Compounded Sterile Products
2015
Best Practices for Maintaining
the Clean Room Environment

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Disclosures

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Acknowledgements

Dr. Joann Gibbs, PharmD, BCPS
Director of Pharmacy at Byrd Regional Hospital

Learning Goals for the Pharmacist

The pharmacist will be able to:

1. Determine a best practice for cleaning their compounding area based on environmental sampling and cleaning product type.
2. Discuss the difference between Disinfectants and Antiseptics and determine the appropriate use of each.
3. Implement an environmental sampling program that follows best practices.
4. Discuss current concerns of regulatory agencies dealing with compounded sterile products.
Learning Goals for the Pharmacy Technician

The pharmacy technician will be able to:
1. Discuss the difference between Disinfectants and Antiseptics and use the products appropriately when cleaning the compounding area.
2. Discuss Best Practices for cleaning and disinfecting the clean room environment.
3. Recognize personal practices that may allow contamination into the clean room.
4. Discuss current concerns of regulatory agencies dealing with compounded sterile products.

What is your professional status?

1. Pharmacist.
2. Pharmacy Student.
3. Pharmacy Technician.
Who is currently working in a facility who produces CSPs?

1. Yes
2. No

USP Compounding Compendium 2015

USP Compounding Compendium 2015

- Highlights and Features
  - Up-to-date text of the five essential compounding chapters of USP-NF
    - <795> Pharmaceutical Compounding-Nonsterile Products
    - <797> Pharmaceutical Compounding- Sterile Products
    - <1160> Pharmaceutical Calculations in Prescription Compounding
    - <1163> Quality Assurance in Pharmaceutical Compounding
    - <1176> Prescription Balances and Volumetric Apparatus

USP Compounding Compendium 2015

- Highlights and Features
  - Supporting General Chapters
    - <71> Sterility Tests
    - <85> Bacterial Endotoxins Test
    - <1151> Pharmaceutical Dosage Forms
  - More than 170 USP-NF monographs for compounded preparations.
    - Baclofen Oral Suspension
    - Lisinopril Oral Suspension
    - Metoprolol Tartrate Oral Suspension
Quality defined as **fitness for use** as defined by the customer.

**Quality in CSPs**

- The product satisfies the stated or implied need.
- The product or service is free from deficiencies.
USP <797>

- A standardized methodology used to assist pharmacists in producing compounded sterile products that are free of deficiency or defect
- Applies to pre-administration manipulations of compounded sterile preparations including compounding, transportation, and storage
- Applies to all compounding personnel without distinction to site or profession- all patients deserve to be protected from errors and contamination

USP <797>

- Notes that *direct contact* is the principal source of contamination in CSPs
- Applies to CSPs given via application, implantation, inhalation, injection, insertion, instillation, and irrigation
- Provides *minimum standard* for practice and quality for compounded sterile preparations of drugs and nutrients based on current scientific information and best sterile compounding practices.
Quality Monitoring

- The practices in place to ensure the desired outcome and includes:
  - Environmental Controls
    - Temperature
    - Humidity
    - Cleanliness
    - Airflow
  - Personnel Control
    - Training
    - Technique

USP (797)—Quality Monitoring

- Deviations from standard in the items we monitor can result in contamination, loss of potency, or other undesirable outcomes.
ISO Class 5 Sources, Buffer Areas, and Ante Areas

Direct Compounding Area

The DCA is only the portion of the Primary Engineering Control dedicated to the task of Aseptic manipulation.
Environmental Controls

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>U.S. FS 209E</th>
<th>ISO, m³</th>
<th>FS 209E, ft³</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Class 1</td>
<td>35.2</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Class 10</td>
<td>352</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Class 100</td>
<td>3,520</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>Class 1,000</td>
<td>35,200</td>
<td>1,000</td>
</tr>
<tr>
<td>7</td>
<td>Class 10,000</td>
<td>352,000</td>
<td>10,000</td>
</tr>
<tr>
<td>8</td>
<td>Class 100,000</td>
<td>3,520,000</td>
<td>100,000</td>
</tr>
</tbody>
</table>

**ISO Classification of Particulate Matter in Room Air**
(limits are in particles of 0.5 µm and larger per cubic meter [current ISO] and cubic feet [former Federal Standard No. 209E, FS 209E])

- ISO 5- LAFW, BSC, CAI, CACI are “Primary Engineering Controls
- Unidirectional airflow for exposure of critical sites is required
- Must maintain ISO 5 during dynamic (in use) working conditions
Environmental Controls

- ISO 7 buffer and ISO 8 ante area are “Secondary engineering controls”
- They Utilize HEPA filter air sources
- Must maintain ISO 7 or 8 during dynamic (in use) working conditions
- Minimum of 30 air changes per hour of HEPA filtered air (15 ACPH with recirculating ISO 5 device)
- Airflow balance testing required at the installation site

Environmental Controls

- ISO 5 Primary engineering control (LAFW, BSC, CAI, CACI) to be in an ISO 7 environment
- Exception: CAI if its design provides ISO 5 and isolation from the room during dynamic operating conditions as placed at your site (including transferring materials in and out) when tested by CETA Guidelines
- Only personnel and materials essential for compounding and cleaning are permitted
Environmental Controls

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Particle counts</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Pressure differential</td>
<td>Every shift or continuously</td>
</tr>
<tr>
<td>Temperature and Humidity</td>
<td>Continuous</td>
</tr>
<tr>
<td>Viable Air Sampling</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Cleaning ISO class 5 environment</td>
<td>At onset of each shift, before batches, after spills or surface contamination, &amp; q 30 min during compounding activities.</td>
</tr>
<tr>
<td>Clean counters, work surfaces, &amp; Floors</td>
<td>Daily</td>
</tr>
<tr>
<td>Clean walls, ceilings, &amp; storage shelving</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

Performing appropriate daily and monthly cleaning are VITAL to risk reduction.
Cleaning

- A mechanical process
- Uses detergent and water
- Removes dirt, debris, and germs
- Prepares the surface for disinfecting

Sanitizing

- A Chemical process
- Decreases the number of microbes to “safe” levels
Disinfecting

- A Chemical process
- Destroys 100% of harmful bacteria, viruses, and fungi
- Does not always kill spores

Sporicidal Agents

- Kill microorganisms
- Kill spores
Question for the Audience

70% Isopropyl Alcohol is a sterilant.
1. True
2. False

Best Practices

- Determine which germicidal detergent you are going to use.
- Appendix II of USP<797> gives a list of agents
  examples: Quaternary ammonium or phenolic
Determine how you are going to purchase it?

- Ready to use
  - No dilution necessary

- Concentrate
  - Requires Dilution
    - Use sterile water for solutions needed to clean inside the Primary Engineering Controls.
    - Can use tap water for diluting solutions for cleaning walls, floors, and other areas.

Documentation

- MSDS for germicidal detergent and sporicidal agent.
- Have a measuring devise with clear instructions on how the agent should be measured.
  - Discourage the practice of estimating measurements
- Keep a preparation log that includes volume of germicide and type of water to prepare it.
Cleaning Supplies

- Must be dedicated to the area. Store in the area by hanging mop on the wall.
- The same mop head can be used in the buffer and ante area if cleaning takes place in the proper order (cleanest to dirtiest area)
  - Ceilings → walls → floors → disposal

Do I need to rotate cleaning agents?

- Resistance to disinfect agents does not develop like it does to antibiotics because they are more are:
  - Applied in a higher concentration
  - Have more biocidal activity
- Rotation is not required or needed.
- Do use a sporicidal agent at least monthly.
Best Practices

Clean the inside of Primary Engineering controls daily with germicidal detergent, allow surfaces to dry, the follow with sterile 70% IPA.

It is a myth that cleaning with IPA daily is enough.

Best Practices

Dilute germicidal agents (if dilution required) with STERILE WATER to clean the inside of the ISO Class 5 space and primary engineering controls.

Tap water has 500 CFU/mL
- Defined by US EPA drinking water standards

Purified water has 100 CFU/mL

Sterile Water for Injection has <10 CFU/mL
- Defined by USP NF standards
Proper Cleaning Technique

❖ Start in the cleanest area and mop yourself out of the room.

❖ Clean in the following the primary engineering controls in the following order.

❖ Ceiling ➔ back ➔ sides ➔ IV bar and hooks ➔ anything in the PEC ➔ deck

Proper Cleaning Technique

❖ Clean using overlapping strokes—pulling one-way.

❖ Scrubbing back and forth tends to spread contamination.
Environmental Sampling

While the content of Chapter <797> was expanded in the Environmental Control section in 2008, the previous Environmental Monitoring section was deleted.

Two subsections form the Environmental Monitoring section were added to this section. These are:

- Viable and Nonviable Environmental Sampling
- Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices, and Cleaning and Disinfection Procedures

Environmental Sampling

Designed to demonstrate that the primary and secondary engineering controls, disinfecting procedures, and work practices result in a suitable environment for aseptic compounding.

- Utilizes several approaches at assess and evaluate
- Electronic Measurement of the total number of airborne particles
- Certification of the ISO 5, 7, & 8 environments every 6 months
Environmental Sampling

- Count the number of airborne viable microorganisms using volumetric air sampling
- Evaluation semi-annually with certification of the ISO 5, 7, & 8 environments
- Glove fingertip monitoring annually for Low and Medium Risk and semi-annually for High Risk Level

Staff Controls

- Personnel Training & Evaluation
  - Personnel who prepare CSPs shall be trained conscientiously and skillfully by expert personnel, multi-media instructional sources, and professional publications in:
    - Garbing procedures
    - Aseptic work practices
    - Achieving and maintaining ISO Class 5 environmental conditions
    - Cleaning and disinfection procedures
Staff Controls

- Personnel Training & Evaluation
  - Adequate training and evaluation must be completed **BEFORE** preparing CSPs
  - Didactic training and pass a written exam
  - Observational evaluation of aseptic work practices and associated media fill
  - Observational evaluation of proper hand hygiene, garbing, and cleaning and disinfection procedures

- Media-fill testing of aseptic work skills:
  - All compounding personnel initially
  - Personnel who prepare Low- and Medium-Risk Level CSPs - **Annually**
  - Personnel who prepare High-Risk Level CSPs - **Semi-annually**
Staff Controls

Personnel Training & Evaluation
- If facilities cleaning and disinfection is performed by support personnel:
  - They must be initially trained in proper hand hygiene, garbing, and cleaning & disinfection procedures
  - Performance evaluation of support personnel shall be performed regularly by a qualified expert

Hand Hygiene and Garbing competency evaluation performed initially and:
- Low- and Medium Risk Level- Annually
- High-Risk Level- Semi-Annually
- Use of Hand Hygiene and Garbing Assessment Form
Staff Controls

- Personnel Training & Evaluation
  - Direct contact contamination is the most likely source of introducing microorganisms
  - Aseptic work practices observational evaluation using Aseptic Technique Observational Audit Form
  - Glove finger tip sampling after completion of the media-fill preparation

- Surface cleaning and disinfection sampling and assessment and employee competency evaluation
- Agar contact plates or swab collection
- Incubation to determine the amount of growth
- Low- and Medium Risk Level- Annually
- High-Risk Level- Semi-Annually
Microbiological Action Levels

<table>
<thead>
<tr>
<th>Classification</th>
<th>Glove Finger Sample</th>
<th>Surface Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 5</td>
<td>&gt; 3 total</td>
<td>&gt; 3 per plate</td>
</tr>
<tr>
<td>ISO Class 7</td>
<td>N/A</td>
<td>&gt; 5 per plate</td>
</tr>
<tr>
<td>ISO Class 8</td>
<td>N/A</td>
<td>&gt; 100 per plate</td>
</tr>
</tbody>
</table>

Staff Controls

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Didactic Training</td>
<td>Prior to working with CSPs, annually 1 hour of CE, and as indicated when processes or products change.</td>
</tr>
<tr>
<td>Garbing, Hand washing, and gloved fingertip sampling</td>
<td>Prior to beginning work with CSPs then observation and testing annually.</td>
</tr>
<tr>
<td>Media Fill Testing</td>
<td>Prior to beginning work with CSPs and annually thereafter.</td>
</tr>
<tr>
<td>Direct Observation</td>
<td>Prior to beginning work with CSPs and annually thereafter.</td>
</tr>
<tr>
<td>Cleaning and Disinfecting testing</td>
<td>Prior to beginning work with CSPs and annually thereafter.</td>
</tr>
</tbody>
</table>
Introduction of Contaminants

- Environmental factors
  - Does your staff really follow cleaning procedures?
  - Is your cleaning supplies adequate for the job?
  - Are your quality monitors being check as prescribed?
  - Are filters being changed according to schedule?

Personnel Cleansing and Garbing

- Remove outer garments and jewelry including piercings above the neck
- Recently there have been questions about iPod earbuds and Bluetooth headsets. These are not directly mentioned in the chapter, but fall under the same category as earrings etc.
- Garb order from dirtiest to cleanest
- Don she covers, hair covers, beard covers (any facial hair) and face masks (any order acceptable)
- Perform hand/arm hygiene
- Don disposable gowns
Dress Properly

- Shoe covers
- Head and facial hair covers
- Face masks
- Sterile gloves
- Non-shedding gowns
- No makeup
- No externally visible piercings
- No long fingernails

Staff Errors

- Does staff have appropriate attention to detail?
  - Alcohol swabs being used only once.
  - Products wiped with sterile IPA prior to putting inside the compounding chamber?
  - Hand washing complied with?
  - Garbing requirements complied with?
    - Jewelry worn
    - Artificial nails
    - Talking, eating, chewing gum
  - Restocking by bringing cardboard into compounding area, increasing particulates.
  - Pharmacists not gowning prior to going into the compounding area.
We are all HUMAN!

Personal practices will **Drift** over time.

Staff members may pick up bad habits from others.

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Questions to Ask

- Is your staff doing it?
- What are they doing it with?

**let me ask you a question**
To answer these questions you must

Directly Observe

your staff working in the compounding area.

Responsibilities of Compounding Personnel

- Fourteen areas of responsibility are cited
  - Emphasis on training and education
  - Emphasis on compounding accuracy
  - Emphasis on avoiding contamination
  - Emphasis on patient safety
Staff will place a higher importance on what leadership inspects.

Leadership

- Educate compounding staff to
- Understand
- Believe
- Buy in to the importance of standards
CSP Risk Categories

- Immediate Use CSPs
- Low-Level
- Low-Risk Level w/ 12 hour or less Beyond Use Date
  - A subsection of Low-Risk Level
- Medium-Risk Level
- High-Risk Level

Determination of Risk Category

- Responsibility of the compounding personnel…. Think about the risk
- No single rule to determination
- Requires professional judgment
- General descriptive statements to aid in compounding personnel
- Study criteria for each risk level… no prescriptive way.
  - Example: Reconstitution of sterile powder before injection versus TPN. What is the risk level?
Determination of Risk Category

Exception: When non-sterile raw materials are used in compounding this will always create a High-Risk Level category.

Putting sterile products into a non-sterile container also qualifies as high-risk level.

Immediate Use Category

- Exempt from all requirements in <797>
- Only simple aseptic measuring and transfer are needed
- NMT 3 sterile non-hazardous drugs
- NMT 2 entries in one container
- No delays/interruptions
- No contact contamination of ingredients or critical sites

Important: STUDY THE CRITERIA FOR EACH CATEGORY
Immediate Use Category

- Dose must be labeled if not administered by the preparer
- Administration must begin within 1 hour after the *start* of preparation
- Dose must be discarded if administration has not begun within 1 hour after the *start* of preparation
- No storing, No recycling

Immediate Use Category

- Some Examples:
  - At a patient’s bedside
  - In an ambulance
  - In an ER
  - In a war zone
  - In a code situation
Low Risk w/12 Hour Beyond Use Date

- Intended to accommodate facilities/satellite pharmacies compounding only low risk level Compounded Sterile Preparations in environments where the primary engineering controls cannot be located within an ISO Class 7, Clean Room or buffer area. There are specific conditions that have to be met, which include the following:

  “The CSPs must be prepared pursuant to a physician's order for a specific patient, and administration of the CSP must commence within 12 hours of preparation, or as recommended by the manufacturer, whichever is earlier”

Low Risk w/12 Hour Beyond Use Date

- The primary engineering control must be in a segregated compounding area not in a high traffic area.

- All personnel cleansing and garbing requirements apply
  - Personnel preparing the CSP must follow requirements in the Personnel Cleansing and Garbing and Additional Personnel requirement sections among other sections, listed in the chapter.

- No Hazardous Drugs

- Administration must begin within 12 hours or as stated in the package insert, whichever is less
Microbiological Beyond-Use Dating

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Room Temp</th>
<th>Refrigerator</th>
<th>Freezer (-25 C &amp; -10 C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Use</td>
<td>1 hour</td>
<td>1 hour</td>
<td>N/A</td>
</tr>
<tr>
<td>Low</td>
<td>48 Hours</td>
<td>14 days</td>
<td>45 days</td>
</tr>
<tr>
<td>Low w/12-hr BUD</td>
<td>12 hours or less</td>
<td>12 hours or less</td>
<td>N/A</td>
</tr>
<tr>
<td>Medium</td>
<td>30 hours</td>
<td>9 days</td>
<td>45 days</td>
</tr>
<tr>
<td>High</td>
<td>24 hours</td>
<td>3 days</td>
<td>45 days</td>
</tr>
</tbody>
</table>

Single/Multiple Dose Vials

- **Single dose vials**
  - Opened or punctured in ISO 5 environment may be used for up to 6 hours.
  - Opened or punctured in worse than ISO 5 must be used within 1 hour or discarded

- **Single Dose Ampuls**
  - MUST be discarded and not stored for any time period
Single/Multiple Dose Vials

- Multiple dose vials
- Contain antimicrobial preservatives
- Designed for entry on multiple occasions
- Beyond use date- 28 days after initial entry unless specified otherwise by the manufacturer
- Beyond use date of 28 days based on USP <51>
  Antimicrobial Preservative Testing

Proprietary/Vial Systems

- ADD-Vantage; Add-a-Vial, Mini Plus, etc.
- Follow manufacturer’s instructions for handling and storing
- These systems and their instructions have been approved by the FDA
Prior to cleaning an area where Hazardous agents are compounded you must:

1. Deactivate hazardous residue with 2% bleach.
2. Rinse hazardous residue away with sterile water.
3. Use sIPA to deactivate hazardous residue.

Hazardous Drugs

Drugs are classified as hazardous if studies in animals or humans indicate that exposures to them have a potential for causing cancer, developmental or reproductive toxicity, or harm to organs.

This hazardous drug section describes the conditions under which Hazardous Drugs can be prepared to concurrently protect compounding personnel from exposure, and patients from microbial and particulate contamination.
Hazardous Drugs as CSPs

Choosing appropriate Primary Engineering Controls

NIOSH recommends ECs that do not recirculate for use with hazardous drugs that volatilize at room temperature. Consider all repercussions prior to determining the best EC for your application

Letter from Ken Mead NIOSH

Hazardous Drugs

Sections Extensively revised in 2008

USP 800 currently in Commentary Phase

Brought into concert with NIOSH Guidelines

BSC vented to the outside is recommended for optimum conditions

Must be located in separate negative pressure ISO Class 7 with ISO Class 7 ante area

Low-volume HDs doses exempted (a limit of 5 per week was indicated in the proposed revision)
Personnel protection specified

Use of closed-system transfer devices must be within BSC or CACI, only in an ISO class 5 environment

Disposal according to state and federal regulations

Consistent with NIOSH guidelines as of 2008

Hazardous Drugs

USP <800>
Uses NIOSH list of Antineoplastic and other Hazardous drugs in healthcare setting.
Requires the healthcare organization assign a compounding supervisor
Covers storage requirements, compounding facility design, supplemental engineering controls.

http://www.usp.org/usp-nf/notices/compounding-notice
Cleaning Hazardous Drug PEC

❖ You must deactivate the hazardous substances before you begin the cleaning process.

❖ Check the MSDS for each drug compounded.
  ❖ Deactivation occurs for many hazardous agents with 2% sodium hypochlorite solution (bleach.
  ❖ Some agents require Sodium Thiosulfate 0.9%

Question for the Audience

❖ USP <979> requires surface sampling on a
  1. Periodic basis.
  2. Monthly basis.
  3. Quarterly basis.
Surface Sampling

- Surface Sampling may be used to evaluate cleaning/disinfecting procedures and work practices
- Required in 2008 update to USP <797>
  - Periodic with locations defined in SOPs and to include all ISO classified areas.
- Best Practices Suggests
  - Weekly for high risk compounders
  - Monthly for low/medium risk compounders

What happens when you get a bad result?

- Identify the location taken of the sample with growth.
  - What type of growth?
  - Does your cleaning products cover this organism?
- Identify the staff member compounding during/prior to sampling.
  - Question about unusual events
  - Cleaning practices.
- Identify the staff member responsible for cleaning prior to sampling.
  - Question about cleaning practices.
  - Question about products used, dilutions, unusual events.
Action Plan

- Immediately do a thorough cleaning cycle as intense as a “Monthly Clean”.
- Pay special attention to the area involved in the sample.
- Clean all supplies stored in the area.
- Document everything for your compliance log.

Board of Pharmacy

- Adopted USP<979> standards for compounding.
- Inspectors are being sent to Critical Point live training “Boot Camp”.
- They are inspecting documents including staff training, environmental controls, evidence of understanding and compliance.
References


References


References


References

