Sterile Compounding & Compliance with USP Chapters <795>, <797> & <800>

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How do pharmacy services impact IC?

Key role in infection control by reducing infection transmission through proper preparation, handling, storage, and management of medications

- **Antimicrobial stewardship programs**
- **Vaccination programs**
- **Proper preparation, handling, and storage of drug products**

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Compounding

Definition

- **Practice in which a licensed healthcare worker combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient**

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Last Week Tonight – September 29, 2019

https://www.youtube.com/watch?v=Nuzi7LISDVo

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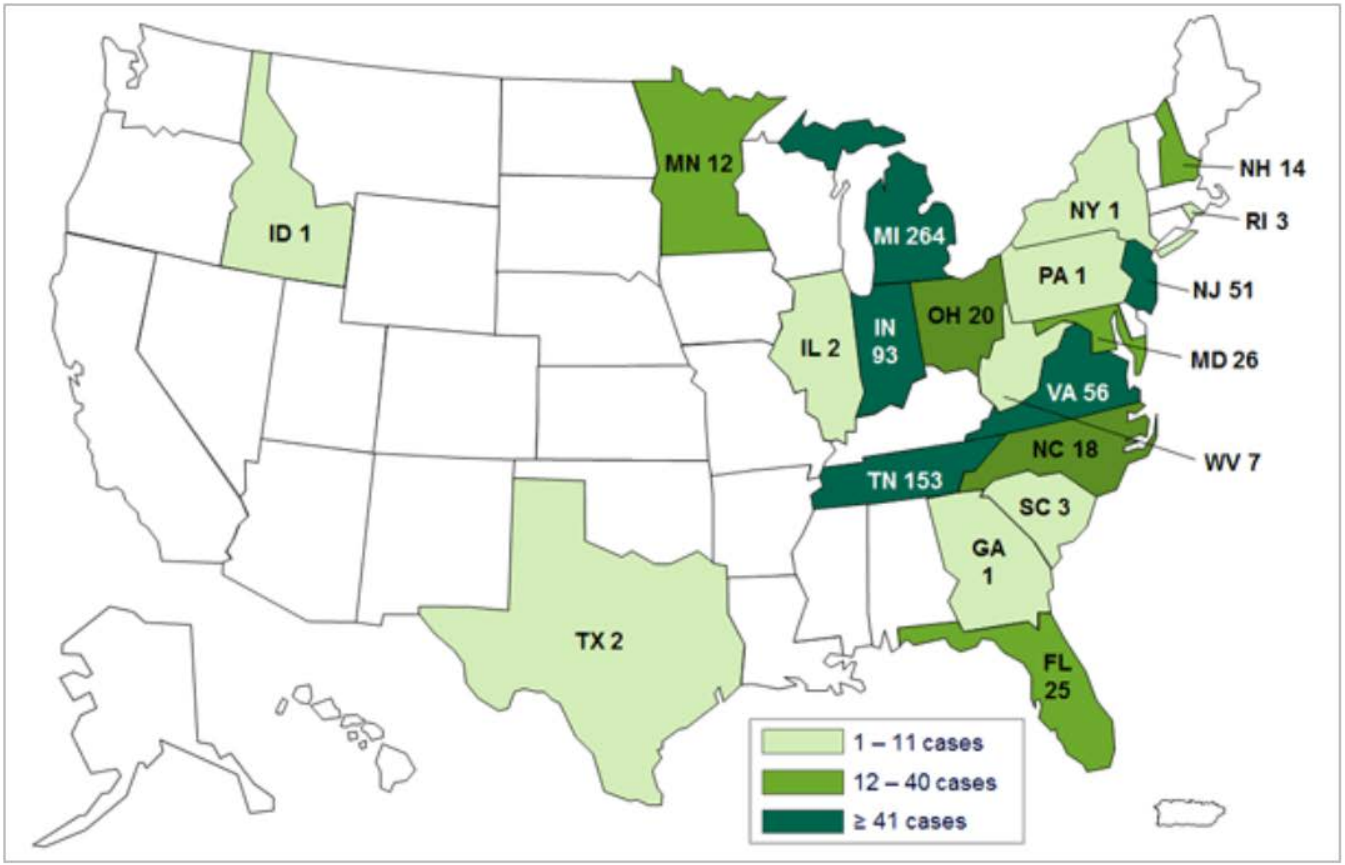
Persons with Fungal Infections Linked to Steroid Injections, by State



https://www.cdc.gov/hai/outbreaks/meningitis-map-large.html

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Healthcare-associated infections (HAIs)

Medication compounding–related infections (MCRI)

A data table from THE PEW CHARITABLE TRUSTS | June 2017

U.S. Illnesses and Deaths Associated With Compounded or Repackaged Medications, 2001-17

Update note: This chart was updated in March 2018 to include newly reported adverse events, and newly reported details of p... replaced the term "pharmacy" with "compounder," to reflect the fact that drugs can be compounded by physicians and outsou...

Pew's drug safety project has identified more than 71 reported compounding errors or potential errors associated with... 2001 to 2017. However, a 2015 survey found that only 30 percent of states (13 of the 43 that responded) require steril... events.[1] Of the states that require reporting, the type of information that is required to be reported may vary, further c... associated with compounded medications. Even in states with strong adverse event reporting requirements, illnesses... linked to the compounding error.[2,3,4] Because many such events may go unreported, this chart is likely an underestima... Contamination of sterile products was the most common error; others were the result of pharmacists' and technician...

Drug compounding can be an interstate operation; pharmacies may prepare medicines in one state and ship them to ... an out-of-state pharmacy shipping into their jurisdiction is held to a different quality or regulatory standard than in-st... state where the compounding error or potential error occurred and the state(s) where the adverse event(s) occurred ... anyone who compounds drugs in any setting across states would help address challenges in regulating out-of-state pl... baseline criteria for preparing safe drugs and protecting patients.

Dozens say they lost eyesight after routine surgery using compounded pharmacy drugs

Unlike FDA-approved drugs, compounded drugs are not government tested, and patients often have no idea -

Year	Reported cases	Reported deaths	Adverse events	Compounding error	Product	State where compounding occurred	State where adverse event(s) occurred	Notes
2017	2		Tissue erosion at injection site	High pH; no glutamine detected in samples[5]	Compounded injectable of glutamine, arginine, and carnitine (GAC)	FL	Not reported	
			Hemorrhagic		Intraocular injectable			

https://www.pewtrusts.org/-/media/assets/2018/03/dsp_us_illnesses_and_deaths_associated_with_compounded_medications_or_repackaged_medications.pdf?la=es&hash=2EE7FE75B985AB095A26658B2D6FE3CBFABAF50C

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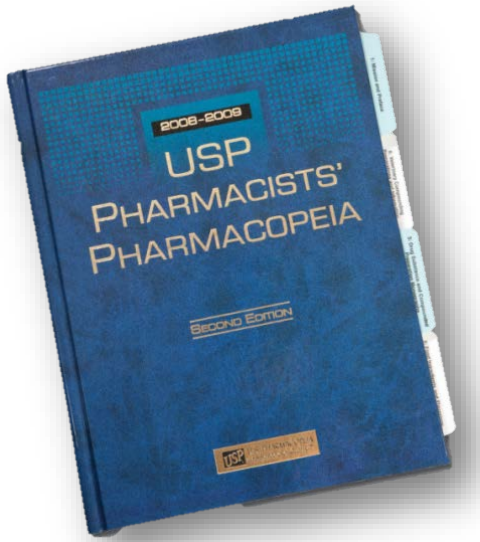
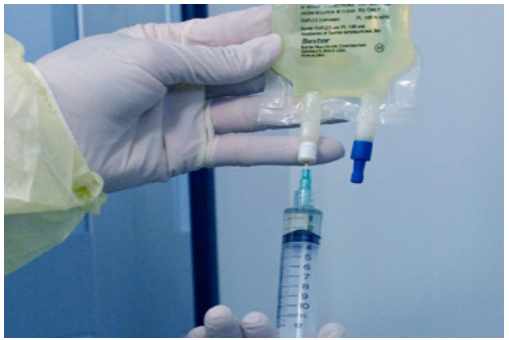
Quality standards for compounded preparations

- **USP (United States Pharmacopeia) – nongovernment, nonprofit scientific organization**
  - Has federal authority to set compounding and manufacturing standards
  - USP Pharmacists' Pharmacopeia is an official publication whose guidelines offer valuable information on nearly every aspect of pharmacy practice
  - USP chapters < 1,000 are enforceable by the FDA.
- **Some states accept USP standards as the state's regulations. But some states have different regulations.**
- **Under FDA guidance, traditional pharmacies (503A) must compound preparations in compliance with USP chapters on pharmacy compounding**
- **Drug Quality and Security Act reaffirmed that ingredients in compounded preparations must adhere to USP standards**



USP chapters

Non-sterile Compounding – USP <795>



Sterile Compounding – USP <797>

Hazardous Drug Handling – USP <800>

Radiopharmaceutical Handling – USP <825>

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Enforcement

FDA

STATE BOARDS OF PHARMACY

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CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

The Joint Commission

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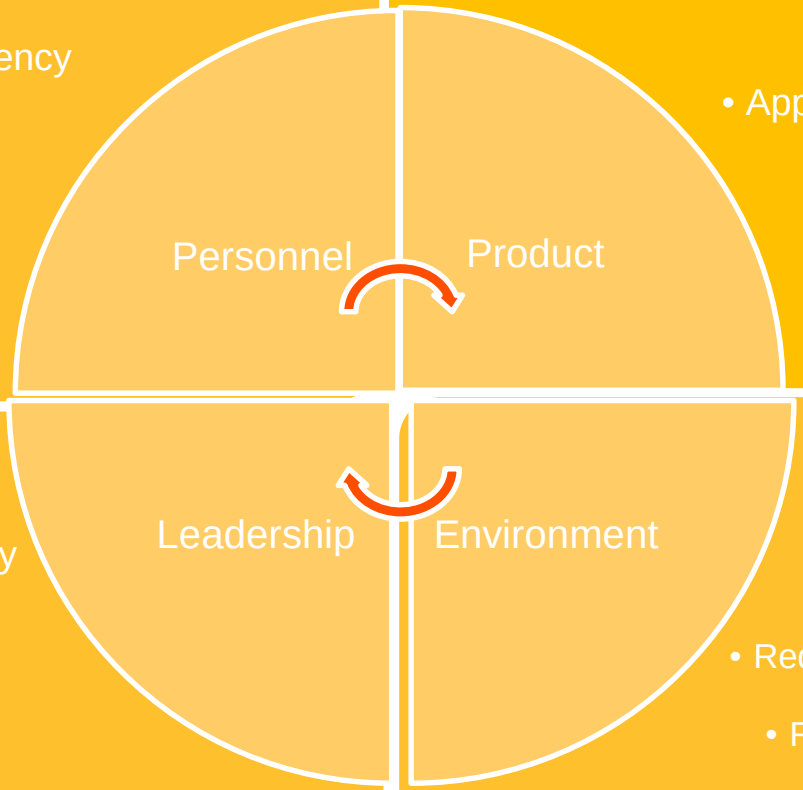
TJC's focus on compounded sterile preparations (CSPs)

- Didactic Competency
- Media Fill Competency
- Finger tip testing competency
- Proper PPE
- Hazardous Med. Competency

- Aseptic technique
- Proper product storage
- Proper product labeling
- Appropriate BUD assignment
- Correct complexity level assessment



- Oversight - Accountability
- Policy Implementation
- Knowledge

- PEC placement
- Testing and Certification
- ISO level designations
- Reduction of highly pathogenic organisms
- Reduction of excessive CFU bacterial growth
- Environmental Controls cleaning

General Chapter <797>: Pharmaceutical Compounding – Sterile Preparations

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Product

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Aseptic technique

- Proper aseptic technique is an essential skill
- Applying the strictest rules and infection prevention principles
  - Conscientious work habits
    - Syringe and needle parts
    - Coring
    - PPE - Gloves
    - Hand washing and hygiene

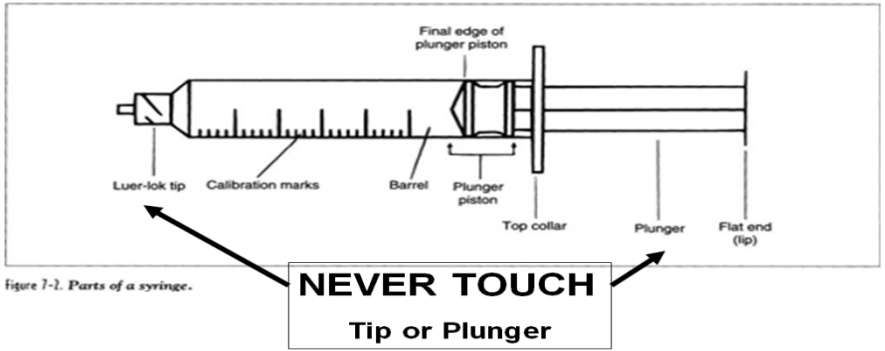
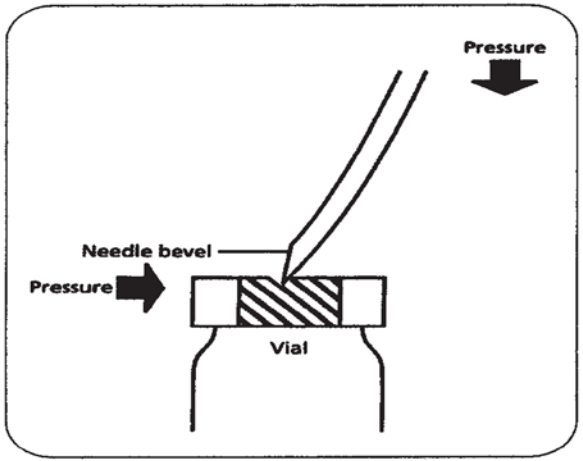


Figure 7-2. *Parts of a syringe.*



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Safe injection practices

- Follow proper infection control practices and maintain aseptic technique during the preparation and administration of injected medications (e.g., perform hand hygiene).
- Never administer medications from the same syringe to more than one patient, even if the needle is changed.
- Never enter a vial with a used syringe or needle.
- Do not use medications packaged as single-dose or single-use for more than one patient.
- Do not use bags of intravenous solution as a common source of supply for more than one patient.
- Limit the use of multi-dose vials and dedicate them to a single patient whenever possible.
- Always use facemasks when injecting material or inserting a catheter into the epidural or subdural space.

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Beyond-use dates (BUDs)

- Multi-dose medication vials with antimicrobial preservatives which have been opened or entered (e.g., needle-punctured), the USP standard is that the BUD is 28 days, unless otherwise specified by the manufacturer.
- Opened or needle-punctured single-dose containers, such as bags, bottles, syringes, and vials of sterile products and CSPs shall be used within 1 hour if opened in worse than ISO Class 5 air quality, and any remaining contents must be discarded.
- If a single-dose vial or container is entered or punctured only in an ISO Class 5 or cleaner air, it may be used up to 6 hours after initial entry or puncture as long as the storage requirements during that 6-hour period are maintained.

Immediate use CSPs

Compounding of CSPs for direct and immediate administration

1. Aseptic processes are followed and written procedures are in place
2. The preparation is performed in accordance with evidence-based information for physical and chemical compatibility of the drugs (e.g., FDA-approved labeling, stability studies).
3. The preparation involves **not more than 3 different sterile products**.
4. Any unused starting component from a single-dose container must be discarded after preparation for the individual patient is complete. Single-dose containers must not be used for more than 1 patient.
5. Administration **begins within 1 hour** following the start of preparation. If administration has not begun within 1 hour following the start of preparation, it must be promptly, appropriately, and safely discarded.
6. Unless administered by the person who prepared it or administration is witnessed by the preparer, the **CSP must be labeled** with the names and amounts of all active ingredients, the name or initials of the person who prepared the preparation, and the exact 1-hour time period within which administration must begin.

Environment

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Compounding suite

Facility design and environmental controls

- **Pressure, temperature, and humidity**
  - Positive vs negative pressure differentials
  - Temperature of 20°or cooler
  - Humidity below 60%
- **Certification of the PEC must include:**
  - Airflow Testing
  - HEPA Filter Integrity Testing
  - Total Particle Counts Testing
  - Smoke Studies
- **Certification of other ISO-classified areas must include:**
  - Airflow Testing - Air changes per hour (ACPH)
    - ISO Class 8 ≥ 20
    - ISO Class 7 ≥ 30
- **Recertification must be done at least every 6 months**

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Environmental monitoring requirements

- **Nonviable airborne particulate sampling**
  - Total particle counts of all ISO-classified areas must be conducted during typical operations every 6 months
- **Viable airborne particulate sampling**
  - Active air sampling of all ISO-classified areas must be conducted during typical operating conditions every 6 months
- **Surface sampling for microbial contamination must be performed in all ISO-classified areas and pass-through chambers connecting to classified areas at least monthly**
  - 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.

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Review, trend, remediation

ISO Class	Air Sampling Action Levels [cfu per cubic meter (1000 liters) of air per plate]	Surface Sampling Action Levels (cfu/device or swab)
5	>1	>3
7	>10	>5
8	>100	>50

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Infection prevention and control (IC) standard IC.02.01.01

- **The hospital implements its infection prevention and control plan.**
- **EP 1: The hospital implements its infection prevention and control activities, including surveillance, to minimize, reduce, or eliminate the risk of infection.**
  - The following components of secondary engineering controls must be checked every six months:
    - Total air particulate count (ISO level)
    - HEPA filter leak test
    - Air exchanges in room
    - Room pressurization
    - Surface microbial sampling (must occur within each ISO classification environment)
    - Air microbial sampling

Cleaning and disinfection

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Minimum frequency

Site	Cleaning	Disinfecting	Applying Sporicidal
Surfaces of sink(s)	Daily	Daily*	Monthly
Pass through(s)	Daily	Daily*	Monthly
Work surface(s) outside the PEC	Daily	Daily*	Monthly
Floor(s)	Daily	Daily*	Monthly
Wall(s), door(s), and door frame(s)	Monthly	Monthly	Monthly
Ceiling(s)	Monthly	Monthly	Monthly
Storage shelving and storage bins	Monthly	Monthly	Monthly

*Many disinfectants registered by the EPA are one-step cleaning and disinfecting agents, which means that the disinfectant has been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step.

Disinfecting agents

Class	Uses	Advantages	Disadvantages
70% Isopropyl Alcohol	Cleaning instruments	Inexpensive	Not as effective
Chlorine Compounds	Bactericidal, fungicidal, sporicidal	Kills hardy viruses	Corrodes metal
Iodophors	Bactericidal, fungicidal, viricidal	Low tissue toxicity; can be used to clean food surfaces	
Phenolic Compounds	Bactericidal, fungicidal, tuberculocidal, viricidal		Unpleasant odor, may have disposal restrictions
Quaternary ammonium compounds (QUATS)	Ordinary housekeeping, bactericidal, fungicidal, viricidal; not as effective as phenols	Less corrosive, odorless, may be used on food surfaces	Does not eliminate spores, TB, bacteria, some viruses layer of soap interferes with activity

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Cleaning supplies

- **All cleaning supplies with the exception of tool handles and holders must be low-linting**
- **Wipers, sponges, and mop heads should be disposable and must be discarded after each cleaning activity**
- **Dispose of cleaning supplies used in the classified areas and SCAs in a manner that minimizes the potential for dispersing contaminants into the air (e.g., with minimal agitation, away from work surfaces).**
- **Reusable cleaning tools must be made of cleanable materials (e.g., no wooden handles)**
  - Must be cleaned before and after each use
- **Dedicated for use in the classified areas or SCA**
  - Must not be removed from these areas except for disposal
  - Must be discarded after an appropriate amount of time
  - Determined based on the condition of the tools

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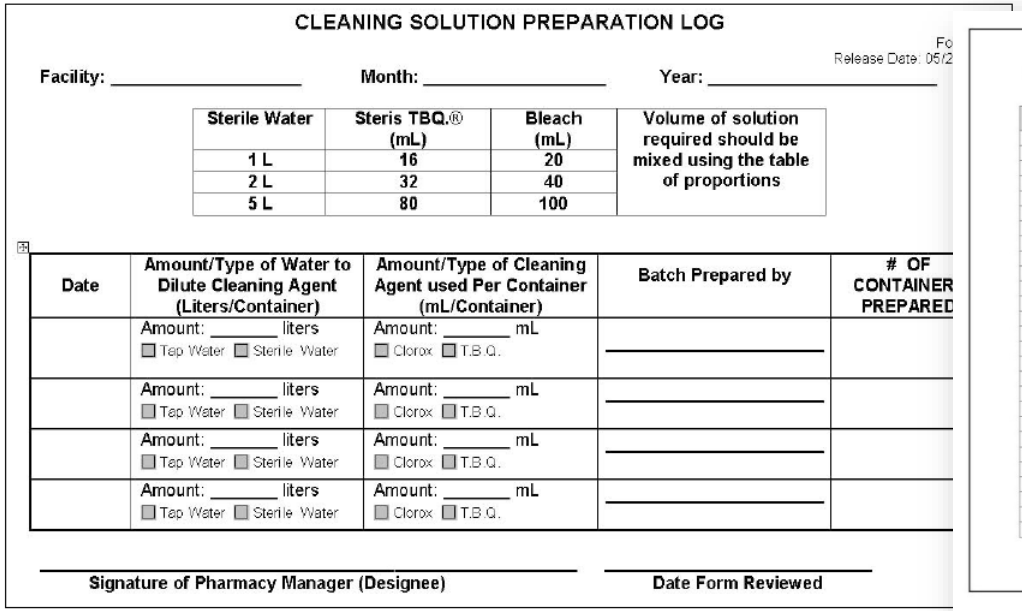
Documentation



CLEANING SOLUTION PREPARATION LOG

Fo
Release Date: 05/2

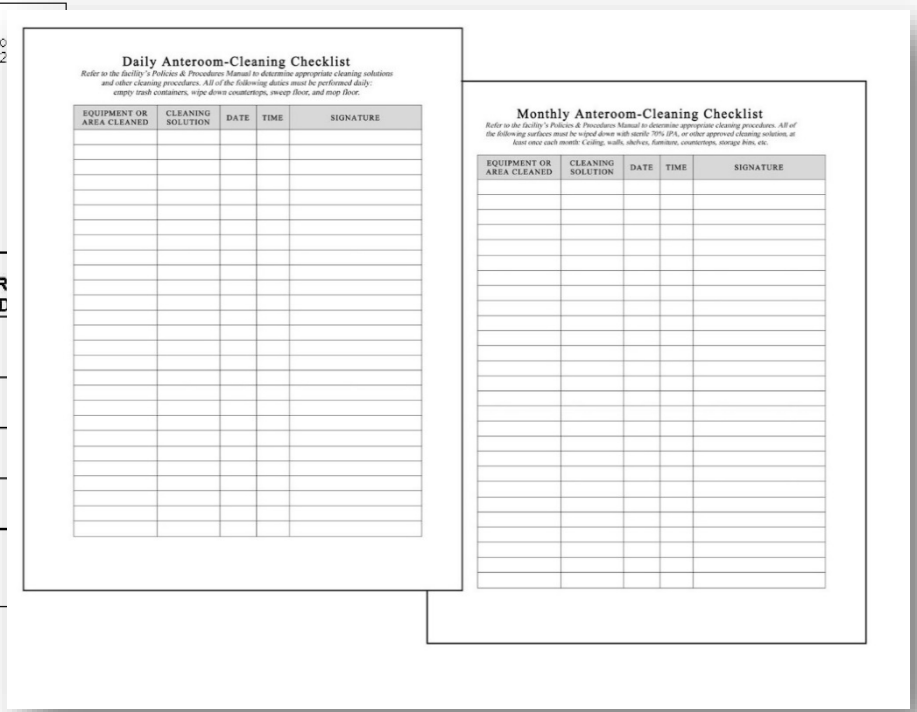
Facility: _____ Month: _____ Year: _____

Sterile Water	Steris TBQ.® (mL)	Bleach (mL)	Volume of solution required should be mixed using the table of proportions
1 L	16	20	
2 L	32	40	
5 L	80	100	

Date	Amount/Type of Water to Dilute Cleaning Agent (Liters/Container)	Amount/Type of Cleaning Agent used Per Container (mL/Container)	Batch Prepared by	# OF CONTAINER PREPARED
	Amount: _____ liters ☐ Tap Water ☐ Sterile Water	Amount: _____ mL ☐ Clorox ☐ T.B.Q.	_____	
	Amount: _____ liters ☐ Tap Water ☐ Sterile Water	Amount: _____ mL ☐ Clorox ☐ T.B.Q.	_____	
	Amount: _____ liters ☐ Tap Water ☐ Sterile Water	Amount: _____ mL ☐ Clorox ☐ T.B.Q.	_____	
	Amount: _____ liters ☐ Tap Water ☐ Sterile Water	Amount: _____ mL ☐ Clorox ☐ T.B.Q.	_____	

_____ _____

Signature of Pharmacy Manager (Designee) Date Form Reviewed



Daily Anteroom-Cleaning Checklist

Refer to the facility's Policies & Procedures Manual to determine appropriate cleaning solutions and other cleaning procedures. All of the following duties must be performed daily: empty trash containers, wipe down countertops, sweep floor, and mop floor.

EQUIPMENT OR AREA CLEANED	CLEANING SOLUTION	DATE	TIME	SIGNATURE

Monthly Anteroom-Cleaning Checklist

Refer to the facility's Policies & Procedures Manual to determine appropriate cleaning procedures. All of the following surfaces must be wiped down with sterile 70% IPA, or other approved cleaning solution, at least once each month: Ceiling, walls, shelves, furniture, countertops, storage bins, etc.

EQUIPMENT OR AREA CLEANED	CLEANING SOLUTION	DATE	TIME	SIGNATURE

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Proposed revisions

Box 7-1. Procedures for Cleaning and Disinfecting the PEC

- Remove visible particles, debris, or residue with an appropriate solution (e.g., *Sterile Water for Injection* or *Sterile Water for Irrigation*) using sterile, low-lint wipers.
- Using a low-lint wiper, apply a cleaning agent, followed by a disinfecting agent, or apply an EPA-registered (or equivalent) one-step disinfectant cleaner to equipment and all interior surfaces of the PEC.
- Ensure the contact time specified by the manufacturer is achieved.
- Using a low-lint wiper, apply sterile 70% IPA to equipment and all interior surfaces in the PEC.
- Allow the surface to dry completely before beginning compounding.

Box 7-2. Procedures for Applying a Sporicidal Agent in the PEC

- Remove visible particles, debris, or residue with an appropriate solution (e.g., *Sterile Water for Injection* or *Sterile Water for Irrigation*) using sterile, low-lint wipers.
- After cleaning and disinfecting (*Box 7-1*), apply the sporicidal agent using a low-lint wiper to all surfaces and the area underneath the work tray. If the sporicidal agent is an EPA-registered (or equivalent) one-step disinfectant sporicidal cleaner, separate cleaning and disinfecting steps are not required.
- Ensure the contact time specified by the manufacturer is achieved.
- Using a low-lint wiper, apply sterile 70% IPA to all interior surfaces, including underneath the work tray.
- Allow the surface to dry completely before beginning compounding.

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Infection prevention and control (IC) standard IC.02.01.01

- **The hospital implements its infection prevention and control plan.**
- **EP 1: The hospital implements its infection prevention and control activities, including surveillance, to minimize, reduce, or eliminate the risk of infection.**
  - Shift duties, daily duties, and monthly cleaning duties are required. Completion must be documented.
  - Regular isopropyl alcohol cannot be used to clean the buffer area/ante area or the ISO Class 5 environment. Sterile alcohol must be used.
  - Detergent must be diluted per instructions for use for quantities of products.

Personnel

Hand hygiene and garbing

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Infection prevention and control (IC) standard IC.01.05.01

- **The hospital has an infection prevention and control plan.**
- **EP 1: When developing infection prevention and control activities, the hospital uses evidence-based national guidelines or, in the absence of such guidelines, expert consensus.**
  - The organization's policy for PPE must include all of the following items:
    - Shoe covers
    - Head and facial hair covers
    - Face mask
    - Non-shedding gown
  - If the organization's policy is correct but staff are not wearing the required PPE, this observation should be scored at Standard IC.02.01.01, EP 2

Infection prevention and control (IC) standard IC.02.01.01

- **The hospital implements its infection prevention and control plan.**
- **EP 1: The hospital implements its infection prevention and control activities, including surveillance, to minimize, reduce, or eliminate the risk of infection.**
  - Handwashing must occur to elbows for a minimum of 30 seconds.
  - Staff must wash hands prior to donning gloves.
  - Gloves should be cleaned with sterile alcohol anytime they are removed from the ISO Class 5 environment or come into contact with a nonsterile surface.
  - A fingernail-cleaning device must be available for use to (and be used by) compounding staff.
  - Compounders are prohibited from wearing external wear (such as jackets, scarves), visible jewelry, and makeup.
  - Staff with upper respiratory infections or skin conditions that cause sloughing of skin (such as sunburn, dandruff, eczema) cannot work in the IV room.

Infection prevention and control (IC) standard IC.02.01.01

- **The hospital implements its infection prevention and control plan.**
- **EP 2: The hospital uses standard precautions, including the use of personal protective equipment, to reduce the risk of infection. (See also EC.02.02.01, EP 4)**
  - Use one alcohol swab per critical site. Note that swabs—not spray bottles—must be used for critical sites
  - Because items must be donned from dirtiest to cleanest, PPE must be donned in order of the dirtiest activity to the cleanest activity: *shoe cover → hair cover → face mask → hand wash → gown → waterless scrub →gloves*
    - Proposed revision:
    - The order of garbing must be determined by the facility and documented in the facility's SOP.
    - If using a RABS, such as a CAI or CACI, disposable gloves (e.g., cotton, nonsterile, sterile) should be worn inside gloves attached to the RABS sleeves. Sterile gloves must be worn over gloves attached to the RABS sleeve

Personnel preparation, hand hygiene, and garbing

- Remove personal outer garments before cleanroom suite entry
  - Facility laundered scrubs considered
  - Footwear considerations
- No earbuds or headphones
- Do not bring electronic devices that are not necessary for compounding or other required tasks into the compounding area
- Nail products (e.g., polish, artificial nails, and extenders) must not be worn
- Wipe eyeglasses, if worn.
- Brushes must not be used for hand hygiene
- Hand dryers must not be used
- A closed system of soap (i.e., nonrefillable container) to minimize the risk of extrinsic contamination must be readily available or in close proximity to the sink

Personnel qualifications

- **Requalification**
  - Persons who fail qualifications/evaluations must undergo immediate requalification through additional training
  - In addition, personnel who fail visual observation of hand hygiene, garbing, and aseptic technique; gloved fingertip/thumb sampling; or media-fill tests must pass three successive reevaluations in the deficient area before they can resume compounding of sterile preparations

Activity	Frequency
Visual Observation	Initially & then annually or every 6 months
Gloved Fingertip Sampling	Initially & then annually or every 6 months
Media-fill Testing	Initially & then annually or every 6 months
Cleaning And Disinfecting	Initially, after a change in procedures, & annually
After A Pause In Compounding	Before resuming duties if pause > 3 month

- **Annual refresher training**

USP Chapter <795> Revisions

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Cleaning and sanitizing

Table 1. Minimum Frequency for Cleaning and Sanitizing Surfaces in Nonsterile Compounding Area(s)

Site	Minimum Frequency
Work surfaces	• At the beginning and end of each shift, after spills, and when surface contamination is known or suspected • Clean and sanitize the work surfaces between compounding CNSPs with different components
Floors	Daily, after spills, and when surface contamination (e.g., splashes) is known or suspected
Walls	Every 3 months, after spills, and when surface contamination (e.g., splashes) is known or suspected
Ceilings	When visibly soiled and when surface contamination is known or suspected
Storage shelving	Every 3 months, after spills, and when surface contamination (e.g., splashes) is known or suspected

Table 2. Minimum Frequency for Cleaning and Sanitizing Equipment in Nonsterile Compounding Area(s)

Site	Minimum Frequency
CVE	• At the beginning and end of each shift, after spills, and when surface contamination is known or suspected • Clean and sanitize the horizontal work surface of the CVE between compounding CNSPs with different components
Other devices and equipment used in compounding operations	• Before first use and thereafter in accordance with the manufacturer's recommendations • If no recommendation is available, after compounding CNSPs with different components

- Purified Water, distilled water, or reverse osmosis water should be used for rinsing equipment and utensils.

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Garbing and hand hygiene

- **Personnel must perform hand hygiene when entering the compounding area**
- **Wash hands and forearms up to the elbows with soap and water for at least 30 seconds.**
  - Jewelry removal
- **Gloves must be worn for all compounding activities.**
- **Gloves should be wiped or replaced before beginning a CNSP with different components**
- **Other garb (e.g., shoe covers, head and facial hair covers, face masks, gowns) should be worn as needed**

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USP Chapter <800>

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USP general chapter <800>: *Hazardous drugs – handling in health care settings*

- The 2nd newest chapter in USP Compounding Compendium
- Describes practice and quality standards for handling hazardous drugs (HDs)
- To promote patient safety, worker safety and environmental protection

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Occupational safety plan

- Entities that handle hazardous drugs (HDs) must incorporate USP Chapter <800> standards into their occupational safety plan.
- The entity's health and safety management system must include:
  - A list of HDs
  - Facility and engineering controls
  - Competent personnel
  - Safe work practices
  - Proper use of appropriate Personal Protective Equipment (PPE)
  - Policies for HD waste segregation and disposal

Proper use of appropriate PPE

Appropriate personal protective equipment (PPE) must be worn when handling HDs including during:

- Receipt
- Storage
- Transport
- Compounding (sterile and non-sterile)
- Administration
- Deactivation and decontamination, cleaning, and disinfecting
- Spill control

Potentially contaminated clothing must not be taken home under any circumstances.

PPE	Specifications
Gloves	• ASTM-tested (Standard D6978) • Two pairs for compounding, administering, managing a spill, and disposal
Gown	• Disposable • Long-sleeved/cuffed • Solid front/ Back closure • Polyethylene-coated polypropylene or other laminate material • ASTM F739-12 tested
Eye and face protection	• Goggles • Face shields in combination with goggles

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Deactivation, decontamination, cleaning & disinfection

Deactivation

- Treatment of an HD contaminant on surfaces with a chemical, heat, ultraviolet light, or another agent to transform the HD into a less hazardous agent
- As listed in the HD labeling or other agents which may incorporate Environmental Protection Agency (EPA)-registered oxidizers (e.g., peroxide formulations, sodium hypochlorite, etc.)

Decontamination

- Inactivation, neutralization, or removal of HD contaminants on surfaces, usually by chemical means
- Materials that have been validated to be effective for HD decontamination, or through other materials proven to be effective through testing, which may include alcohol, water, peroxide, or sodium hypochlorite

Cleaning

- The process of removing soil (e.g., organic and inorganic material) from objects and surfaces, normally accomplished by manually or mechanically using water with detergents or enzymatic products
- Germicidal detergent

Disinfection (For Sterile Manipulations)

- The process of inhibiting or destroying microorganisms
- EPA-registered disinfectant and/or sterile alcohol as appropriate for use

https://www.epa.gov/pesticide-registration/selected-epa-registered-disinfectants

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USP Chapters <795>, <797>, and <800>

http://www.usp.org/compounding/updates-on-standards

Enforcement delay

Appeals to USP Chapters <795>, <797>, and <825>

- Beyond use dating (BUD) provisions in all three Chapters
- Removal of language allowing the use of alternative technologies and techniques in USP Chapter <797>
- Applicability of the standards in veterinary practice

Appeals denied on August 16th

- Per USP's Bylaws, review panel can be requested
- Per USP's Bylaws, official date of a standard under appeal must be postponed while an appeal is pending

Delay of implementation announced on September 23rd

- If the appeal is denied, the USP Chapters may become enforceable on June 1, 2020
- If the appeal is remanded, enforcement may be delayed until at least December 1, 2021 due to the need to update the Chapters and open review of the changes for public comment

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No delay for USP Chapter <800>

USP Chapter <800> - *Hazardous Drugs – Handling in Health Care Settings*

- Will become official on December 1, 2019
- While the other Chapters remain postponed, USP Chapter <800> is “informational and not compendially applicable”
- USP encourages utilization of USP Chapter <800> in the interest of advancing public health
- Regulators may make their own determinations regarding the enforceability of <800>
  - CMS
  - Accreditation Organizations
  - State Boards of Pharmacy

Email drugcompounding@vizientinc.com for more information

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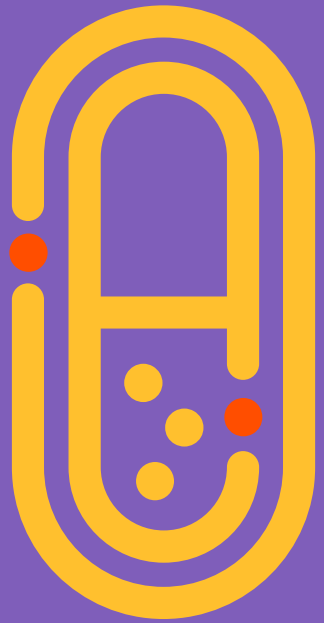
Questions



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