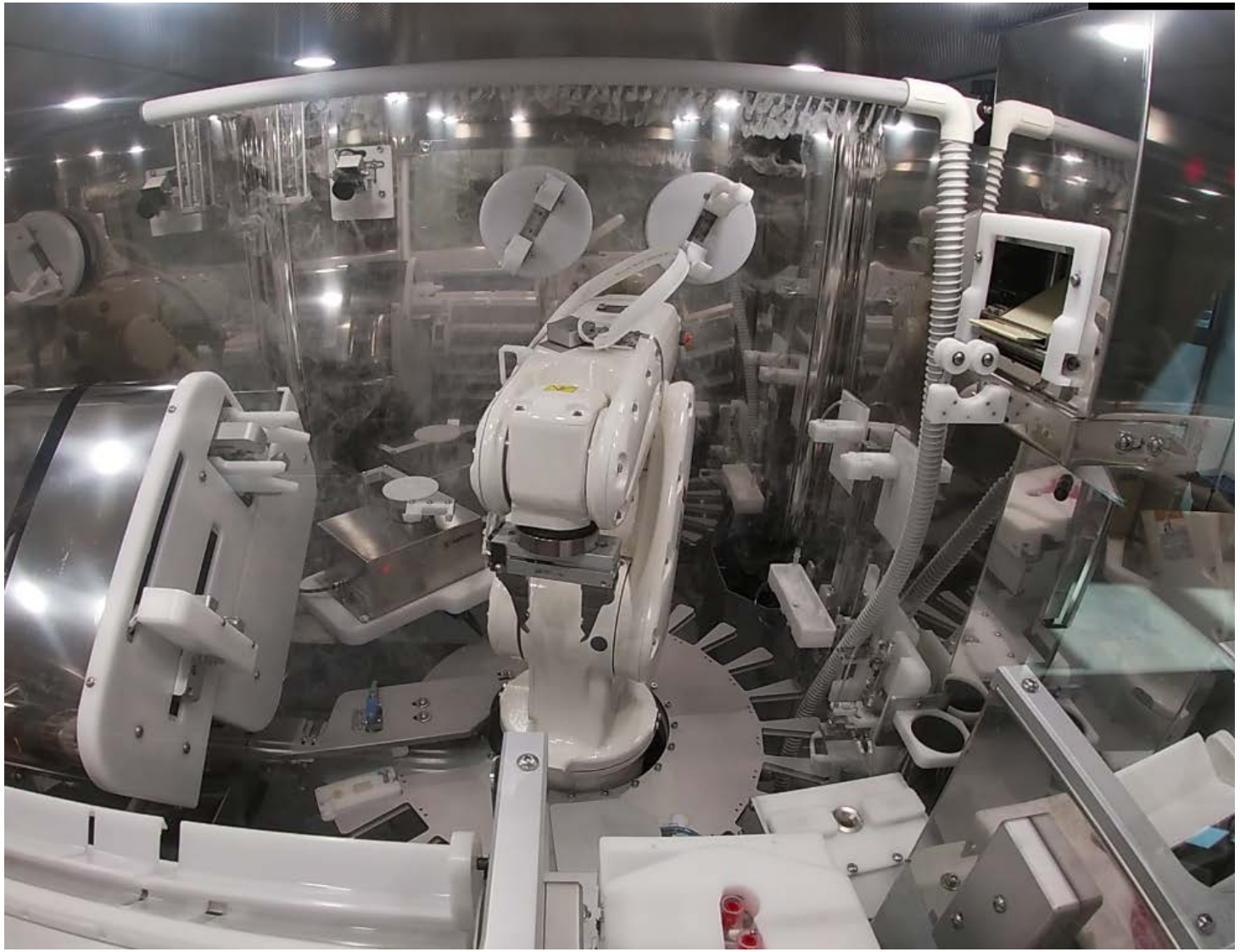


PECs: Laminar Airflow Systems (LAFs)

Provide ISO Class 5 air or better and unidirectional HEPA filtered air

IVLFZ: Integrated vertical laminar flow zone

- **Static AND dynamic** smoke studies **MUST** verify continuous flow of HEPA-filtered air
- **MUST be** documented (with video)



PECs: Laminar Airflow Systems (LAFs)

Provide ISO Class 5 air or better and unidirectional HEPA filtered air

Robotic Enclosure: Allowed with smoke studies attesting room air does not enter the PEC during compounding process

PECs: Restricted Access Barrier System

RABS:

- Compounding aseptic isolators (CAIs)
- Compounding aseptic containment isolators (CACIs)

For Category 1 CSPs: Place in Segregated compounding area

For Categories 2/3 CSPs: Place in cleanroom suite

Transfer Chamber Recovery Time:

- MUST be documented as provided by the manufacturer
- MUST have internal procedures documented to ensure staffs allows for recovery time during compounding operations

https://www.nuaire.com/-/media/Project/Nuaire/Public-Site/Products-900x900-tinypng/NU-PR797_cai_5.jpg

Facilities and Engineering Control

TEMPERATURE	HUMIDITY
❖ Temperature (T) ***SHOULD*** be maintained at 20 or cooler ▪ To provide comfortable conditions for garbed personnel	❖ Humidity (H) ***SHOULD*** be maintained at 60% or lower ▪ To minimize risk of microbial proliferation

❖ T & H controlled by HVAC system

❖ **MUST be monitored / readings MUST be Documented & described in SOP**

- in each room (Ante Room / Buffer Room / SCA)
- each day that compounding is performed
- either manually or by a continuous recording device

❖ Monitoring **devices MUST be verified** for accuracy at least <u>every 12 months</u> or as required by the manufacturer

Facilities and Engineering Controls

Room Type	Pressure Differential	
	2008	2022
Buffer-area with physical separation through walls and doors to ante-area	0.02-0.05 iwc	No less than 0.020 iwc
Ante-area to general pharmacy area	Not less than 0.02 iwc	No less than 0.020 iwc
	Pressure differentials MUST be monitored continuously **Values MUST be reviewed** and recorded every shift	Pressure differentials MUST be monitored continuously **Values MUST be reviewed** and recorded on days when compounding is occurring

Facilities and Engineering Controls

	Air Exchanges (ACPHs)	
	2008	**2022**
Buffer Area	≥ 30 ACPH ISO-7	≥ 30 ACPH ISO-7
Ante-area	≥ 30 ACPH ISO-7	≥ 30 ACPH ISO-7 **≥ 20 ACPH ISO-8**

At least 15 ACHP in room MUST come from HVAC HEPA Filters in the ceiling

Microbiological Air and Surface Sampling

DIANEYSIS AVENDANO

Microbiological Air Sampling

2008	Frequency	Incubation of Media
Low/Medium Risk	Every 6 months	Incubated at a temperature that promotes growth of bacteria and fungi TSA or Malt Extract Temperature ranges
High Risk	Every 6 months	

2022	Frequency	Incubation of Media

Categories 1 & 2	At least every 6 months	• Incubated at a temperature that promotes growth of bacteria and fungi.
		• Both **plates** could be TSA, or TSA and Malt Extract (MEA)/Sabouraud dextrose agar (SDA)
		  • **COAs required**
		• **Incubation and Temperature procedures must follow directions in Box 5**
		  • **Incubate at 30°–35° for no less than 48 hrs, followed by 20°–25° for no less than 5 additional days**
		  • May use one plate incubated at two different temperatures or
		  • May use 2 plates incubated at two different temperatures (less time)

Category 3	At least Monthly	

Surface Sampling

2008	Frequency	Incubation of Media
Low/Medium Risk	Periodically	• Filled with general solid agar growth medium and neutralizing agents • TSA with lecithin and polysorbate 80 • **Shall be incubated at 30° to 35° for 48 — 72 hours**
High Risk		

2022	Frequency	Incubation of Media

Categories 1 & 2	At least monthly	• Surface sampling media devices must contain general microbial growth media supplemented with neutralizing additives
		  • COAs required
		• **Incubation and Temperature procedures must follow directions in Box 6**
		  • **Incubate at 30°–35° for no less than 48 hrs, *followed by* 20°–25° for no less than 5 additional days**
		  • May use one plate incubated at two different temperatures or
		  • May use 2 plates incubated at two different temperatures (less time)

Category 3	• At least weekly
	  • Prior to assigning a BUD longer than the limits established in Table 13
	  • At the end of each batch before cleaning and disinfection occurs	

MUST also be conducted in conjunction with media-fill testing for aseptic manipulation		

Incubators


22C
Thermo
SCIENTIFIC
Fungal
HERATHERM
37C
Thermo
SCIENTIFIC
Bacterial
HERATHERM

Microbiological Air and Surface Sampling ACTION LEVELS

Air Sampling Action Levels [cfu/cubic meter (1000 liters) of air/media device]		
	2008	**2022**
ISO Class 5	>1	>1
ISO Class 7	>10	>10
ISO Class 8	>100	>100

Surface Sampling Action Levels (cfu/media devise)		
	2008	**2022**
ISO Class 5	>3	>3
ISO Class 7	>5	>5
ISO Class 8	>100	>50

2008	**2022**
If levels exceeded, the cause must be investigated, and corrective action must be taken	
Regardless of number of cfu recovered, Highly pathogenic organisms (identified at least to the genus level) MUST be immediately remediated	**IF levels exceeded**: an attempt must be made to identify any microorganism recovered to the genus level with the assistance of a microbiologist

Cleaning and Disinfecting

ILEANA SOTO

Cleaning and Disinfecting

USP <797> 2008	USP <797> 2022
Cleaning	**Cleaning**
Disinfection	**Disinfection**
	Applying sporicidal disinfectant
	Sterile IPA 70%

FREQUENCY	USP <797> 2008	USP <797> 2022
ISO – 5 PECs	• At the beginning of each shift • No longer than 30 minutes in between batches	• Before initiating compounding • On days when compounding occurs • If the compounding process takes more than 30min do not interrupt
Classified Areas	Daily	Daily on days when compounding occurs
Sporicidal	Not addressed	Weekly – Category 3 Monthly – Category 1 and 2

Cleaning and Disinfecting

- Cleaning supplies (e.g., wipers, sponges, pads, and mop heads):
  - MUST be low lint
  - Should be disposable
  - Reusable cleaning tools must be dedicated for use
- Cleaning and disinfecting supplies used **in the PEC must be sterile**
  - Sterile cleaning agent, Sterile disinfecting agent, Sterile sporicidal disinfectant, Sterile water, and Sterile 70% IPA
  - Tools inside PEC MUST be cleaned and disinfected prior to use in a PEC

Sterilization and Depyrogenation

DIANEYSIS AVENDANO

Sterility/Endotoxin Testing

- **Terminal sterilization = PNSU 10^6** **PNSU: Probability of a non-sterile unit**
  - ✓ STEAM / DRY HEAT / IRRADIATION
- **Sterilization by filtration is NOT terminal sterilization = Aseptic Processing**
- **Batch Size: <u>Limited to 250 final yield units</u>**

✓ 1-39 units (single batch): Test 10% of batch
✓ ≥ 40 units: Minimum quantity to be tested follows Table 2 & Table 3 of USP 71

	STERILITY TESTING (USP <71>)	ENDOTOXIN TESTING (USP <85>)
Category 1	Not Required	Not Required
Category 2	If assigning a BUD requiring sterility testing	Compounding from one or more nonsterile ingredients
Category 3	Required	Compounded from one or more nonsterile ingredients
	• Preferred method: Membrane Filtration • Method Suitability Test: **MUST be** performed to ensure contamination can be recovered	• Endotoxin Limit (EL): as described in CSP monograph • MUST not exceed EL for the appropriate route of administration (IV vs Epidural/intrathecal) for humans or target animal

BUD Levels

DIANEYSIS AVENDANO

Beyond Use Date

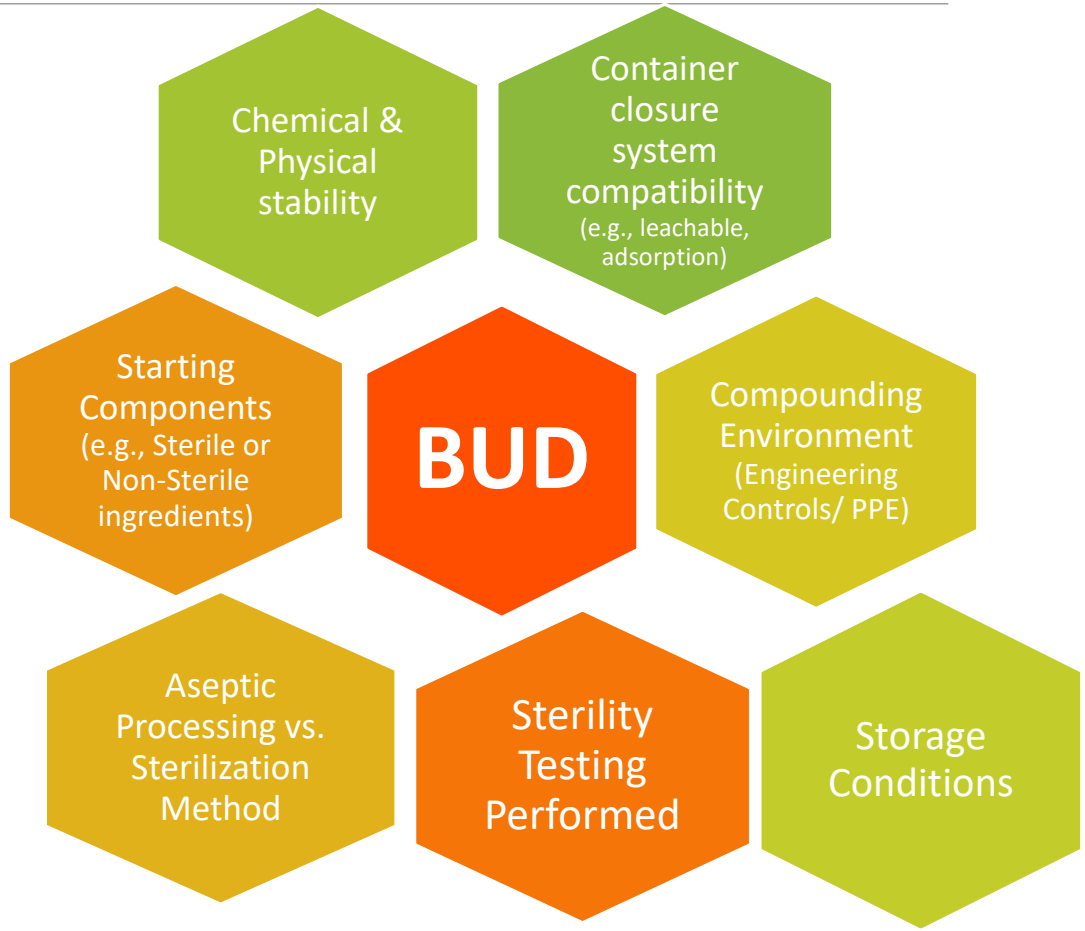
Date after which a CSP MUST be discarded and NOT USED

Determined by compounder from the date/time the preparation is INITIATED

DOES NOT limit the time the CSP is administered (infused)

Considers STABILITY AND STERILITY

The CSP MUST remain chemically and physically stable and MUST maintain its integrity for the duration of the BUD assigned based on storage conditions



BUD – Category 1 CSPs

Risk Level USP <797> 2008	Controlled Room Temperature 20°C to 25°C (68° to 77 °F)	Controlled Cold Temperature (Refrigerated) 2°C and 8°C (36° and 46 °F)	Controlled Frozen Temperature −25°C and −10°C (−13° and 14 °F)
	BUD	BUD	BUD
LOW RISK WITH 12 HOUR BUD			
▪ Certified PEC located in area that meets USP Chapter <797> criteria for segregated compounding area ▪ No sinks in room with PEC ▪ Other requirements such as hand hygiene, garbing, cleaning and disinfecting, viable and non-viable environmental sampling and personnel training and competency are followed	**12 hours**	**12 hours**	**N/A**

Category 1 CSP
Prepared in Segregated Compounding Area (SCA)

STORAGE CONDITIONS	
Controlled Room Temp. (20°–25°)	Refrigerator (2°–8°)
≤ 12 hrs	≤ 24 hrs

CAN ALSO BE PREPARED IN CLEANROOM SUITE

A shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table

USP <797> 2008 BUDs

Risk Level	Controlled Room Temperature **20°C to 25°C (68° to 77 °F)**	Controlled Cold Temperature (Refrigerated) **2°C and 8°C (36° and 46 °F)**	Controlled Frozen Temperature **−25°C and −10°C (−13° and 14 °F)**
	BUD	**BUD**	**BUD**
LOW			
▪ At least ISO class 5 air ▪ ≤ 3 sterile products ▪ ≤ 2 entries into any one container	**48 hours**	**14 days**	**45 days**
MEDIUM			
▪ At least ISO class 5 air ▪ > 3 sterile products ▪ ≥ 3 entries into any one container ▪ Pooling ingredients from multiple sterile products for a CSP that will be administered to multiple patients or to one patient on multiple occasions”	**30 hours**	**9 days**	**45 days**
HIGH			
▪ Non-sterile ingredients or sterile ingredients exposed to air quality < ISO class 5 for > 1 hour ▪ Compounding personnel improperly garbed ▪ Nonsterile CSPs stored greater than 6 hours before being sterilized	**24 hours**	**3 days**	**45 days**

BUD- Category 2 CSPs

Category 2 CSPs Prepared in Cleanroom Suite (Buffer Room and Ante Room)					
Compounding Method	Sterility Tested Done and Passed	Starting Ingredients	Controlled Room Temp. (20°–25°)	Refrigerator (2°–8°)	Freezer (-25°to –10°)
Aseptically processed	**NO**	Prepared with at least one **non-sterile** component	1 day	4 Days	45 Days
		Prepared with only sterile components	4 Days	10 Days	45 Days
	YES	-	30 Days	45 Days	60 Days
Terminally Sterilized	**NO**	-	14 Days	28 Days	45 Days
	YES	-	45 Days	60 Days	90 Days

A shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table

BUD – Category 3 CSPs

Category 3 CSPs Prepared in Cleanroom Suite (Buffer Room and Ante Room)					
Compounding Method	Sterility Tested Done and Passed	****All applicable tests for Category 3 passed**	Controlled Room Temp. (20°–25°)	Refrigerator (2°–8°)	Freezer (-25°to –10°)
Aseptically processed	YES	YES	60 Days	90 Days	120 Days
Terminally Sterilized	YES	YES	90 Days	120 Days	180 Days

Applicable tests for category 3 CPSs include: supporting stability data obtained using a **stability indicating analytical method (e.g., **forced degradation studies** to differentiate between active ingredients and degradants/impurities), prepared according to exact formulation described in stability data, with closure systems of same materials as supported by study, with analytical methods as described **in USP 1225**, and documentation describing methodology, **validation and results MUST be available for inspection**. Refer to section 14 of USP 797 for additional requirements

A shorter BUD must be assigned when the physical and chemical stability of the CSP is less than the BUD limit stated in the table

Compounding Multiple Dose CSPs

Designed to contain more than one dose, intended to be entered or penetrated multiple times, and usually contains a preservative

- **MUST be prepared** as a Category 2 or Category 3 CSP
- BUD: up to **28 days** if:
  - Supported by antimicrobial effectiveness testing (USP 51)
  - Container closure system integrity test passed (USP 1207)

NON-PRESERVED Multi-dose aqueous topical ophthalmic CSPs

- Antimicrobial effectiveness testing not required if
  - Prepared as category 2 or 3
  - For single patient use
  - Labeled to be discarded after opening with:
    - 24 hours when stored at RT or 72 hours when stored Refrigerated

Conventionally Manufactured Products as Components

	2008	2022
Conventionally Manufactured Single Dose Containers	**Entered or punctured only in an ISO Class 5 or cleaner air**	
	BUD: 6 hours	**BUD: 12 hours** **Storage requirements during that 12-h period must be maintained**
Conventionally Manufactured Multiple-dose Containers	BUD: 28 days	BUD: 28 days
Conventionally Manufactured Bulk Packages	**The closure shall be penetrated only one time** BUD: Time frame as labeled storage conditions	Use according to the manufacturer's labeling

	2022
Compounded Single Dose CSPs as Stock Solutions	Entered or punctured only in an ISO Class 5 or cleaner air **BUD: 12 hours** Storage requirements during that 12-h period must be maintained **In use time limit not intended to restrict the BUD of the final CSP**

Standard Operating Procedures (SOPs) and Documentation

- SOP for garbing and hand hygiene
- Documentation of Personnel training, competency assessments, qualifications, and validations
- Documentation of Certification report results, smoke studies, and corrective actions
- Documentation of Environmental monitoring (air, surface) results and their review
- Equipment records
- SOP for Sterilization/Depyrogenation and documentation of efficacy verification
- Daily monitoring reports (Temp. /Humidity /Pressure differentials/ Incubator temperatures)
- SOPS for component receipt and handling
- SOPs and records for cleaning, disinfecting and sporicidal application
- Master formulation records and compounding records

SOPs MUST be communicated to staff and MUST be reviewed every 12 months

MFRs vs CRs

Master Formulation Records are required for:	Compounding Records are required for
For all CSPs prepared from non-sterile ingredients	For all compounded category 1, 2, and 3 CSPs
CSPs prepared for more than one patient	Immediate-use CSPs prepared for more than one patient

These records can be in the form of a prescription, a medication order or label. They can be stored electronically (e.g., workflow management system) as long as retrievable and containing all the required information.

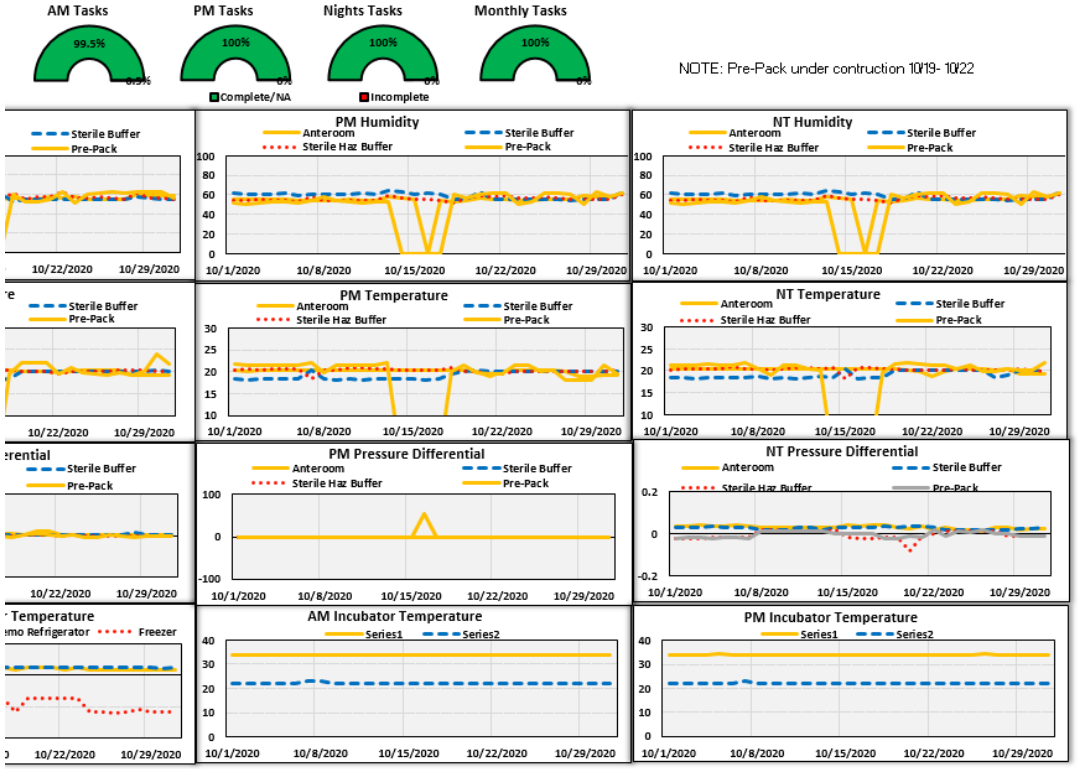
Quality Assurance & Control

DIANEYSIS AVENDANO

Quality Control Program

Elements to ensure safe compounding practices

- Trainings/ Competency
- SOPs, MFRs CRs
- Certification Reports
- Environmental testing and monitoring
- Equipment records (e.g., calibration, maintenance reports)
- Release inspections
- Complaints/ADRs investigations
- Investigations / Corrective Actions



The End

Final Recommendations:

- ✓Gap analysis
- ✓Trainings
- ✓Staffing requirements
- ✓Budget and financials
- ✓Assess readiness for November 1st, 2023 implementation

Questions?

Dianeysis H. Avendano Pharm.D., BCSP, BCSCP

http://linkedin.com/in/dianeysis-avendano-ab703460

Ileana Soto Pharm.D., BCSCP

https://urldefense.com/v3/__http://linkedin.com/in/ileana-soto-b2a43129__;!!LqvVzw!RETEHYLnCm8Pva3D1i7y051q7ZCT0qcBbyWStxrRMTSnbSrd5BaUN0jVGnXuVxi0eSw1enARpP6wDw$

ACPE Accreditation
Request for Continuing Education

- Following the webinar attendees will receive a link to evaluate the presentation (SurveyMonkey link) . The evaluation will be used as verification of attendance and for CE purposes.
- **The link to the evaluation will be active until July 5th at noon. PLEASE complete by the deadline.**
- Allow 1-2 weeks following the deadline for CE reporting to CE Broker and CPE Monitor.
- Contact fshp@fshp.org if you do not receive aa link to the evaluation.