USP General Chapters <797> & <800> Environmental Monitoring

Participants will be in listen only mode.
9 a.m. (PST)

Presented by:

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- Complete survey within 24 hours.
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Outline

- Introduction to general chapter USP <797>
- Personnel training
- Environmental monitoring and sampling
- Investigation of excursions and remediation
- USP <800> – Handling of hazardous drugs in healthcare facilities

Revision of Chapters <795>, <797> & <800>

Update on Appeals Panel Decision

General Chapters <795> and <797>

The Appeals Panel **has granted** the appeals to General Chapters <795> and <797> and is remanding the chapters to the Compounding Expert Committee (CMP EC) with the recommendation for further engagement on the issues raised concerning the beyond-use date provisions.

Implications:

The currently official chapters of <795> (last revised in 2014) and <797> (last revised in 2008) remain official.

General Chapters <800>

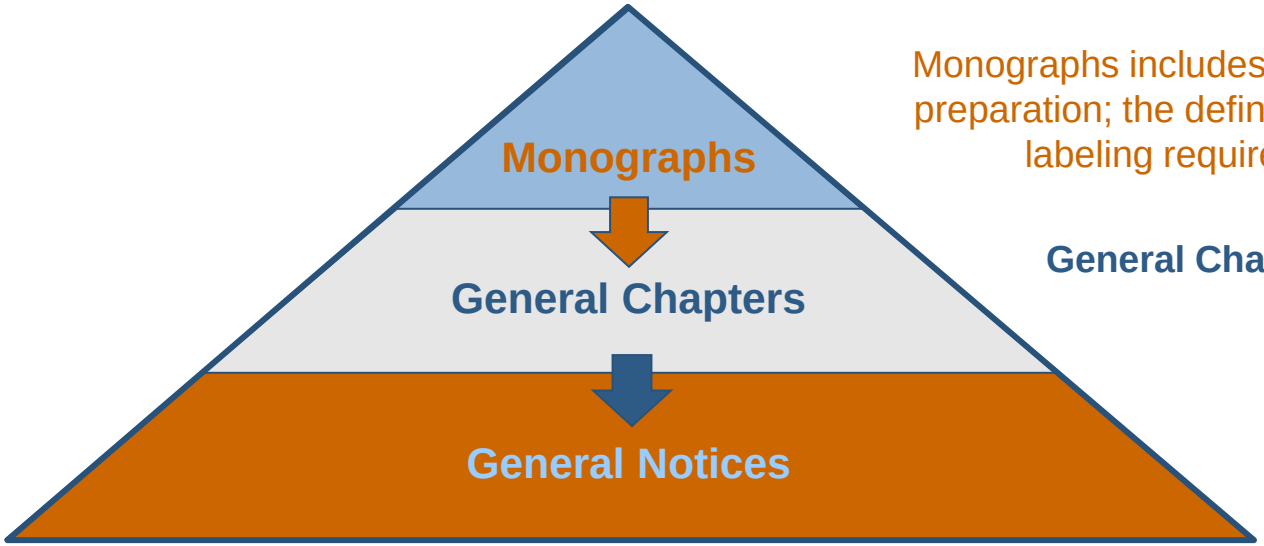
The new General Chapter <800> was made official on December 1st, 2019.

<795> Pharmaceutical Compounding – Nonsterile Preparations
<797> Pharmaceutical Compounding – Sterile Preparations
<800> Hazardous Drugs – Handling in Healthcare Settings

What is USP <797>?

- *USP-NF* establishes standards for medicines, food ingredients and dietary supplements.

- General Chapter USP <797> establishes best practices and regulations for the production of compounded sterile preparations.



Monographs includes the name of the ingredient or preparation; the definition; packaging, storage, and labeling requirements; and the specification.

General Chapters establish procedures, methods and practices.

General Notices help with the interpretation of *USP–NF* standards

Abbreviations and Terms

Abbreviations:

USP-NF: United States Pharmacopeia – National Formulary

CSP: Compounded Sterile Preparation

PEC: Primary Engineering Controls

BUD: Beyond Use Dating

DCA: Direct Compounding Area

CAI: Compounding Aseptic Isolator

BSC: Biological Safety Cabinet

Terms:

Clean Room

Buffer Area

Ante Area

Aseptic Processing

Preparation

Product

USP General Chapters

General Chapters in the *USP-NF*

- Numbered below <1000>
  - Compendium and discretionary State requirements
  - Made applicable through general notices, monographs or another applicable general chapters below <1000>
- Numbered <1000> to <1999>
  - Informal chapters
- Numbered <2000> and above
  - Dietary supplements

Sterile Compounding

Sterile compounding is…

…combining, diluting, pooling, reconstituting or otherwise altering a drug or bulk drug substance to create a sterile preparation.

This includes:

- **Altering the dosage form or delivery system of a drug**
- **Altering the strength of a drug**
- **Combining components or active ingredients**
- **Preparing a drug product from chemicals or bulk drug substances**

USP <797> applies to all persons who prepare and all places where compounded sterile preparations (CSPs) are made for humans or animals.

Compounded Sterile Preparations

Examples of CSPs:

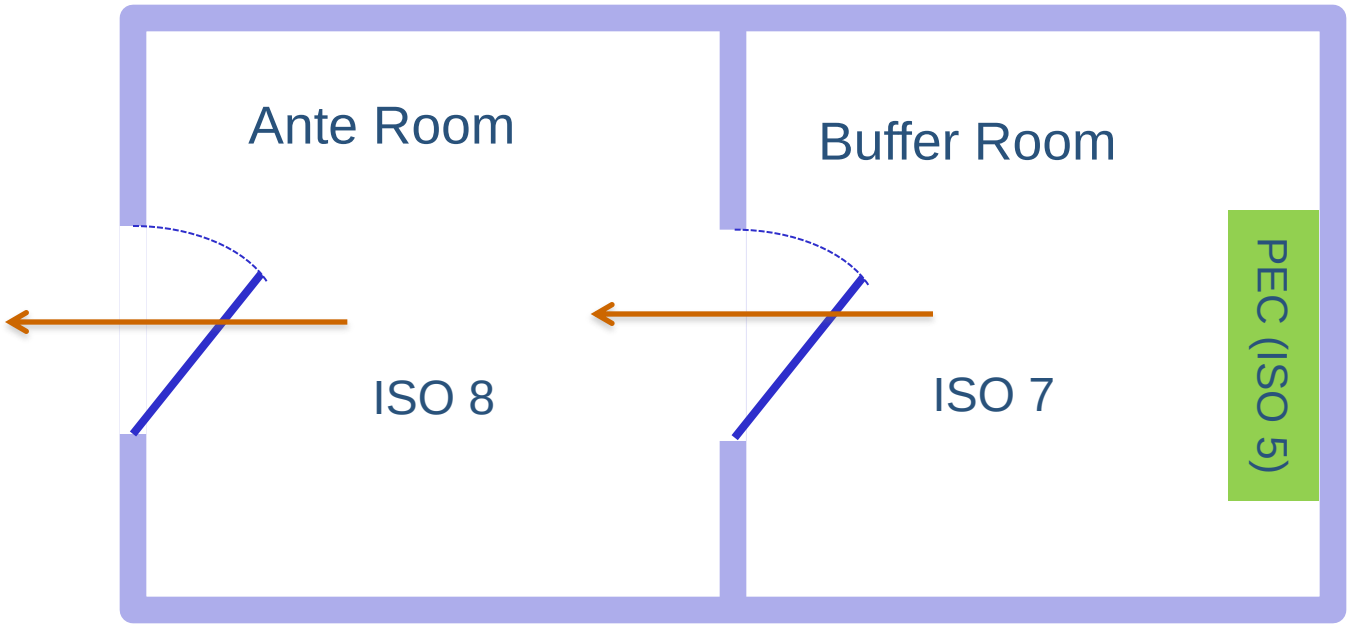
- Injections
- Total Parenteral Nutrition (TPN)
- Preparations for pulmonary inhalations
- Baths and soaks for live organs and tissues
- Irrigations for internal body cavities
- Implants

Scope of USP <797>

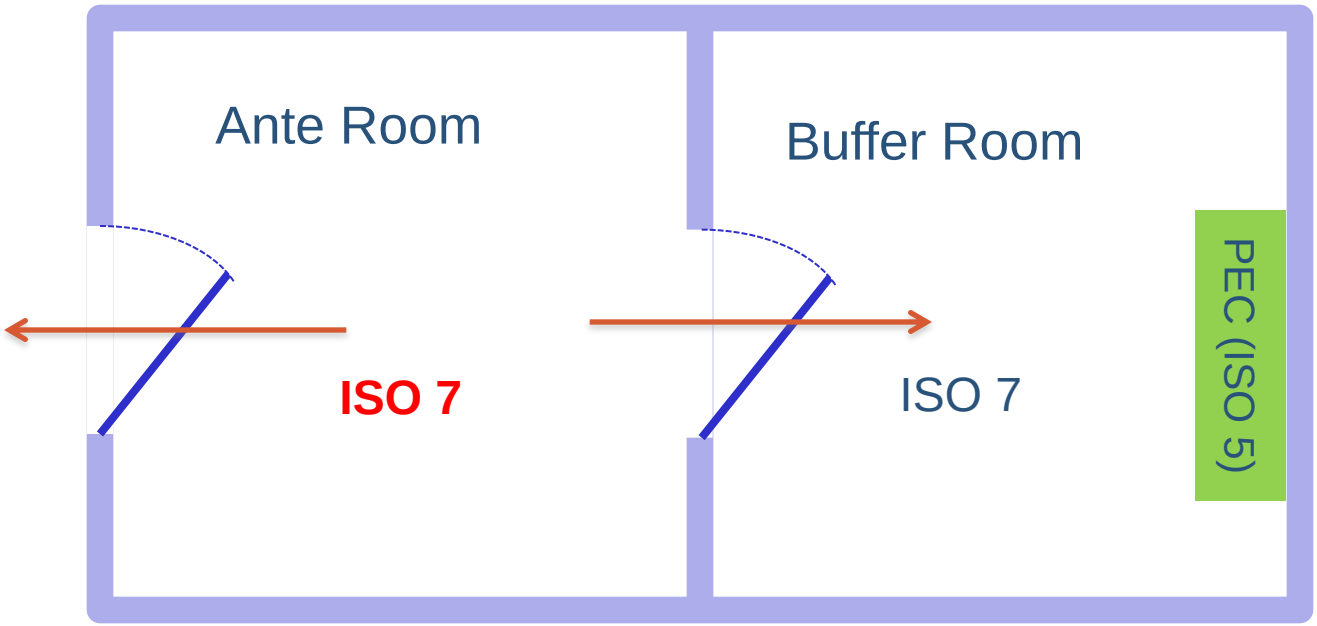
Practices out of Scope for USP <797>

- Sterile radiopharmaceutical compounds – USP <825>
- Preparations per approved product labelling
  - Single dose, single patient
  - Labeling must include diluent, strength, storage time, container closure system
- Immediate use CSPs
  - Single patient – prepared from not more than three different sterile products
  - Unused medication from a single dose vial must be discarded
  - Administration must begin within four hours
  - Must be appropriately labelled if not administered by preparer

Cleanroom Design



Cleanroom: Hazardous Compounding



Mission of Chapter <797>

Goal of USP <797>:

Minimize harm, including death to humans and animals that could result from

- Microbial contamination (non-sterility)
- Excessive bacterial endotoxins
- Variability from the intended strength of active ingredients
- Physical and chemical incompatibilities
- Chemical and physical contaminants
- Use of ingredients of inappropriate quality

Revision – Risk Categories

Risk categories (low risk, medium risk and high risk compounding) have been collapsed in the new revision. However, the 2008 version remains official at this time

Low Risk

No more then 3 sterile products

CSPs administered within 48 hrs (RT), 14 days (refrigerated), 45 days (frozen)

Medium Risk

Complex manipulations

CSPs administered to more then one patient or same patient multiple occasions
BUD: 30 hrs (RT), 9 days (ref.), 45 days (frozen)

High Risk

Produced with non-sterile components or process exposed to worse than ISO5 for >1 hr

Requires terminal sterilization
BUD: 24 hrs (RT), 3 days (ref.), 30 days (frozen)

Immediate and emergency use CSPs are not subject to same requirements

Personnel Training

Any person handling CSPs and/or accessing the compounding area must be trained

- A designated person is responsible for overseeing the training program
- Visual observation, training and testing of compounding personnel may be performed by
  - ✓ A designated person or an assigned trainer

Written training program including:

- Specifics of required competencies
- Frequency of training
- Process for evaluating competencies
- Visual observation, written or electronic test
- Documentation of training results

Personnel Training (cont'd)

Personnel must demonstrate and be tested for core competencies initially and every 12 months in:

- ✓ Hand hygiene
- ✓ Garbing
- ✓ Cleaning and disinfection
- ✓ Calculations, measuring and mixing
- ✓ Aseptic technique
- ✓ Achieving and/or maintaining sterility and apyrogenicity
- ✓ Use of equipment
- ✓ Documentation of compounding process
- ✓ Principles of HEPA-filtered unidirectional airflow within the ISO 5 area
- ✓ Proper use of primary engineering controls (PECs)
- ✓ Principles of movement of materials and personnel within the compounding area

Personnel Training – Microbial Testing

Gloved fingertip testing

- Press all fingers of one hand including thumb on a media plate (e.g. TSA w/ polysorbate 80 & lecithin) after performing hand hygiene and garbing procedure.
- Initial qualification – three times with no growth on either plate (left and right hand).
- Continued qualification – testing every 6 months with a maximum of 3 cfu for both hands combined.
- Isolator box: test sterile gloves placed over the equipment gloves.

Personnel Training – Microbial Testing (cont'd)

Media fill testing

- Simulation used to qualify processes and personnel engaged in sterile compounding to ensure that the processes and personnel are able to prepare CSPs without contamination.
- Initial qualification and every 6 months thereafter.
- Replace ingredients with soybean-casein digest medium (TSB) and perform most challenging procedures that the trainee may encounter.
- Media fill test kits may be used.

Personnel Training – Summary

Training Module	Frequency	Threshold
Testing of all core competencies	Every 12 months	Observation, test scores, etc.
Gloved fingertip testing[1]	Every 6 months	Zero cfu initially (3 times), ≤3 cfu for continuous qualification
Media fill testing[2]	Every 6 months	No growth

[1] Incubation 30°C to 35°C for no less than 48 hours (2008 version)

[2] Incubation 20° to 25° or at 30° to 35° for a minimum of 14 days (2008 version)

Facility Design and Environmental Monitoring

Sterile compounding facilities must be designed, outfitted, and maintained properly to minimize the risk of contamination of CSPs.

Required air quality for various areas is achieved via:

- Facility design
- Primary engineering controls (PECs)
- Secondary engineering controls (SECs)
- HEPA filtration, ventilation, air flow

Cleanroom Design

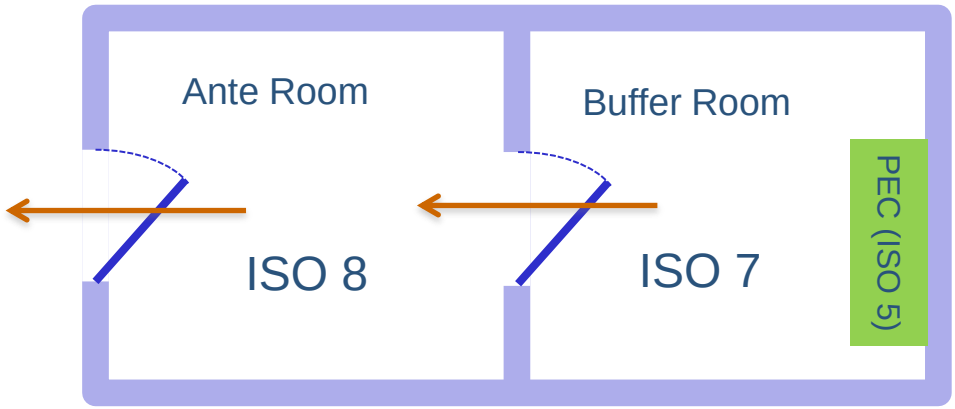
Cleanroom suite

- ISO-classified ante-room and buffer room is separated from the surrounding unclassified areas of the facility.
- Air flow - specific design and monitoring required.
- Ante room with line of demarcation for clean and dirty area or two ante rooms required.

Segregated compounding area (SCA)

- PEC may be located within an unclassified area, without an ante-room or buffer room.
- Must be located away from windows, doors, traffic etc. which may adversely affect air quality.

Air quality – Cleanroom Suite



Total Particle Counts

ISO Class	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1 µm	5 µm	FED STD 209 Class
ISO 1	10	2					
ISO 2	100	24	10	4			
ISO 3	1,000	237	102	35	8		1
ISO 4	10,000	2,370	1,020	352	83		10
ISO 5	100,000	23,700	10,200	3,520	832	29	100
ISO 6	1,000,000	237,000	102,000	35,200	8,320	293	1000
ISO 7				352,000	83,200	2,930	10000
ISO 8				3,520,000	832,000	29,300	100000
ISO 9				35,200,000	8,320,000	293,000	

Direct Compounding Area → ISO 5

Buffer Room → ISO 7

Ante Room → ISO 8

Air flow (2008 revision)

For rooms providing a physical separation through the use of walls, doors, and pass-throughs, a minimum differential positive pressure of 0.02- to 0.05-inch water column is required. No less then 30 ACPH for buffer and ante rooms.

Air Flow

Air change requirements for SECs in new revision (2019)

Compounding Area	Air Change Per Hour (ACPH)
Unclassified SCA	No requirement
ISO class 7 room(s)	≥ 30 ACPH
ISO class 8 room(s)	≥ 20 ACPH

- **In a cleanroom suite the minimum positive differential pressure from cleanroom classification with higher quality to the next (e.g. ISO7 to ISO8) must be at least 0.02 inch water column.**
- **Pressure differential must be monitored, recorded and reviewed.**

Air Monitoring – Total Particle Count

ISO 14644: Rule of thumb: # samples=Square Root of the clean room area, at least 1 minute & 2 Liters / sample

Area [m2] less than or equal to	Minimum # of samples locations (90% confidence level)
2	1
10	5
32	8
56	11
104	16
190	21
500	26

Air Monitoring of Viable Particles

- ✓ Air sampling in each classified area every 6 months (same frequency as certification of PEC)
- ✓ Volumetric sampling under dynamic conditions:
  - 1000 liters minimum for all areas
  - 2008 version: 400 to 1000 liters
- ✓ During typical operating conditions every six months.
- ✓ Use general microbiological growth medium (e.g. TSA).

Air Sampling

In addition to routine air monitoring every 6 months testing is also performed

- In conjunction with the certification of new facilities and equipment
- After any servicing of facilities or equipment
- In response to identified problems (e.g., positive growth in sterility tests of CSPs)
- In response to identified trends (e.g., repeated positive gloved fingertip and thumb sampling results, failed media fill testing, or repeated observations of air or surface contamination)
- In response to changes that could impact the sterile compounding environment (e.g., change in cleaning agents)

Air Sampling – Media and Incubation

Media:

“A general microbiological growth media that supports the growth of bacteria and fungi must be used (e.g., TSA).”

For high risk compounding use fungal media (e.g., MEA) **in addition.**

Incubation:

30°C to 35°C for 48 to 72 hours (TSA)

26° to 30° for 5 to 7 days (MEA).

Air Sampling Thresholds

Action levels for classified areas (USP <797>)

ISO Class	Air Sampling Action Levels (CFU/m3)*
5	>1
7	>10
8	>100

* All action levels must be based on sampling in the vicinity of exposed materials/articles during compounding operations.

Surface Sampling

Surface sampling routinely (typically done with air sampling and/or personnel qualification testing).

- All classified areas and pass-through chambers connecting to classified areas including

  ✓ The interior of the PEC and the equipment contained in it

  ✓ Staging or work area(s) near the PEC

  ✓ Frequently touched surfaces

When conducted, surface sampling must be performed at the end of compounding activity or shift, but before the area has been cleaned and disinfected.

Surface Sampling (cont'd)

Contact Plates or Paddles (24 – 36 cm^2)

- Easy to use
- Accurate
- Less handling

Swabs

- Can sample curved surfaces
- Convenient
- Less expensive

Surface Samples – Media and Incubation

Media:

A general microbiological growth media that supports the growth of bacteria and fungi (e.g., TSA) containing neutralizing additives (e.g., lecithin and polysorbate 80). For high risk compounding use fungal medium (e.g., MEA) **in addition.**

Incubation:

30°C to 35°C for 48 to 72 hours (TSA)

26° to 30° for 5 to 7 days (MEA).

Surface Sampling Thresholds

Action levels for classified areas (USP <797>)

Surface sampling

ISO Class	USP <797> 2008 Revision cfu per sample	USP <797> 2019 Revision cfu per sample
5	>3	>3
7	>5	>5
8	>100	**>50**

2019 Revision – Summary of Changes

Changes concerning Environmental Monitoring

- **Sample volume:** At least 1000 liters (previously 400 – 1000 liters).
- **Frequency of testing:** Surface testing changes from “periodically” to monthly requirement.
- **Media and incubation:** Default becomes dual incubation of one sampling plate (e.g., TSA); alternatively the use of 2 media plates per location is allowable.
- **Genus identification:** Identifications to at least genus level are no longer required for samples with counts below the thresholds for colony counts.
- **Threshold levels:** Remain largely the same with the exception of ISO8 surface samples (2019 revision 50 cfu per sample).

Data Evaluation and Remediation

- Evaluate cfu counts against action levels (air and surface).
- Examine counts in relation to previous data and trends.
- **If levels exceed thresholds** an attempt must be made to identify any microorganism recovered to the genus level (current version requires all colonies to be identified and corrective action for any “highly pathogenic” organisms).
- Implement and document corrective action plan (e.g., facility improvements, personnel training, cleaning and disinfection, HEPA filter replacement).

Cleaning and Disinfection

Site	Cleaning & Disinfection	Sporicidal Application
Removable work tray of PEC	Daily*	Monthly
Pass through(s)	Daily	Monthly
Work surfaces (outside PEC)	Daily	Monthly
Floor(s)	Daily	Monthly
Wall(s), door(s) and door frame(s)	Monthly	Monthly
Ceiling(s)	Monthly	Monthly
Storage shelfing and bins	Monthly	Monthly
Equipment outside PEC	Monthly	Monthly

* Work surface daily, underneath work surface monthly

Cleaning and Disinfection (cont'd)

Cleaning and disinfection inside PEC and equipment inside PEC

- Clean and disinfect all interior surfaces of the PEC daily and when surface contamination is known or suspected.
- Apply sterile 70% IPA to the horizontal work surface at least every 30 minutes or after compounding is completed.
- Apply sporicidal agent monthly.

Documentation

Documentation is Key to Providing Good USP Services…

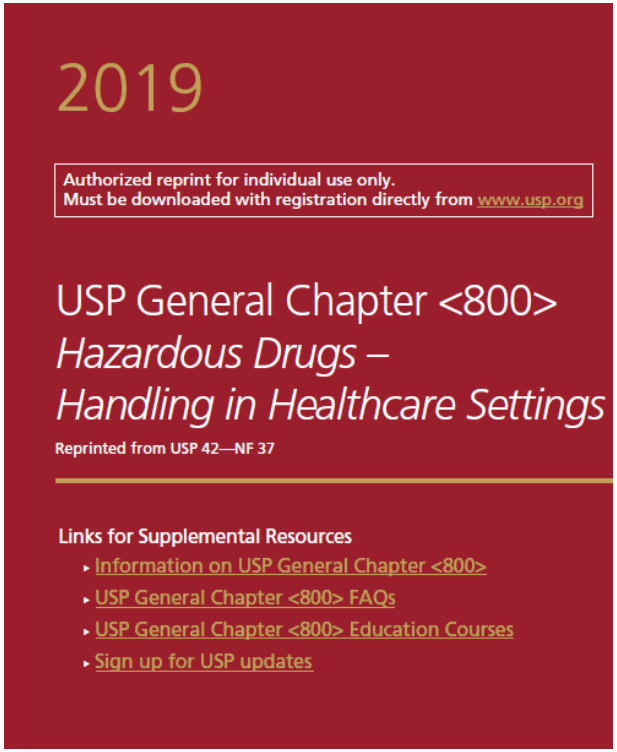
- Copy or original certificate of sterility
- Equipment calibration and training certificates
- Maps to indicate environmental samples
- Document time of sampling also in reference to other activities
- Records for cleaning activities, investigations, results of monitoring…

General Chapter USP <800>

Chapter <800> builds on the standards established by other compounding chapters

- **<795> Pharmaceutical Compounding – Nonsterile Preparations**
- **<797> Pharmaceutical Compounding – Sterile Preparations**

Adds the element of containment of hazardous drugs



USP <800>

Purpose

… to promote patient safety, worker safety and environmental protection.

Scope

… applies to all healthcare personnel who handle (store, prepare, transport and administer) hazardous drugs (HD).

Intended use

… pharmacists, pharmacy technicians, nurses, physicians, physician assistants, home healthcare workers, veterinarians, and veterinary technicians.

Abbreviations

HD: Hazardous Drug

ACPH: Air Changes Per Hour

C-SCA: Containment Segregated Compounding Area

C-PEC: Containment Primary Engineering Control

C-SEC: Containment Secondary Engineering Control

CSTD: Closed System Drug-Transfer Device

CACI: Compounding Aseptic Containment Isolator

CVE: Containment Ventilated Enclosure

API: Active Pharmaceutical Ingredient

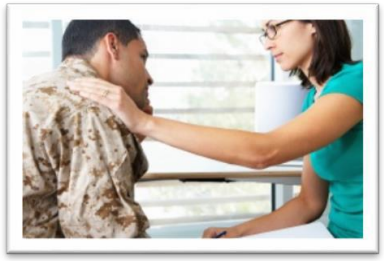
HD Exposure

Exposure applies to all healthcare personnel…

Pharmacy Technicians

Veterinarians & Technicians

Nurses



Home Healthcare Workers

Exposure also applies to all healthcare entities…

Patient Treatment Clinics

Storage Facilities

Types of Exposure

Some activities that may result in exposure can include…

- Opening hazardous drug orders
- Crushing tablets or opening capsules
- Expelling air from syringes filled with hazardous drugs
- Administering hazardous drugs whether intravenous, epidural or oral
- Handling hazardous drugs during the preparation or cleaning process
- Maintenance activities of potentially contaminated equipment and devices

Handling used syringes

Crushing and/or opening tablets

Administering hazardous drugs

Cleaning up HD spills

Two principles of safety

Containment

- Separate, fixed walls
- Negative Pressure

Dilution

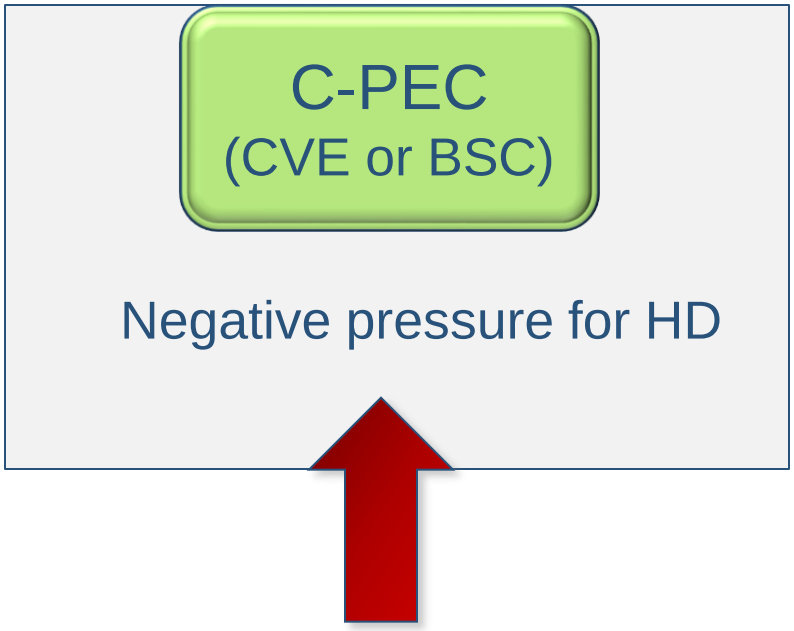
- External ventilation
- Air Changes Per Hour (ACPH)

Primary Engineering Controls

Biological Safety Cabinet (BSC)

Compounding Aseptic Containment Isolator (CACI)

Non-Sterile HD Compounding



Compounding Engineering Controls

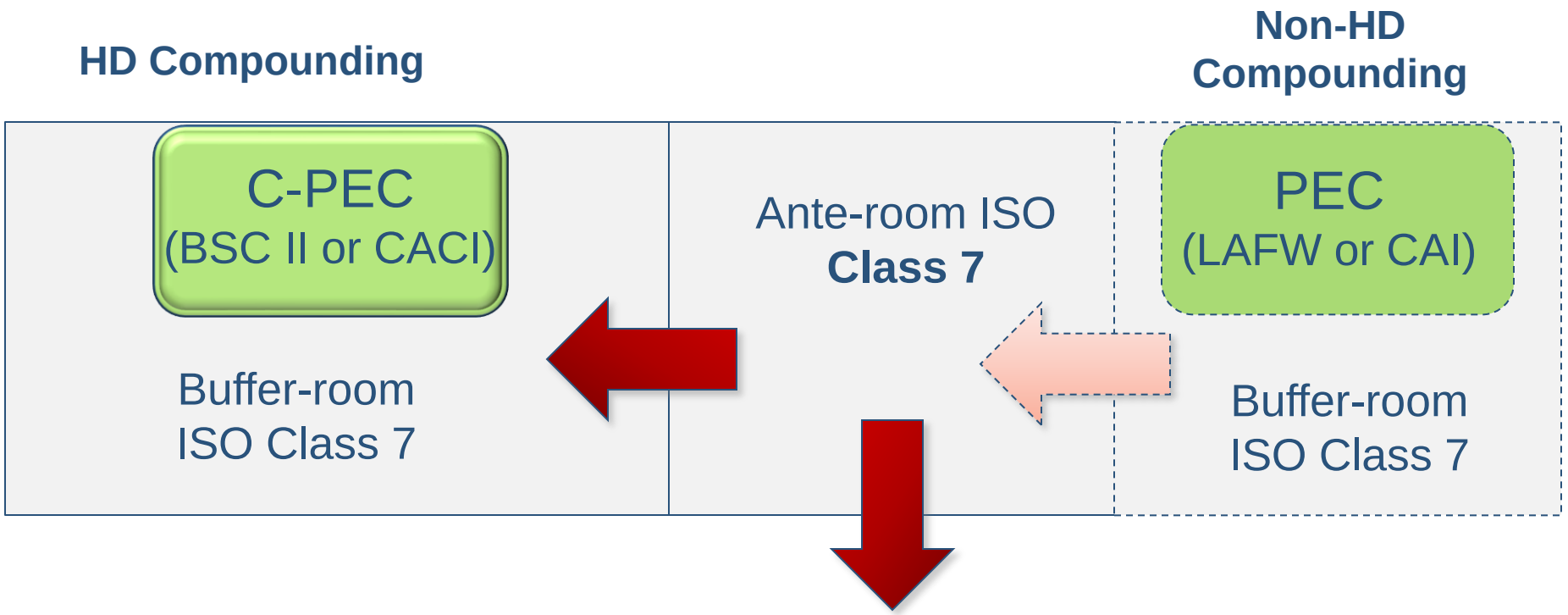
C-SEC Requirements

- ✓ Physically separated
- ✓ Externally vented (or redundant HEPA filters in series)

Air exchange:

- ✓ 12 ACPH
- ✓ Negative pressure between 0.01 – 0.03” wc relative to adjacent areas

Sterile HD Compounding



Sterile Compounding – Clean Room

Ante-room Requirements

- ✓ Minimum of 30 ACPH of HEPA filtered air
- ✓ Positive pressure
- ✓ ISO Class 7 or better

Example only: various set-up options possible

HD…What are we talking about?

American Society of Hospital Pharmacists (ASHP) (1990)	National Institute for Occupational Safety and Health (NIOSH) (2004)
Genotoxicity	Genotoxicity
Carcinogenicity	Carcinogenicity
Teratogenicity or fertility impairment	Teratogenicity/Developmental toxicity
Serious organ toxicity at low dose	Reproductive Toxicity
	Organ toxicity at low doses
	Structure/toxicity profiles of new drugs that mimic existing HDs

NIOSH List

Published in 2004, 2012, 2016.

https://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf

HD Testing – Tier One Drugs

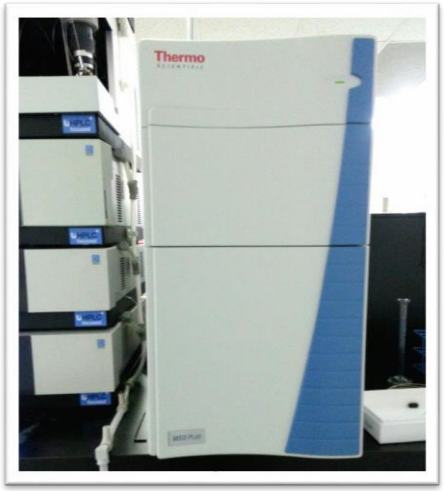
Tier One Drugs

(Up to 5 drugs can be offered per panel)

- Cyclophosphamide
- Doxorubicin Hydrochloride
- Doxorubicin Hydrochloride Liposome
- 5-FU (Fluorouracil Injection)
- 5-FU (Fluorouracil—Topical)
- Fluoroplex (Fluorouracil—Topical)
- Fluorouracil Injection
- Fluorouracil—Topical
- Gemcitabine Hydrochloride
- GEMCITABINE-CISPLATIN
- GEMCITABINE-OXALIPLATIN
- Gemzar (Gemcitabine Hydrochloride
- Ifex (Ifosfamide)
- Ifosfamide
- Ifosfamidum (Ifosfamide)
- Methotrexate
- Methotrexate LPF (Methotrexate)
- Mexate (Methotrexate)
- Mexate-AQ (Methotrexate)
- Paclitaxel
- Paclitaxel Albumin-stabilized Nanoparticle Formulation

Reporting Limit for Wipe Samples is less than 1 nanogram per square centimeter (1ng/cm^2)

ANALYSIS BY LC/MS



HD Testing – Second Tier Drugs

Second Tier Drugs

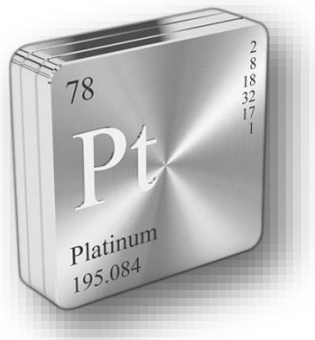
- Anastrozole
- Bexarotene
- Bicalutamide
- Bleomycin
- Bortezomib
- Busulfan
- Busulfex (Busulfan)
- Capecitabine
- CARBOPLATIN- TAXOL
- Chlorambucil
- Cisplatin
- Cladribine
- Clofarabine
- Cytarabine
- Cytarabine Liposome
- Daunorubicin Hydrochloride
- Docetaxel
- Docetaxel
- Dox-SL (Doxorubicin Hydrochloride Liposome)
- Epirubicin Hydrochloride
- Etopophos (Etoposide Phosphate)
- Etoposide
- Exemestane
- Fareston (Toremifene)
- Farydak (Panobinostat)
- Faslodex (Fulverstrant)
- FEC
- Femara (Letrozole)
- Filgrastim
- Fludara (Fludarabine Phosphate)
- Flutamide
- Fulvestrant
- Idamycin (Idarubicin Hydrochloride
- Idarubicin Hydrochloride
- Imatinib Mesylate
- Irinotecan Hydrochloride
- Leuprolide Acetate
- Megace (Megestrol Acetate)
- Megestrol Acetate
- Melphalan
- Mercaptopurine
- Methazolastone (Temozolomide)
- Mitoxantrone Hydrochloride
- Mitozytrex (Mitomycin C)
- Nelarabine
- Oxaliplatin
- Pemetrexed Disodium
- Tamoxifen Citrate
- Temozolomide
- Thioguanine
- Toposar (Etoposide)
- Vincasar PFS (Vincristine Sulfate)
- Vincristine Sulfate
- Vincristine Sulfate Liposome

Analytical Monitoring for Secondary Chemo Drugs

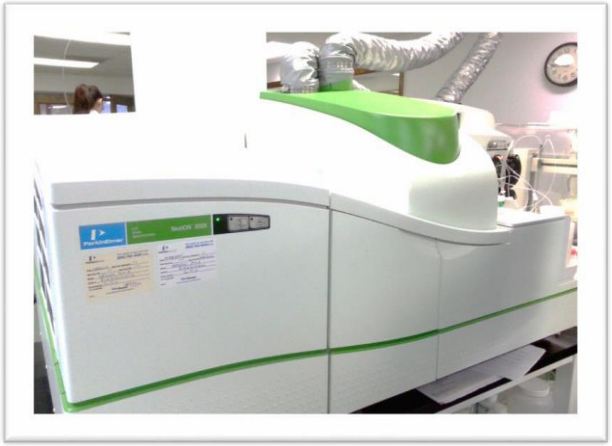
The list of chemo drugs can be individually analyzed upon request, but **may <u>not</u> be added to a Tier 1 panel** due to the nature of the chemistry involved in the analysis.

Reporting Limit for Wipe Samples is less than 1 nanogram per square centimeter (1ng/cm^2)

HD Testing – Platinum Containing Drugs



ANALYSIS BY ICP-MS



Analysis Includes

- Cisplatin
- Carboplatin
- Oxaliplatin

Detection limits below 0.2 ng/cm^2

Sampling

Eurofins EMLab P&K's USP<800> Sampling Kit

- Straight forward, easy-to-use kit
- Reporting limit for wipe samples is less than 1 nanogram per square foot (1ng/cm^2)
- Results within 7 days
- No need to ship samples cold
- Free shipping via US Postal Service in the same mailer
- Test for the most commonly requested chemotherapy and high potency hazardous drugs
- Stay in compliance with new USP<800> guidelines

Environmental Monitoring for HD

Environmental wipe sampling for HD surface residue **should** be performed routinely (e.g., initially at least every 6 months, or more often as needed, to verify containment). Surface wipe sampling **should** include:

- Interior of the C-PEC and equipment contained in it
- Pass-through chambers
- Surfaces in staging or work areas near the C-PEC
- Areas adjacent to C-PECs (e.g., floors directly under C-PEC, staging, and dispensing area)
- Areas immediately outside the HD buffer room or the C-SCA
- Patient administration areas

Summary

- ✓ The general chapters USP <797> & USP <800> outline requirements for the handling of sterile preparations (USP <797>) and hazardous drugs (USP <800>) to avoid harm to humans and animals.
- ✓ The revision of USP<797> was published in June 2019 but due to appeals is not active yet until further notice.
- ✓ General Chapter USP<800> became official in December, 2019.
- ✓ Be aware of changes in environmental monitoring for USP<797>.
- ✓ Consider testing for HD residues.

Continuing Education Units (CEUs)

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Thank you for joining us!

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