ADVANCED TRAINING IN STERILE COMPOUNDING COMPLIANCE AND INSPECTION

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HOME STUDY OVERVIEW

» Learning Objectives
- Define sterile compounding
- Identify enforceable aspects of USP Chapter <797> and <800>

» Content Areas
- Preparation of Compounded Sterile Preparations (CSPs)
- Hazardous Drugs (HD) – Handling in Healthcare Settings
- Beyond-use Dates (BUDs)
- CSP Categories
- Facility Operations - Primary Engineering Controls

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HOME STUDY RESPONSIBILITIES

» Thoroughly familiarize yourself with the following:
- View the recorded home study videos
- Review USP. Chapters (online.uspnf.com/uspnf)
  - <797> Pharmaceutical Compounding – Sterile Preparations
  - <800> Hazardous Drugs – Handling in Healthcare Settings
- Review NIOSH List of Hazardous Drugs in Healthcare Settings, 2024

» Arrive to the live course prepared to begin in-depth training that builds on the home study foundational knowledge.

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FACULTY & DISCLOSURES

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» Disclosures
- George Smith reports a honoraria from ARL Bio Pharma, consulting with Intelliguard and ARxIUM.

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INTRODUCTION TO STERILE COMPOUNDING

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GEORGE'S DEFINITION OF STERILE COMPOUNDING

Sterile compounding involves preparing medication that is free from both bacteria, viruses, spores and other infectious microorganisms as well as non-viable particulate that can cause harm. The medications are typically administered intravenously (IV), through injection, inhaled or directly in the eyes.

The environment in which a compound is prepared (e.g., PEC, cleanroom) is not *sterile*; it is considered **aseptic**. An aseptic setting is a carefully controlled environment that is designed to mitigate the risk of contamination to the preparation through minimization of particulate.

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WHAT & WHO IS USP?

Who is USP?

United States Pharmacopeia (USP) is an independent, scientific nonprofit organization focused on building trust in the supply of safe, quality medicines.

What does USP do?

The organization publishes **standards** that can be enforced by regulatory bodies such as the FDA, The Joint Commission (TJC), Centers of Medicare Services (CMS), State Board of Pharmacy, etc.

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https://www.usp.org/frequently-asked-questions/usp-and-its-standards

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USP STERILE COMPOUNDING STANDARDS

USP<797> describes the **minimum standards** to be followed for the preparation of compounded sterile preparations (CSPs) for human and animal drugs. Sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation.

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CURRENT COMPOUNDING DEFINITIONS

FDA U.S. FOOD & DRUG ADMINISTRATION

Drug compounding is often regarded as the process of combining, mixing, or altering ingredients to ***create a medication*** tailored to the needs of an individual patient.

USP

Sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation.

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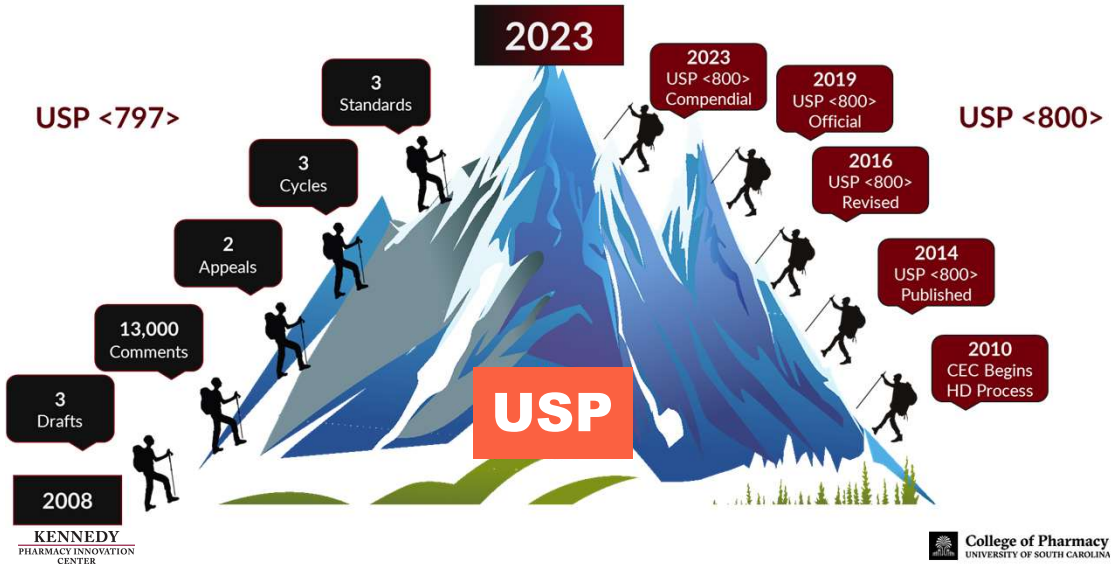
HOW DID WE GET HERE ...



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USP CHAPTER <797> SECTIONS

PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

1	INTRODUCTION AND SCOPE
2	PERSONNEL TRAINING AND EVALUATION
3	PERSONAL HYGIENE AND GARBING
4	FACILITIES AND ENGINEERING CONTROLS
5	CERTIFICATION AND RECERTIFICATION
6	MICROBIOLOGICAL AIR AND SURFACE MONITORING
7	CLEANING, DISINFECTING, AND APPLYING SPORICIDAL DISINFECTANTS AND STERILE 70% IPA
8	INTRODUCING ITEMS INTO THE SEC AND PEC
9	EQUIPMENT, SUPPLIES, AND COMPONENTS
10	STERILIZATION AND DEPYROGENATION
11	MASTER FORMULATION AND COMPOUNDING RECORDS
12	RELEASE INSPECTIONS AND TESTING
13	LABELING
14	ESTABLISHING BEYOND-USE DATES
15	USE OF CONVENTIONALLY MANUFACTURED PRODUCTS AS COMPONENTS
16	USE OF CSPs AS COMPONENTS
17	SOPs
18	QUALITY ASSURANCE AND QUALITY CONTROL
19	CSP HANDLING, STORAGE, PACKAGING, SHIPPING, AND TRANSPORT
20	DOCUMENTATION
21	COMPOUNDING ALLERGENIC EXTRACTS

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General Chapter: USP. Pharmaceutical Compounding—Sterile Preparations ⟨797⟩. In: USP-NF. Rockville, MD: USP; May 1, 2024.DOI: https://doi.usp.org/USPNF/USPNF_M99925_08_01.html

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USP CHAPTER <800> SECTIONS

HAZARDOUS DRUGS—HANDLING IN HEALTHCARE SETTINGS

1	INTRODUCTION AND SCOPE
2	LIST OF HAZARDOUS DRUGS
3	TYPES OF EXPOSURE
4	RESPONSIBILITIES OF PERSONNEL HANDLING HAZARDOUS DRUGS
5	FACILITIES AND ENGINEERING CONTROLS
6	ENVIRONMENTAL QUALITY AND CONTROL
7	PERSONAL PROTECTIVE EQUIPMENT
8	HAZARD COMMUNICATION PROGRAM
9	PERSONNEL TRAINING
10	RECEIVING
11	LABELING, PACKAGING, TRANSPORT AND DISPOSAL
12	DISPENSING FINAL DOSAGE FORMS
13	COMPOUNDING
14	ADMINISTERING
15	DEACTIVATING, DECONTAMINATING, CLEANING, AND DISINFECTING
16	SPILL CONTROL
17	DOCUMENTATION AND STANDARD OPERATING PROCEDURES
18	MEDICAL SURVEILLANCE

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General Chapter: USP. Hazardous Drugs—Handling in Healthcare Settings ⟨800⟩. In: USP-NF. Rockville, MD: USP; July 1, 2020. DOI: https://doi.usp.org/USPNF/USPNF_M7808_07_01.html

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USP CHAPTER <825> SECTIONS

RADIOPHARMACEUTICALS—PREPARATION, COMPOUNDING, DISPENSING, AND REPACKAGING

1	INTRODUCTION
2	RADIATION SAFETY CONSIDERATIONS
3	IMMEDIATE USE OF STERILE RADIOPHARMACEUTICALS
4	PERSONNEL QUALIFICATIONS, TRAINING, AND HYGIENE
5	FACILITIES AND ENGINEERING CONTROLS
6	MICROBIOLOGICAL AIR AND SURFACE MONITORING
7	CLEANING AND DISINFECTING
8	ASSIGNING BUD
9	DOCUMENTATION
10	PREPARATION
11	COMPOUNDING
12	DISPENSING
13	REPACKAGING
14	QUALITY ASSURANCE AND QUALITY CONTROL

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General Chapter: USP. Radiopharmaceuticals — Preparation, Compounding, Dispensing, and Repackaging ⟨825⟩. In: USP-NF. Rockville, MD: USP; January 1, 2024. DOI: https://doi.usp.org/USPNF/USPNF_M11915_05_01.html

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TERMINOLOGY & ACRONYMS

» USP Chapters
- <795> Nonsterile Compounding
- <797> Sterile Compounding
- <800> Hazardous Drugs (HD)
- <825> Radiopharmaceuticals

» ISO standards for air quality (ISO 3 – ISO 8)

» Primary Engineering Control (PEC)
- A device or zone that provides an ISO Class 5 or better air quality environment for sterile compounding.

» Beyond-use Dates (BUDs)
- The date, or hour and the date, after which a CSP must not be used, stored, or transported. The date is determined from the date and time the preparation is compounded.

» Facilities:
- Anteroom - a transition area between a cleanroom (like a buffer room) and a non-clean space
- Buffer room - a controlled environment where sterile compounding or mixing of medications occurs

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SIGNIFICANT CHANGES TO USP <797>

- Compounding Risk Levels → Categories
- Cleanroom Suite to Segregated Compounding Areas (SCA)
- Training & Competencies
- Microbiological Surveillance Program
- Handling of Hazardous Drugs

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USP <797> BEYOND-USE DATES

USP<797> differentiates among a provision and three categories for CSPs, **primarily based on the state of environmental control under which they are compounded**, the probability for microbial growth during the time they will be stored, and the period within which they must be used.

Longer Beyond-Use Date Limits

Immediate-Use	Compounded in an *uncontrolled* environment. Hand washing/hygiene not required.
Category 1	Compounded under the least controlled environmental conditions. Hand washing/hygiene & garbing required.
Category 2	Require additional environmental controls and testing than Category 1 CSPs. Hand washing/hygiene & garbing required.
Category 3	Require robust environmental controls (e.g., frequency, sterile garb) and testing compared with Category 2 CSPs. Hand washing/hygiene & full garb required.

Increased Sterility Assurance

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USP General Chapter <797>: Pharmaceutical Compounding - Sterile Preparations. May 1, 2024.

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SUMMARY

- Sterile compounding direction is guided by:
  - USP
  - FDA
  - Professional Judgement
- USP has no regulatory authority on its own
- Standards of practice have and will continue to be journey and evolution
- USP Beyond-Use Date (BUD) limits are primarily based upon the environment in which compounding occurs

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USP CHAPTER <800> HAZARDOUS DRUGS-HANDLING IN HEALTHCARE SETTINGS

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HAZARDOUS DRUG (HD)

NIOSH definition of HDs:

Any drug identified by one of the following six criteria:

1. Carcinogenicity
2. Teratogenicity or developmental toxicity
3. Reproductive toxicity in humans
4. Organ toxicity at low dose in humans or animals
5. Genotoxicity
6. New drugs that mimic existing HDs in structure or toxicity

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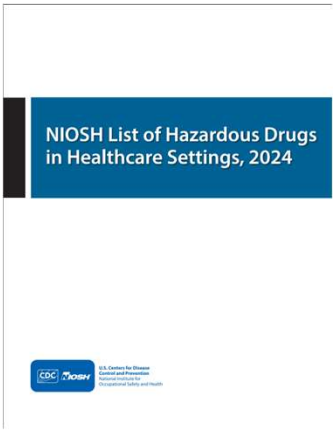
HAZARDOUS DRUG (HD)

NIOSH's approach for handling hazardous drugs involves dividing them into two groups:

Table 1:

- HD with the Manufacturer's Special Handling (MSHI)
- Known to be a human carcinogen listed on the National Toxicology Program (NTP)
- Group 1(known carcinogen), Group 2A (probable human carcinogen) listed by the International Agency for Research on Cancer (IARC)

Table 2: All other HDs on the NIOSH list



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WHAT, WHERE, & WHO?

⟨800⟩ HAZARDOUS DRUGS—HANDLING IN HEALTHCARE SETTINGS

1. INTRODUCTION AND SCOPE

This chapter describes practice and quality standards for handling hazardous drugs (HDs) to promote patient safety, worker safety, and environmental protection. Handling HDs includes, but is not limited to, the receipt, storage, compounding, dispensing, administration, and disposal of sterile and nonsterile products and preparations.

This chapter applies to all healthcare personnel who handle HD preparations and all entities that store, prepare, transport, or administer HDs (e.g., pharmacies, hospitals and other healthcare institutions, patient treatment clinics, physicians' practice facilities, or veterinarians' offices). Personnel who may potentially be exposed to HDs include, but are not limited to: pharmacists, pharmacy technicians, nurses, physicians, physician assistants, home healthcare workers, veterinarians, and veterinary technicians.

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USP <800> INTRODUCTION

Entities that handle HDs must incorporate the standards of this chapter into their occupational safety plan. The entity's health and safety management system must, at a minimum, include:

- A list of HDs
- Facility and engineering controls
- Competent personnel
- Safe work practices
- Proper use of appropriate Personal Protective Equipment
- Policies for HD waste segregation and disposal

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FACILITIES AND ENGINEERING CONTROLS USP CHAPTER <800> *HAZARDOUS DRUGS – HANDLING IN HEALTHCARE SETTINGS*

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FACILITIES AND ENGINEERING CONTROLS

"Hazardous Drugs (HDs) must be handled under conditions that promote patient safety, worker safety, and environmental protection."

- Signs must be posted to alert people of the hazard.
- Access to areas where HDs are handled must be limited to authorized personnel.
- Areas where HDs are handled must be away from breakrooms and refreshment areas to reduce the risk of exposure.

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FACILITIES AND ENGINEERING CONTROLS

» Designated areas must be available for:

- Receipt and unpacking
- Storage of HDs
- Non-sterile HD compounding (if performed)
- Sterile HD compounding (if performed)

» Negative pressure from surrounding areas is required to minimize the risk of exposure to HDs.

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STORAGE OF HDS

- HDs must be stored in a room that is vented outside, under negative pressure, with at least 12 air changes per hour (ACPH).
  - Negative pressure dedicated storeroom
  - Negative pressure buffer room

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ENGINEERING CONTROLS FOR CONTAINMENT

- Containment – Primary Engineering Control (C-PEC)
- Containment – Secondary Engineering Control (C-SEC)
- Supplemental Engineering Controls

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STERILE HD COMPOUNDING

Configuration	C-PEC	C-SEC	Max BUD
ISO Class 7 buffer with an ISO Class 7 ante-room	• Externally vented • Examples: Class II BSC or CACI	• Externally vented • 30 ACPH • Negative pressure between 0.01 and 0.03 inches water column relative to adjacent areas	As described in <797>
Unclassified C-SCA	• Externally vented • Examples Class II BSC or CACI	• Externally vented • 12 ACPH • Negative pressure between 0.01 and 0.03 inches water column relative to adjacent areas	As described in <797>

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5. Facilities and Engineering Controls for Sterile HD Compounding from U.S. Pharmacopeial Convention. Chapter <800> Hazardous Drugs – Handling in Healthcare Settings. *USP 43-NF 38*.

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CHARACTERISTICS OF CONTAINMENT PRIMARY ENGINEERING CONTROLS (C-PECS)

1. ISO Class 5 or better air quality
2. Unidirectional airflow
3. Negative Air pressure
4. Externally exhausted

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AIR QUALITY STANDARDS

- ISO Class 7 or better air quality for **both** the anteroom and the negative pressure buffer room.
- Total particle count testing must be performed under *dynamic operating conditions*.

ISO Class	Maximum Particle Count (particles of 0.5 micron and larger per cubic meter of air)
3	35.2
4	352
5*	3520
6	35,200
7	352,000
8	3,520,000

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AIR CHANGES PER HOUR (ACPH)

» Cleanroom Suite with HD Buffer Room
- ≥ 30 ACPH of HEPA-filtered air for both the ante-room and the buffer room.

» Containment Segregated Compounding Area
- ≥ 12 ACPH of exhausted air

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PRESSURE DIFFERENTIALS

- The ante-room must maintain a positive pressure of at least 0.020-inch water column relative to all adjacent unclassified areas.
- An HD buffer room must have a negative pressure difference between 0.01 and 0.03-inches water column relative to adjacent areas.
  - Unclassified → Pos ≥ 0.020" w.c. (Anteroom) → Neg 0.01-0.03" w.c. (HD buffer room)
- Continuous pressure monitoring is required for a cleanroom suite, containment segregated compounding area, and HD storage.

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CONTAINMENT – SECONDARY ENGINEERING CONTROLS

- Cleanroom suite
  - Anteroom
  - Negative pressure buffer room
- Containment segregated compounding area

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HD ANTE-ROOM

- ISO Class 7 or better air quality.
- Minimum of 30 air changes per hour of HEPA-filtered air.
- *Positive* pressure of at least 0.020-inch water column between the anteroom and adjacent unclassified areas.
- Hand-washing sink must be at least 1 meter away from the entrance to the HD buffer room.

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HD BUFFER ROOM

- ISO Class 7 or better air quality.
- Minimum of 30 air changes per hour (ACPH) of HEPA-filtered air.
- Maintain a *negative* pressure *between* 0.01- and 0.03-inches water column relative to the adjacent areas.
- Externally vented.
  - *Exhausted air.*

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CLOSED-SYSTEM DRUG-TRANSFER DEVICE (CSTD)

- NIOSH description of CSTD:"*A drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system.*"
- CSTDs should be used when compounding HDs when the dosage form allows
- CSTDs must be used when administering antineoplastic HDs when the dosage form allows

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HAZARD COMMUNICATION PROGRAM

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HAZARD COMMUNICATION PROGRAM – FACILITY REQUIREMENTS

- This is an Occupational Safety and Health Administration (OSHA) requirement of all workplaces where employees are exposed to hazardous chemicals.
- Is a written plan describing how the standard will be implemented in that facility. May be part of multiple separate policies.
- Responsibility usually is a function of a Safety Department and/or its designated person (facility specific).

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HAZARD COMMUNICATION PROGRAM – FACILITY REQUIREMENTS

- Entity must develop SOP's to ensure training in all aspects of hazard use. (i.e. receipt, transport, etc.)
- Must include:
  - How HD containers are marked and labeled.
  - SDS for each HD they use.
  - Ensure that the SDS's are readily accessible.
  - Personnel who will be working with HD's must be provided information and training prior to initial work.
  - Personnel must confirm in writing that they understand the risks of handling HD's.

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DISPOSAL OF HDS

- Must comply with local, state and federal regulations.
- All personnel who perform custodial waste removal and cleaning activities in HD handling areas must be trained in appropriate procedures.
- **TRACE** ("RCRA empty") chemotherapy waste – yellow bin.
- **BULK** chemotherapy waste – black RCRA (Resource Conservation and Recovery Act).

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DISPOSAL OF HDS

- TRACE ("RCRA empty") chemotherapy waste –
- YELLOW bin

- BULK chemotherapy waste – BLACK RCRA
- (Resource Conservation and Recovery Act)

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Images: http://www.medline.com/product/Chemotherapy-Sharps-Collectors-by-Becton-Dickinson/Z05-PF64971
https://mfimedical.com/products/bemis-2-gallon-rcra-waste-container

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DEACTIVATION, DECONTAMINATING, CLEANING AND DISINFECTING WITH HAZARDOUS AGENTS

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DEACTIVATION, DECONTAMINATING, CLEANING AND DISINFECTING WITH HAZARDOUS AGENTS

» Personnel must be properly trained in appropriate procedures to protect themselves and environment from contamination

» PPE resistant to hazardous agents to include:
- 2 pair ASTM tested chemo gloves
- Eye protection and face shield if there is possibility of splash hazard
- Impermeable disposable gowns
- Respiratory protection if needed

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DEACTIVATION, DECONTAMINATING, CLEANING AND DISINFECTING WITH HAZARDOUS AGENTS

» Written Policy & Procedure must include:
- Procedures for cleaning
- Cleaning agents used
- Dilutions used if applicable
- Frequency of cleaning
- Documentation

» Cleaning of non-sterile and sterile compounding areas must comply with <795> and <797>

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DEACTIVATION, DECONTAMINATING HAZARDOUS AGENTS

» DEACTIVATION of HD
- Renders compound inactive or inert with chemical, heat, UV light or another agent.
- Oxidizer (ex. Sodium hypochlorite – bleach or hydrogen peroxide/peroxyacetic acid solution).
- No one proven method for deactivating all compounds.

» DECONTAMINATION of area where HD is compounded
- Physical removal of HD residue from non-disposable surfaces.
- Transferring to disposable wipes, pads or towels.
- Discarded as contaminate HD waste.

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CLEANING AND DISINFECTING HAZARDOUS AGENTS

» CLEANING
- Process that removes contaminants (ex. soil, microbial contamination, HD residue)
- Water + germicidal detergent

» DISINFECTING
- Process of destroying microorganisms
- Sterile alcohol 70%
- Sterile compounding areas

Products should be applied with wipes, not sprayed

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DECONTAMINATION REMINDER PER USP 800

» Decontamination must occur:
- Between compounding of different HD products
- At least daily (when used)
- Any time spill occurs
- Before/after certification

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DEACTIVATION, DECONTAMINATING, CLEANING AND DISINFECTING WITH HAZARDOUS AGENTS

» Areas below work tray must be decontaminated at **least monthly**.
- Complete the Deactivation, Decontamination, Cleaning of other areas 1st.

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Images contributed by program faculty

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BEYOND-USE DATES & CSP CATEGORIES

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PRODUCTS VS PREPARATIONS

»**Product:**
- A commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the FDA.

»**Compounded Sterile Preparation (CSP):**
- A preparation intended to be sterile that is created by combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug *product* or bulk drug substance.

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EXPIRATION DATES VS BUDS

Expiration Date

»Assigned by the *manufacturer*.

»Determined by product-specific studies using extensive analytical and performance testing.

Beyond-Use Date

»Assigned by a *pharmacist*.

»Determined using evidence-based information for physical and chemical compatibility of the drugs and following USP Chapter <797> guidelines.

BUDs and expiration dates are not the same.

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EXPIRATION DATE

»The time during which a product can be expected to meet the requirements of the USP-NF monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions.

»Applies to all conventionally manufactured products, APIs, or added substances.

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USP <797> Table 11

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BEYOND-USE DATE

- The date, or the hour and date, beyond which the preparation must not be used and must be discarded.
- The BUD is determined from the date and time compounding of the CSP began.
- The BUD must not exceed the shortest expiration date *or* BUD of any of the starting components.
- Applies to all CSPs.
- *One day is equivalent to 24 hours.**

* Defined in 2023 release

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BEYOND-USE DATE

- The BUD is not intended to limit the time during which the CSP is administered (e.g., infused).
- For example:
  - An IV preparation is scheduled to begin 1 hour before the assigned BUD. It is scheduled as a 2-hour infusion. Can it be administered?
  - A sterile ophthalmic preparation with a 10-day BUD is scheduled for administration once per day for 14 days. Can it be administered?

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USP <797> FAQs 159, 160

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ESTABLISHING A BUD

- The BUD limits are based on the risk of microbial contamination. Either by not achieving sterility or by not maintaining sterility.
- The CSP formulation must remain chemically and physically stable, and its packaging must maintain its integrity for the duration of BUD.

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USP <797> 14.3

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FACTORS THAT MAY AFFECT *STERILITY*

- The environment in which the CSP is prepared
  - Classified environment
  - Unclassified environment
- *Aseptic processing* versus *terminal sterilization*
- Starting components
  - Sterile
  - Nonsterile
- Planned storage conditions
  - Controlled room temperature
  - Refrigeration
  - Frozen

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FACTORS THAT MAY AFFECT *STABILITY*

»The chemical and physical stability properties of the drug and/or its formulation

»Storage conditions

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STORAGE CONDITIONS

»Storing CSPs in colder conditions has been shown to retard microbial growth of most microorganisms.

»Colder conditions may affect the chemical and physical stability of a CSP.

»BUDs are not additive. If changes in storage require a shorter BUD, the CSP must be used within the new BUD and can never exceed the original BUD.

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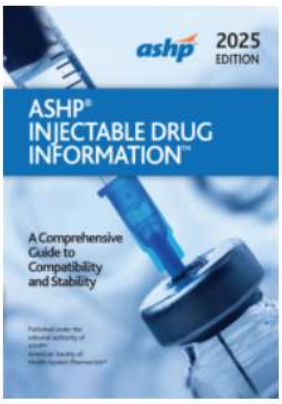
COMPATIBILITY/STABILITY RESOURCES

»Resources to check compatibility of components
- Package labeling
- Drug databases with compatibility checking features
  - Micromedex / Kings
- Reference books
  - Trissel's Stability Guide to Compounded Formulations
  - ASHP Injectable Drug Information
  - King's Guide to Parenteral Admixtures



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COMPATIBILITY/STABILITY RESOURCES
CALCIUM / PHOSPHATE INCOMPATIBILITY

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Drug Incompability Example.mp4

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ASEPTIC PROCESSING AND STERILIZATION METHODS

Aseptic Processing

»Compounding with only sterile starting ingredient(s).

»Compounding with nonsterile ingredient(s) followed by sterilization by filtration.

Terminal Sterilization

»Includes compounding with sterile and/or nonsterile starting ingredient(s).

»Requires a sterilization process of sealed final containers intended to achieve a PNSU of 10^{-6}.

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USP <797> 14.2.1 Terminal sterilization methods and aseptic processing

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BUD LIMITS FOR CATEGORY 1 CSPS

Storage Conditions	
Controlled Room Temperature (20˚ to 25˚)	Refrigerator (2˚ to 8˚)
≤ 12 hours	≤ 24 hours

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USP <797> Table 12

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BUD LIMITS FOR CATEGORY 2 CSPS

Preparation Characteristics		Storage Conditions		
Compounding Method	Sterility Testing Performed and Passed*	Controlled Room Temperature (20˚to 25˚)	Refrigerator (2˚ to 8˚)	Freezer (-25˚ to -10˚)
Aseptically Processed CSPs	No	Prepared from one or more nonsterile components		
		1 days	4 days	45 days
		Prepared from only sterile starting components		
		4 days	10 days	45 days
	Yes	30 days	45 days	60 days
Terminally Sterilized CSPs	No	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

*USP <71>

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USP <797> Table 13

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BUD LIMITS FOR CATEGORY 3 CSPS

Preparation Characteristics	Storage Conditions		
Compounding Method	Controlled Room Temperature (20˚to 25˚)	Refrigerator (2˚ to 8˚)	Freezer (-25˚ to -10˚)
Aseptically Processed, sterility tested, and passing all applicable test for Category 3 CSPs	60 days	90 days	120 days
Terminally sterilized, sterility tested, and passing all applicable tests for Category 3 CSPs	90 days	120 days	180 days

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USP <797> Table 14

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ADDITIONAL FACILITY AND PERSONNEL REQUIREMENTS FOR CATEGORY 3 CSPS

- »Increasing the storage time of a CSP introduces additional risk for chemical degradation, physical incompatibilities, compromised container closure systems, and microbial growth.
- »To address these risks and maintain a higher state of environmental control, additional requirements must be met.
  - Training and competency
  - Garbing requirements
  - Environmental monitoring
  - CSP testing

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USP <797> 14.4.1 Assigning Category 3 BUDs

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ADDITIONAL CSP TESTING REQUIREMENTS FOR CATEGORY 3 CSPS

- »Initial CSP testing
  - Stability-indicating method study supporting the extended BUD
  - Particulate matter for injections (USP <788>) or particulate matter for ophthalmic solutions (USP <789>)
  - Container closure-integrity test (USP <1207>)
- »Ongoing CSP testing
  - Sterility test (USP <71>) or validated alternative method USP <1223>
  - Endotoxin test, if using any nonsterile components (USP <85>)

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USP <797> 14.4.3 & 14.4.4

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STABILITY DATA REQUIREMENTS FOR CATEGORY 3 CSPS

- The BUD assigned to a Cat 3 CSP requires stability data using a stability-indicating analytical method.
- The study must be able to distinguish the active ingredient from its degradants and impurities and quantify the amount of active ingredients.
- The Cat 3 CSP must be prepared according to the exact formulation that was tested.
- The Cat 3 CSP must be packaged and stored in the same container closure system that was tested.

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USP <797> 14.4.3 Stability Requirements Category 3 CSPs

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CONVENTIONALLY MANUFACTURED PRODUCTS

Product	Assigned BUD
Single-dose containers	Up to 12 hours if punctured in ISO Class 5 or cleaner air and the storage requirements are maintained.
Multiple-dose containers	Up to 28 days after puncturing the container unless otherwise specified on the labeling.
Pharmacy bulk packages	Must be punctured in an ISO Class 5 PEC and must be used according to the manufacturer's labeling.
Ampules	Single-dose ampules must not be stored for any time.
Proprietary bag and vial systems	Docking and activation for *immediate* administration is not considered compounding. Docking for *future activation* and administration is considered compounding and must be done in an ISO Class 5 and the BUD must not exceed the manufacturers labeling.

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CSP STOCK SOLUTION BUDS

- **BUD of a compounded stock solution**
  - BUD per <797>

Day 1
- Stock solution bag compounded
  - 10-day BUD refrigerated

- **BUD of final CSP made from stock Solution**
  - Stock solution BUD minus days stored

Day 3
- Patient CSP drawn from stock solution (first pierce)
  - 7-day BUD refrigerated (10 day minus 3 day)

- **Pierced stock solution container BUD**
  - 12 hours

Day 3
- Stock Solution bag treated as a single dose container
  - 12-hour BUD

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USP <797> 16.2, USP FAQ: 191

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22

FACILITIES AND ENGINEERING CONTROLS FOR STERILE COMPOUNDING

Primary Engineering Controls

Richard Capps, PharmD, DPLA
Pharmacy Manager
Prisma Health Oconee Memorial Hospital, Seneca, SC

UNIVERSITY OF South Carolina College of Pharmacy

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ENGINEERING CONTROLS

Engineering controls are the equipment we use to reduce or eliminate exposure of a preparation to contamination or to reduce or eliminate exposure of our personnel to hazardous substances.

- Primary Engineering Controls (PECs)
- Secondary Engineering Controls (SECs)
- Supplemental Engineering Controls (CSTDs)

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PRIMARY ENGINEERING CONTROL (PEC)

"A device or zone that provides an ISO Class 5 air quality environment for sterile compounding."

A PEC is often referred to as an "ISO Class 5 environment."

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<797> Glossary

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CHARACTERISTICS OF PRIMARY ENGINEERING CONTROLS (PEC)

- ISO Class 5 or better air quality
  - HEPA filtered air
- Unidirectional airflow
  - Horizontal laminar airflow hood
  - Vertical laminar airflow hood
- Air pressure management
  - Positive air pressure
  - Negative air pressure
- Externally vented (hazardous C-PEC)

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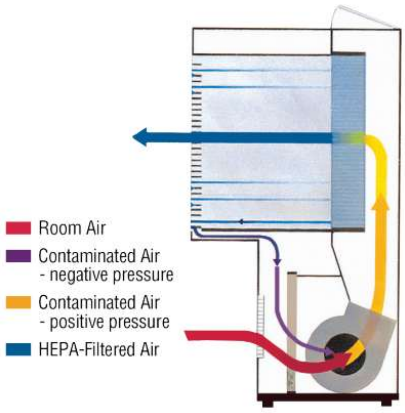
HOW A PEC WORKS

Room air is drawn in through a pre-filter to remove large particle contaminants, such as dust and lint. The air passes through a HEPA filter and then into the workspace of the PEC. The air exiting the HEPA filter is clean and unidirectional. The clean air flows across the entire work surface in parallel lines and at a uniform speed. Based on the type of PEC, the air pressure within the PEC will be either positive pressure or negative pressure.



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https://bakerco.com/images/uploads/assets/210D000F_Operators_Manual.pdf

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ISO CLASSIFICATION OF PARTICULATE MATTER IN ROOM AIR

ISO Class	Maximum Particle Count (particles of 0.5 micron and larger per cubic meter of air)
3	35.2
4	352
5	3520
6	35,200
7	352,000
8	3,520,000

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5. Facilities and Engineering Controls for Sterile HD Compounding from U.S. Pharmacopeial Convention. Chapter <800> Hazardous Drugs - Handling in Healthcare Settings. *USP 43-NF 38*.

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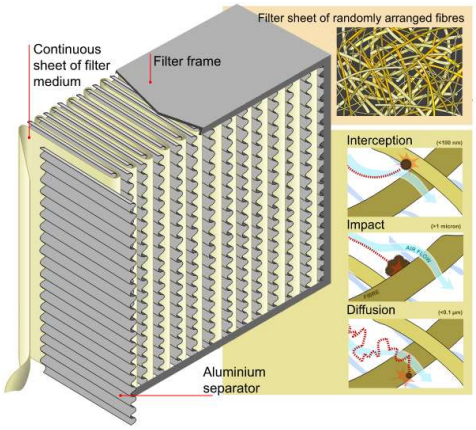
HIGH-EFFICIENCY PARTICULATE AIR (HEPA) FILTERS



- HEPA filters have a minimum particle collection efficiency of 99.97% for particles with a mass median diameter of 0.3 µm.
- A 0.3 µm particle is the most likely particle size to pass through a HEPA filter. HEPA filters are more efficient at removing particles that are larger or smaller than 0.3 µm.

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By LadyofHats - Public Domain, https://commons.wikimedia.org/w/index.php?curid=4552953

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HIGH-EFFICIENCY PARTICULATE AIR FILTERS

- HEPA filters do an excellent job removing contaminants from the air and creating a clean compounding environment.
- HEPA filters are not effective at removing vapors, gases, or odors.
  - Many hazardous drugs form gas vapors, even at room temperature. Because HEPA filters do not remove gas vapors, the exhaust from hazardous drug compounding must be vented outside the building.
    - Examples of HDs that form gas vapors at room temperature include: carmustine, cisplatin, cyclophosphamide, etoposide, thiotepa, nitrogen mustard, and 5-FU.

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UNIDIRECTIONAL AIRFLOW

"Air within a PEC moving in a single direction in a uniform manner and at sufficient velocity to sweep particles away from the DCA."

Direct Compounding Area (DCA):

"A critical area within the ISO Class 5 PEC where critical sites are exposed to unidirectional HEPA-filtered air, also know as first air."

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<797> Glossary
Image: https://www.nuaire.com/resources/never-cover-the-airflow-grill-on-a-biosafety-cabinet-article

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UNIDIRECTIONAL AIRFLOW

- The unidirectional airflow in a LAFW is horizontal. The air moves from the HEPA filter through the work zone and into the buffer room or segregated compounding area.
- The unidirectional airflow in a BSC, CAI, or CACI is vertical. The air moves downward from the HEPA filter through the work zone and is drawn away by air exhaust grills in the front and back of the work surface.
- *…compounders must understand how to utilize unidirectional airflow to maintain first air in the DCA.*

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<797> 4.2.3

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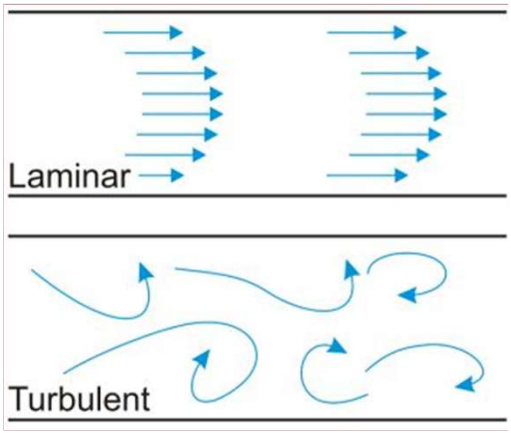
TURBULENT AIRFLOW



Particulate levels are reduced over time by *diluting* the air with HEPA filtered air.

https://www.cadillacmeter.com/cadillac-meter/piping-requirements-for-flow-meter-installation/

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AIR PRESSURE

» **Positive Pressure**

- A net displacement of air out of a space.
- Used to protect an environment from outside contamination by less clean air.

» **Negative Pressure**

- A net displacement of air into a space.
- Used to contain potentially hazardous drugs from escaping and contaminating the work environment.

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PECS FOR NON-HAZARDOUS STERILE COMPOUNDING

- **Laminar Airflow Systems** (LAFS)
  - Laminar Airflow Workbenches (LAFW)
  - Integrated Vertical Laminar Flow Zones (IVLFZ)
  - Class II Biological Safety Cabinets (BSC)
- **Restricted-access Barrier System** (RABS)
  - Compounding Aseptic Isolator (CAI)
- **Pharmaceutical Isolator**

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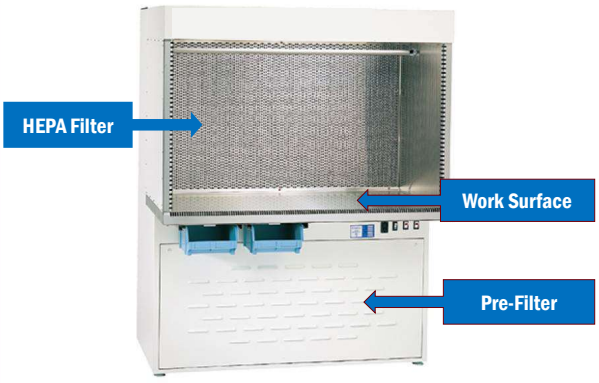
LAMINAR AIRFLOW WORKBENCH (LAFW)



- These are open-faced devices with the airflow moving through the device, past the compounder and into the room.
- LAFWs should be kept running continuously.

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https://bakerco.com/images/uploads/assets/EdgeGARD_Brochure-UPDATED-Aug_19.pdf

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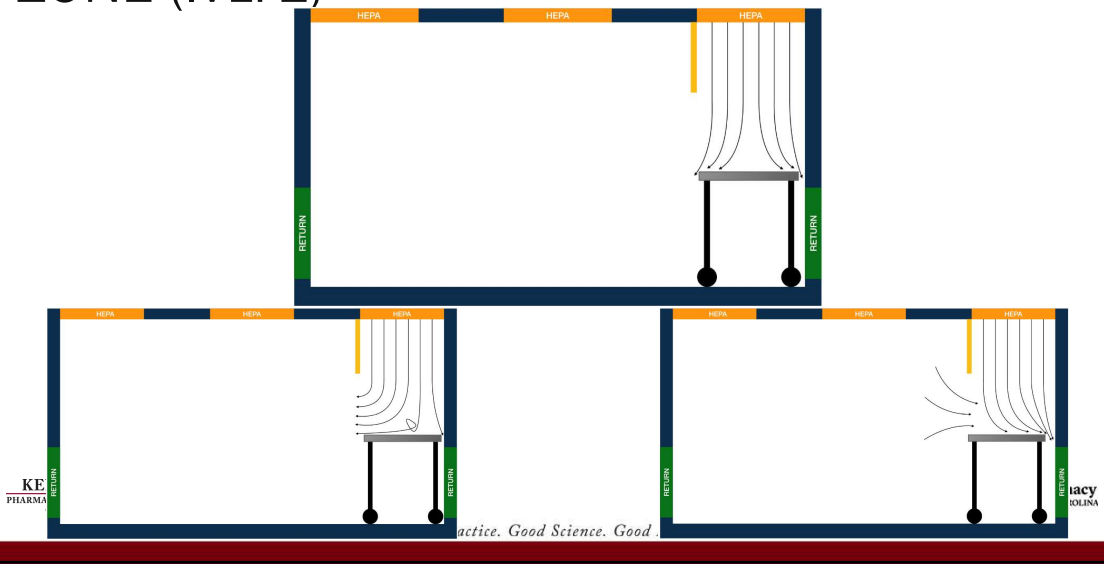
INTEGRATED VERTICAL LAMINAR FLOW ZONE (IVLFZ)



15

INTEGRATED VERTICAL LAMINAR FLOW ZONE

- An IVLFZ must be located within an ISO Class 7 or cleaner buffer room.
- An IVLFZ works by placing HEPA filters above the entire work area and through the proper placement of air returns behind the work area.
- Dynamic airflow smoke pattern testing across the entire work area is needed (with video) to document that the IVLFZ is working correctly.

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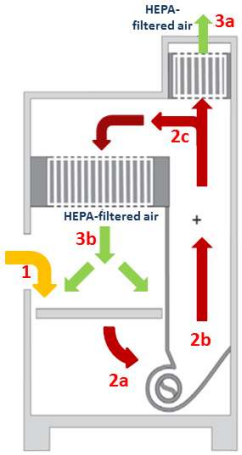
CLASS II TYPE A1 BIOLOGICAL SAFETY CABINET (BSC)

- Operates under positive pressure and exhausted into the room.
- Airflow
  - 70% recirculated through the HEPA filter.
  - 30% exhausted from the device into the room.
- A Class II type A1 BSC is not approved for hazardous drugs.



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MIT Environmental Health & Safety Office
https://ehs.mit.edu/site/biosafety/biosafety-cabinets

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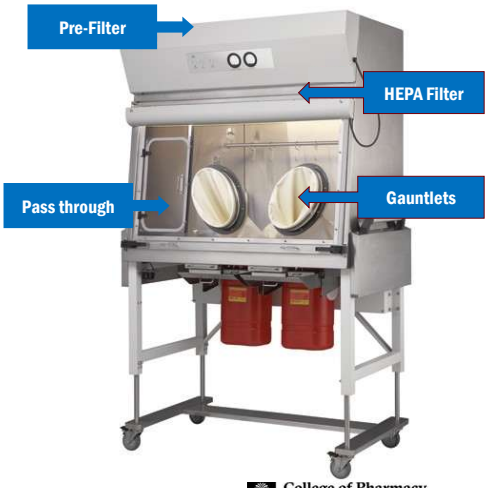
COMPOUNDING ASEPTIC ISOLATOR (CAI)

- Operates under positive pressure and exhausted into the room.
- The ingress and egress of materials is through a pass-through chamber.
- Disposable gloves *should* be worn inside the gloves attached to the CAI.
- Sterile gloves *must* be worn over the gloves attached to the CAI.
- SOPs must include the *recovery time*.



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https://www.nuaire.com/products/pharmacy-isolators

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PHARMACEUTICAL ISOLATORS

- A pharmaceutical isolator provides isolation from the surrounding area and maintains ISO Class 5 air quality during dynamic operating conditions.
- A pharmaceutical isolator must have these 4 elements:
  - Controlled workspace
  - Transfer devices(s)
  - Access devices(s)
  - Integral decontamination system
- Located inside of an ISO Class 8 positive pressure room.
  - An anteroom is not needed.

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PHARMACEUTICAL ISOLATORS

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Image provided by Germfree Laboratories, Inc.

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PLACEMENT OF PECS

PEC Type	Device Type	Placement for Compounding Category 1 CSPs	Placement for Compounding Category 2 and 3 CSPs
LAFS	LAFW	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
	IVLFZ	N/A	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
	BSC	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
RABS	CAI or CACI	Unclassified SCA	ISO Class 7 positive pressure buffer room with an ISO Class 8 positive pressure ante-room
Pharmaceutical isolator	Pharmaceutical isolator	Unclassified SCA	ISO Class 8 positive pressure room

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Table 5. 2023 USP - 797 Pharmaceutical Compounding - Sterile Preparations

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PLACEMENT OF PECS

- Placement must not allow surrounding less clean air to impact the air quality within the PEC. Contamination sources include:
  - Air currents from doors or from the HVAC
  - Other personnel
  - Water sources
  - What operations are adjacent to an SCA
- Placement of the PEC must allow for cleaning around the PEC.

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PECS FOR HAZARDOUS STERILE COMPOUNDING (C-PEC)

- **Laminar Airflow Systems** (LAFS)
  - Biological Safety Cabinets (BSC)
    - Class II, Type A2 BSC
    - Class II, Type B1 BSC
    - Class II, Type B2 BSC
    - Class III BSC
- **Restricted-access Barrier System** (RABS)
  - Compounding Aseptic Containment Isolator (CACI)
    - Recirculating
    - Total Exhaust

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BIOLOGICAL SAFETY CABINETS (BSC)

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CLASS II TYPE A2 BSC

- 70% Recirculated / 30% Exhausted
- If used for HDs, it must be vented to the outside through an exhaust canopy.
- *Acceptable* for most HDs

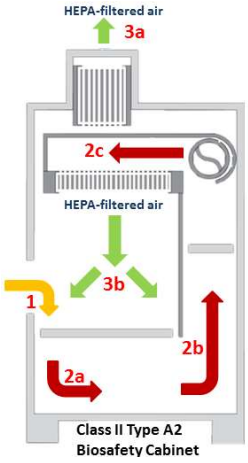

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Image source: https://ehs.mit.edu/site/biosafety/biosafety-cabinets

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CANOPY CONNECTION

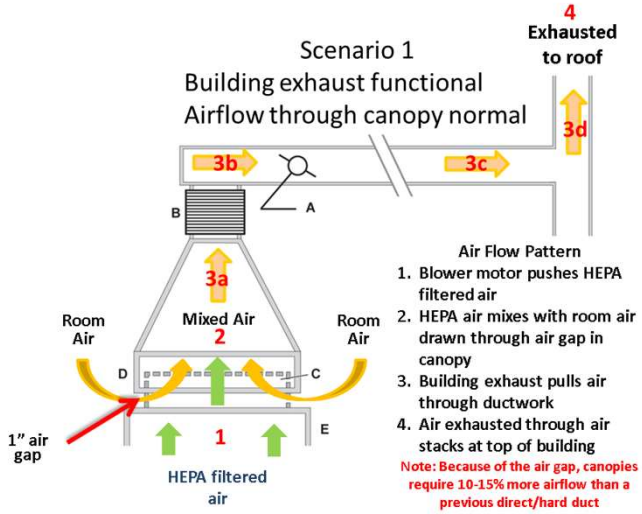

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Image source: https://ehs.mit.edu/site/biosafety/biosafety-cabinets

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CLASS II TYPE B1 BSC

- 30% Recirculated / 70% Exhausted
- Must be vented to the outside with a hard connection
- Designed for compounder to work in the back half of the hood

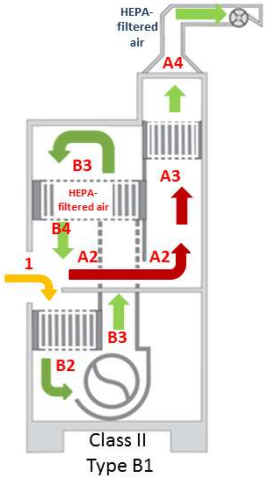

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Image source: https://ehs.mit.edu/site/biosafety/biosafety-cabinets

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CLASS II TYPE B2 BSC

- 100% Exhausted
- Must be vented to the outside with a hard connection

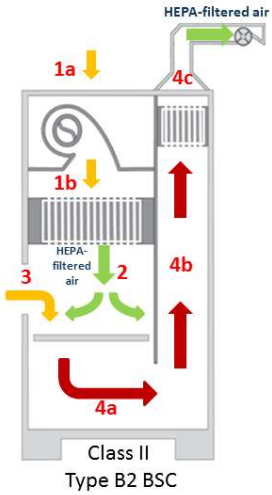

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Image source: https://ehs.mit.edu/site/biosafety/biosafety-cabinets

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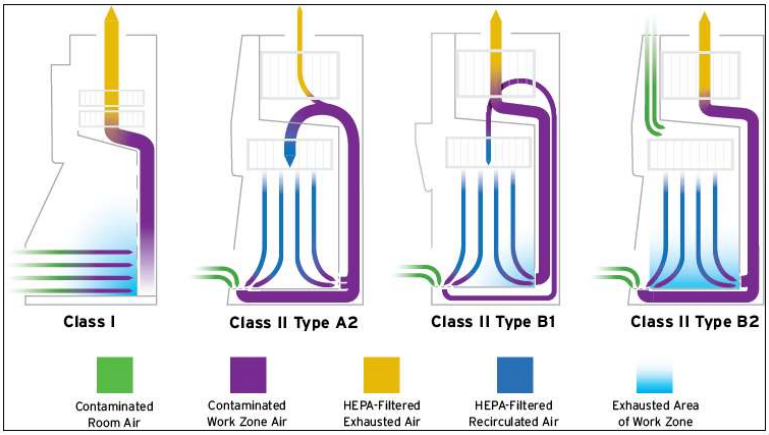
BSC EXHAUSTED WORK ZONES



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https://www.nuaire.com/resources/fume-hood-vs-biosafety-cabinet

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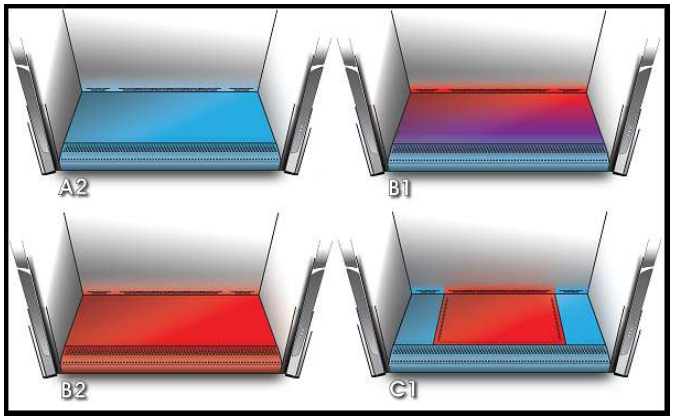
BSC EXHAUSTED WORK ZONES



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https://en.wikipedia.org/wiki/Biosafety_cabinet

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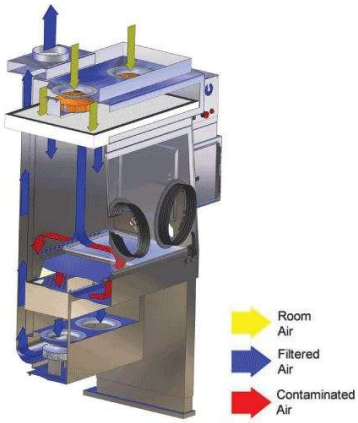
COMPOUNDING ASEPTIC CONTAINMENT ISOLATOR (CACI)



- Operates under negative pressure and must be vented outside.
- May recirculate or may be total exhaust
- Must clean the area beneath the work surface.

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Image: https://www.germfree.com/equipment/compounding-aseptic-containment-isolator

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COMMON ISSUES OF PECS / CPECS

- Sterile gloves must always be worn while compounding.
- Prefilters must be inspected based on the manufacture's recommendations.
- Should be operated continuously.
  - Helps to maintain the air quality within the PEC.
  - Contributes to the air quality of a positive pressure buffer room.
  - The PEC *must* remain on if it contributes to the required ACPH.
  - Contributes to the negative pressure of a negative pressure buffer room.

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NONSTERILE HD COMPOUNDING CONTAINMENT - PEC

- C-PEC
  - Externally vented (preferred) or redundant HEPA filters in series.
  - Examples CVE, CACI, Class I or II BSC
- Used for handling HDs
  - Needed for crushing, splitting, or using a powdered API
  - Not needed for counting and repackaging

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Image source: www.germfree.com

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Many see a path to a good
occupation.
A few are driven to change and
innovation.

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