<797> Pharmaceutical Compounding—Sterile Preparations

Summary

(Added by MS) – This document summarizes the current version of USP <797>, specifically as it pertains to environmental conditions, worker and product safety, and microbial sampling. Underlined portions of text are new language in the document.

The primary differences between the proposed chapter <797> and the current version include:

- A requirement for increasing air quality in the buffer zone / clean zone from ISO 8 to ISO 7.

- Provides more specific guidance and definition relating to environmental conditions in the clean room environment; i.e. 30 ACH, positive pressure differential of 0.02 – 0.05” w.g.; etc.

- Includes an entire section on controlling hazardous drugs. Requirements include - separate negative pressure room with appropriate hazardous drug BSC and continuous monitoring of negative pressure; ISO 7 anteroom; specialized storage requirements; etc.

- More clearly defines environmental sampling recommendation

USP <797> Introduction

The objective of USP <797> is to describe conditions and practices to prevent harm, including death, to patients that could result from microbial contamination (nonsterility), variability in the intended strength of ingredients, chemical and physical contamination, and 5) incorrect types and qualities of ingredients in Compounded Sterile Preparations (CSPs).

Nonsterile CSPs are potentially most hazardous to patients when administered into body cavities, central nervous and vascular systems, eyes, and joints; and when used as baths for live organs and tissues. When CSPs contain excessive bacterial endotoxins, they are potentially most hazardous to patients when administered into the central nervous system.

The standards in USP <797> are intended to apply to all persons who prepare CSPs and all places where CSPs are prepared, e.g., hospitals and other healthcare institutions, patient treatment clinics, pharmacies, and physicians’ practice facilities.

Potential Sources of Contamination

Potential sources of contamination include, but are not limited to:
1. Skins cells, sweat, or other solid or liquid matter from compounding personnel and objects

2. Nonsterile components incorporated before sterilization

3. Poor environmental conditions in the restricted compounding environment

4. Prolonged presterilization procedures with aqueous preparations

5. Nonsterile dosage forms used to compound CSPs.

**Definitions**

**Anteroom** — An anteroom is an ISO Class 8 or better area where personnel perform hand hygiene and garbing procedures, staging of components, order entry, CSP labeling, and other high-particulate generating activities. It is also a transition area that 1) provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas and 2) that reduces the need for the heating, ventilating and air conditioning (HVAC) control system to respond to large disturbances. ¹

**Aseptic Processing (see Microbiological Evaluation of Cleanrooms <1116>)** — Aseptic processing is a mode of processing pharmaceutical and medical products that involves the separate sterilization of the product and of the package (containers-closures or packaging material for medical devices) and the transfer of the product into the container and its closure under microbiologic critically controlled conditions.

**Beyond-Use Date (see General Notices and Requirements and Pharmaceutical Compounding—Nonsterile Preparations <795>)** — For the purpose of this chapter, the beyond-use date is the date or time after which the CSPs shall not be stored or transported. The beyond-use date is determined from the date or time the preparation is compounded.

**Biological Safety Cabinet, Class II (BSC)** — The BSC is a ventilated cabinet for personnel, product, and environmental protection having an open front with inward airflow for personnel protection, downward HEPA filtered laminar airflow for product protection, and HEPA filtered exhausted air for environmental protection.

**Buffer Area, Buffer or Core Room, Buffer or Cleanroom Areas, Buffer Room Area, Buffer or Clean Area** — This is an ISO Class 7 area where the primary engineering control area (see below) is physically located. Activities that occur in this area include the preparation and staging of components and supplies used when compounding CSPs.

¹ American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc. (ASHRAE), Laboratory Design Guide.
Cleanroom (see Microbiological Evaluation of Cleanrooms <1116> and also Buffer Area) — A cleanroom is a room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface, and personnel gear are not exceeded for a specified cleanliness class.

Critical Area — A critical area is an ISO Class 5 environment.

Critical Sites — Critical sites include sterile ingredients of CSPs and locations on devices and components used to prepare, package, and transfer CSPs that provide opportunity for exposure to contamination.

Disinfectant — An agent that frees from infection, usually a chemical agent but sometimes a physical one, and that destroys disease-causing pathogens or other harmful microorganisms but may not kill bacterial spores. It refers to substances applied to inanimate objects.

Negative Pressure Room — A room that is at a lower pressure compared to adjacent spaces and, therefore, the net flow of air is into the room.

Primary Engineering Control — It is a device or room that provides an ISO Class 5 environment for the exposure of critical sites when compounding CSPs. Such devices include, but may not be limited to, laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs), and compounding aseptic isolators (CAIs).

Preparation — For the purposes of this chapter, a preparation, or a CSP, is a sterile drug or nutrient compounded in a licensed pharmacy or other healthcare-related facility pursuant to the order of a licensed prescriber; the article may or may not contain sterile products.

Product — For the purposes of this chapter, a product is a commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the U.S. Food and Drug Administration (FDA). Products are accompanied by full prescribing information, which is commonly known as the FDA-approved manufacturer’s labeling or product package insert.

Positive Pressure Room — A positive pressure room is one that is at a higher pressure compared to adjacent spaces and, therefore, the net airflow is out of the room.²

Sterilization by Filtration — Passage of a fluid or solution through a sterilizing grade filter to produce a sterile effluent.

**Terminal Sterilization** — Terminal sterilization is the application of a lethal process, e.g., steam under pressure or autoclaving, to sealed containers for the purpose of achieving a predetermined sterility assurance level (SAL) of usually less than 10⁻⁶, i.e., or a probability of less than one in one million of a nonsterile unit.³

**Unidirectional Flow (see U.S. Food and Drug Administration, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice)**—An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

**CSP Microbial Contamination Risk Levels**

The appropriate risk level—low, medium, or high—is assigned according to the corresponding probability of contaminating a CSP with (1) microbial contamination (microbial organisms, spores, and endotoxins) and (2) chemical and physical contamination (foreign chemicals and physical matter).

**Risk Criteria (General Criteria)**

**Low-Risk Conditions** — The CSPs are compounded with aseptic manipulations entirely within ISO Class 5 or better air quality using only sterile ingredients, products, components, and devices.

**Medium-Risk Conditions** — Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple occasions.

The compounding process includes complex aseptic manipulations other than the single-volume transfer. Additionally, the compounding process requires unusually long duration, such as that required to complete dissolution or homogeneous mixing.

**High-Risk Conditions** — Nonsterile ingredients, including manufactured products for routes of administration, are incorporated or a nonsterile device is employed before terminal sterilization. Additionally, high risk conditions would include CSPs with sterile ingredients that lack effective antimicrobial preservatives, and if sterile surfaces of devices and containers in the preparation, transfer, sterilization, and packaging of CSPs are exposed to air quality worse than ISO Class 5 for longer than 1 hour.

High risk conditions would also occur, if before sterilization, nonsterile procedures such as weighing and mixing are conducted in air quality worse than ISO Class 7; compounding

personnel are improperly garbed and gloved; or water-containing preparations are stored for more than 6 hours.

**Storage of Low, Medium, and High Risk Preparations**

Additionally, for Low, Medium, and High risk preparations, in the absence of passing a sterility test (see Chapter <71>), the storage periods cannot exceed the following time periods:

<table>
<thead>
<tr>
<th>Risk Condition</th>
<th>Storage Time at Room Temp</th>
<th>Refrigeration Temp</th>
<th>Freezer Temp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>≤ 48 hours</td>
<td>≤ 14 days</td>
<td>≤ 45 days</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>

**Immediate Use CSPs**

For the purpose of emergency or immediate patient care, CSPs are exempted from the requirements described in this chapter when all of the following criteria are met:

1. Only simple aseptic measuring and transfer manipulations are performed with not more than three (3) sterile nonhazardous commercial drug and diagnostic radiopharmaceutical drug products, including an infusion or diluent solution.

2. Unless required for the preparation, the preparation procedure occurs continuously without delays or interruptions and does not exceed 1 hour.

3. At no point during preparation and prior to administration are critical surfaces and ingredients of the CSP directly exposed to contact contamination such as human touch, cosmetic flakes or particulates, blood, human body substances (excretions and secretions e.g., nasal and oral), and nonsterile inanimate sources.

4. Administration begins not later than one (1) hour following the start of preparing the CSP.

5. When the CSP is not administered by the person who prepared it, or its administration is not witnessed by the person who prepared it, the CSP shall bear a label listing patient identification information such as name and identification number(s), the names and amounts of all ingredients, the name or initials of the person who prepared the CSP, and the exact 1-hour beyond-use time and date.
6. If administration has not begun within one (1) hour following the start of preparing the CSP, the CSP is promptly and safely discarded. Immediate Use CSPs shall not be stored for later use.

7. Because of known safety risks of hazardous drugs to healthcare workers and other nonpatients who may be exposed to them, hazardous drugs such as cancer chemotherapy drugs and all those on the National Institute for Occupational Safety and Health list (NIOSH) shall not be prepared as Immediate Use CSPs 4.

**Preparation of Hazardous Drugs**

Hazardous drugs shall be prepared in an ISO Class 5 environment. All hazardous drugs shall be prepared in a Class II or III biological safety cabinet (BSC) or CAI. 5

The ISO Class 5 BSC or CAI for hazardous drugs shall be inside an ISO Class 7 room that is separated by a physical wall from other preparation areas. This separate room should be negatively pressurized relative to ISO 7 or better anteroom.

Note that an anteroom leading to a positive pressure room may be ISO Class 8 but an anteroom leading to a negative pressure room shall meet at least ISO Class 7 criteria so that air drawn into the negative pressure environment is of the same ISO Class 7 quality.

A pressure indicator shall be installed that can be readily monitored for correct room pressurization. The BSC and CAI for hazardous drugs optimally shall be 100% vented to the outside air through HEPA filtration (see the Ventilated cabinet section at [http://www.cdc.gov/niosh/docs/2004-165/](http://www.cdc.gov/niosh/docs/2004-165/)).

Hazardous drugs shall be stored separately from other inventory, preferably within a containment area such as a negative pressure room. The storage area must have at least 12 air exchanges per hour (ACPH) to dilute and remove airborne contaminants.

Hazardous drugs shall be handled with caution using appropriate chemotherapy gloves during distribution, receiving, stocking, inventorying, preparing for administration, and disposal. 6 Appropriate personnel protective equipment (PPE) shall be worn when compounding. Appropriate PPE may include gowns, face masks, eye protection, hair covers, shoe covers or dedicated shoes, and double gloving.

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In facilities that prepare a very low volume of hazardous drugs (e.g., less than 5 preparations/week), the use of two tiers of containment, e.g., CSTD within a BSC or CAI that are located in a non-negative pressure room is acceptable.

Training and Quality Assurance

All personnel who perform routine custodial waste removal and cleaning activities in storage and preparation areas shall be trained in appropriate procedures to protect themselves and prevent contamination. The training shall include at least the following:

1. Safe aseptic manipulation practices;
2. Negative pressure techniques when utilizing BSC or CAI;
3. Correct use of CSTD devices;
4. Containment, clean-up, and disposal procedures for breakages and spills; and
5. Treatment of personnel contact and inhalation exposure.

Facility Design and Environmental Controls

Compounding facilities are physically designed and environmentally controlled to minimize airborne contamination contacting critical sites. Primary engineering controls typically include, but are not limited to, LAFWs, BSCs, and CAIs, which provide an ISO Class 5 environment for the exposure of critical sites.

Buffer zones or cleanrooms are designed to maintain at least ISO Class 7 conditions for 0.5-µm particles under dynamic conditions and ISO Class 8 conditions for 0.5-µm and larger particles under dynamic conditions for the anterooms and ante-areas.

The CSP work environment is designed to have the cleanest work surfaces (primary engineering controls) located in a buffer area. The buffer area should be segregated from surrounding, unclassified spaces to reduce the risk of contaminants being blown, dragged, or otherwise introduced into the filtered unidirectional airflow environment and this segregation should be continuously monitored.

For rooms providing a physical separation, through the use of walls, doors and pass-throughs, a minimum differential positive pressure of 0.02 to 0.05 inches water column is required.

For cleanrooms or buffer zones not physically separated from the anteroom, the principle of displacement airflow should be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 feet
per minute (fpm) or more from the buffer room across the line of demarcation into the ante-area.

**Air Exchange** - An ISO Class 7 cleanroom supplied with HEPA filtered air shall receive an ACPH of not less than 30. If the room has an ISO Class 5 recirculating device, a minimum of 15 ACPH through the room supply HEPA filters is adequate providing the combined ACPH is not less than 30.

HEPA filtered supply air is introduced at the ceiling with low-wall mounted returns, creating a general top-down dilution of room air with HEPA filtered make-up air. Ceiling mounted returns are not recommended. All HEPA filters should be efficiency tested using the most penetrating particle size and should be leak tested at the factory and then leak tested again in situ after installation.7

**Furniture, Equipment, Supply Considerations**

Furniture, equipment, and supplies should be nonpermeable, nonshedding, cleanable, and resistant to disinfectants so they can be readily cleaned. Also, the surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the buffer area should be smooth, impervious, free from cracks and crevices, and nonshedding.

If ceilings consist of inlaid tiles, the tiles should be impregnated with a polymer to render them impervious to particulate and hydrophobic. Walls may be constructed of flexible material (e.g., heavy gauge polymer), panels locked together and sealed, or of epoxy-coated gypsum board.

Preferably, floors are overlaid with wide sheet vinyl flooring with heat-welded seams and coving to the sidewall. The exterior lens surface of ceiling lighting fixtures should be smooth, mounted flush, and sealed.

The buffer area shall not have sinks or floor drains. Work surfaces should be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are easily cleaned. Carts should be of stainless steel wire, nonporous plastic, or sheet metal construction with good quality, cleanable casters to promote mobility. Storage shelving, counters, and cabinets should be smooth, impervious, free from cracks and crevices, nonshedding, and cleanable.

Placement of devices (e.g., computers and printers) and objects (e.g., carts and cabinets) that are not essential to compounding in buffer zones and cleanrooms is dictated by their

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7 By definition (IEST RP CC 001.4), HEPA filters are a minimum of 99.97% efficient when tested using 0.3-µm thermally generated particles and a photometer or rated at their most penetrating particle size using a particle counter.
effect on the required environmental quality of air atmospheres and surfaces, which must be verified by monitoring.

Cleaning And Disinfecting The Sterile Compounding Areas

The cleaning and disinfecting practices and frequencies in this section apply to direct and contiguous compounding areas (DCCAs), which include ISO Class 5 compounding areas for exposure of critical sites as well as buffer rooms, anterooms, and ante-areas (see Table 2).

These procedures shall be conducted at the beginning of each work shift and when there are spills or environmental quality breaches. Before compounding is performed, all items are removed from the DCCA and all surfaces are cleaned of loose material and residue from spills, followed by an application of a residue-free disinfecting agent.

Table 1: Minimum Frequency of Cleaning and Disinfecting Sterile Compounding Areas

<table>
<thead>
<tr>
<th>Site</th>
<th>Minimum Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 5 Primary Engineering Control (e.g., LAFW, BSC, CAI)</td>
<td>At the beginning of each shift</td>
</tr>
<tr>
<td>Counters and easily cleanable work surfaces</td>
<td>Daily</td>
</tr>
<tr>
<td>Floors</td>
<td>Daily</td>
</tr>
<tr>
<td>Walls</td>
<td>Monthly</td>
</tr>
<tr>
<td>Ceilings</td>
<td>Monthly</td>
</tr>
<tr>
<td>Storage shelving</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

All cleaning tools, such as wipers, sponges, and mops, are nonshedding and dedicated to use in the buffer or clean area. Floor mops may be used in both the buffer or clean area and anteroom area, but only in that order. Most wipers are discarded after one use.

Supplies and equipment removed from shipping cartons are wiped with a disinfecting agent, such as IPA. Wiping with small IPA swabs that are commercially available in individual foil-sealed packages is preferred for disinfecting stoppers on bags and vials before they are pierced with sterile needles and for necks of ampuls before they are broken.
Personnel Cleansing and Garbing

**Persons with Active illness** - When persons have rashes, sunburn, weeping sores, conjunctivitis, active respiratory infection shall be excluded from working in ISO Class 5 and ISO Class 7 compounding areas until their condition is remedied.

Before entering the clean area, compounding personnel must remove personal outer garments (e.g., bandannas, coats, hats, jackets, scarves, sweaters, vests); all cosmetics; and all hand, wrist, and other body jewelry that can interfere with the effectiveness of PPE (e.g., fit of gloves and cuffs of sleeves, or visible body piercing above the neck).

The wearing of artificial nails or extenders is prohibited while working in the sterile compounding environment. Natural nails must also be kept neat and trimmed.

Personnel must don the following PPE and perform hand hygiene in an order that proceeds from the dirtiest to cleanest activities. Garbing activities considered the dirtiest include donning of dedicated shoes or shoe covers, head and facial hair covers (e.g., beard covers in addition to face masks), and face mask/eye shield. Eye shields are optional unless working with irritants like germicidal disinfecting agents.

After donning dedicated shoes or shoe covers, head and facial hair covers, and face masks, perform a hand hygiene procedure by removing debris from underneath fingernails using a nail cleaner under running warm water followed by vigorous hand washing. Wash hands and arms to the elbows for at least 30 seconds with either a plain (nonantimicrobial) soap, or antimicrobial soap, and water while in the anteroom/ante-area. The use of antimicrobial scrub brushes is not recommended as they can cause skin irritation and skin damage. Hands and forearms will be completely dried using either a lint-free disposable towels or an electronic hand dryer. After completion of hand washing, don nonshedding disposable gowns with sleeves that fit snugly around the wrists.

Once inside the clean area, prior to donning sterile, powder-free gloves, antiseptic hand cleansing must be performed using an alcohol-based surgical hand scrub with persistent activity12 (e.g., alcohol-based preparations containing either 0.5% or 1.0% chlorhexidine gluconate) following manufacturers’ recommendations. Allow hands to dry thoroughly before donning sterile gloves.

Sterile gloves shall be the last item donned before compounding begins. Routine application of 70% IPA should occur throughout the compounding day and whenever nonsterile surfaces (e.g. vials, counter tops, chairs, and carts) are touched.

When compounding personnel must temporarily exit the ISO Class 7 environment during a work shift, the exterior gown, if not visibly soiled, may be removed and retained in the ISO Class 8 anteroom/ante-area, to be re-donned during that same work shift only. However, shoe covers, hair and facial hair covers, face mask/eye shield, and gloves must be replaced.
with new ones before re-entering the ISO Class 7 clean environment along with performing proper hand hygiene.

During high-risk compounding activities that precede terminal sterilization, such as weighing and mixing, compounding personnel shall be garbed and gloved the same as when performing compounding in an ISO Class 5 environment. Properly garbed and gloved compounding personnel who are exposed to air quality that is either known or suspected to be worse than ISO Class 8 must re-garb PPE along with washing their hands properly, performing antiseptic hand cleansing with a waterless alcohol-based surgical scrub, and donning sterile gloves upon re-entering the ISO Class 7 clean area. When CAIs2 are the source of the ISO Class 5 environment, the garbing and gloving requirements for compounding personnel should be as described above, unless the isolator manufacturer can provide written documentation based on validated environmental testing that any component(s) of PPE or personnel cleansing are not required.

Environmental Monitoring

Environmental Sampling Plan - The plan should include location, sample method, volume of air sampled, frequency of sampling, time of day as related to activity in the compounding area, and action levels.

Air Sample Method – Impaction is the preferred method of culturable air sampling (such as with the PBI SAS). The 2006 draft clearly precludes the use of the settling plates. Collect as much air as possible without drying the media (ideally 1000 cubic-feet).

Surface Sample Method - Surface sampling is recommended but not required. Surface sampling should only be performed when no compounding activity is occurring on or near the surface to be tested. Surface sampling can be accomplished using contact plates and/or swabs. Sample areas should be defined on the sample plan or form. The sample size usually ranges from 24 to 30 cm².

Selected sampling sites should include multiple locations within each ISO Class 5 environment and in the ISO Class 7 and 8 areas. Also, sampling shall be performed at locations that are prone to contamination during compounding activities and during other activities like staging, labeling, gowning, and cleaning.

Reporting - Monitoring and trending of the data generated by the sampling program can detect changes in the microbial bioburden.

Sample Media - A general microbiological medium such as trypticase soy broth or agar (TSA) should be used to support the growth of bacteria. Malt extract agar (MEA) or some other media that supports the growth of fungi should also be used.
**Gloved Finger Sampling** – Contact agar plates are used to sample gloved fingertips after compounding CSPs immediately after exiting the ISO Class 5 environment. Glove fingertip sampling must occur outside of the ISO Class 5 environment. Do not disinfect gloves with IPA immediately prior to sampling. Personnel should “touch” the agar with the fingertips of both hands in a manner to create a slight impression in the agar.

Table 2: Environmental Monitoring Sampling Schedule (previous monitoring recommended every 6 months)

<table>
<thead>
<tr>
<th>Environmental Monitoring Event</th>
<th>Low-Risk Level CSPs</th>
<th>Medium-Risk Level CSPs</th>
<th>High-Risk Level CSPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required air sampling</td>
<td>Once a month</td>
<td>Once a month</td>
<td>Weekly</td>
</tr>
<tr>
<td>Required glove fingertip sampling¹</td>
<td>Weekly</td>
<td>Weekly</td>
<td>Daily</td>
</tr>
<tr>
<td>Recommended ISO surface sampling</td>
<td>Weekly</td>
<td>Weekly</td>
<td>Daily</td>
</tr>
</tbody>
</table>

¹ At least one individual or 10% of the compounding personnel, whichever is larger, to be sampled.

**Sampling Plate Incubation Period** - Trypticase soy broth or agar (TSA) should be incubated at between 33 °C and 37 °C for 2 days. Malt extract agar (MEA) or other suitable fungal media should be incubated at between 26 °C and 30 °C for 7 days.

**Reporting of Data** - Environmental monitoring data shall be collected and trended as a means of evaluating the overall control of the compounding environment. The number of discrete colonies of microorganisms are counted and reported as cfu and documented on an environmental monitoring form. Counts from air monitoring need to be transformed into cfu/cubic meter of air and evaluated for adverse trends.

Action levels shall be determined based on baseline data gathered. Table 4 should only be used as a guideline or as interim levels until baseline data has been gathered. When action levels are exceeded, an investigation into the source of the contamination shall be conducted.
Table 3: Action Levels (Counts) of Microbial Colony-Forming Units (cfu) per Cubic Meter of Air or Contact Plates

<table>
<thead>
<tr>
<th>ISO Class of Sampled Location</th>
<th>Sampled Sources and Their Action Levels (Counts) of Microbial cfu</th>
<th>Active Airborne (required)</th>
<th>Glove Fingertip (required)</th>
<th>Inanimate Surfaces (recommended)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>&gt; 3</td>
<td>&gt; 3</td>
<td>&gt; 3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>&gt; 20</td>
<td>not required</td>
<td>&gt; 20</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>&gt; 100</td>
<td>not required</td>
<td>&gt; 100</td>
<td></td>
</tr>
</tbody>
</table>

The cfu action levels are adapted from those in Microbiological Evaluation of Cleanrooms and Other Controlled Environments <1116>.

At least one cubic meter, m, or 1000 liters, L, of air must be sampled.

Particle Counts - Certification that each ISO classified area, e.g., ISO Class 5, ISO Class 7, and ISO Class 8 is within established guidelines shall be performed no less than every 6 months and whenever the LAFW, BSC, or CAI is relocated or the physical structure of the buffer room or anteroom/area has been altered.

Pressure Guage or velocity meter shall be installed to monitor the pressure differential or airflow between the cleanroom and anteroom and the anteroom and the general pharmacy area. The results should be reviewed and documented on a daily basis in a log. The pressure between the ISO Class 7 and general pharmacy area should not be less than 5 Pa (0.02-inch water column, w.c.). Facilities used to compound low-risk CSPs utilizing directional airflow should maintain a minimum velocity of 0.2 m/s (40 fpm).

Written Training and Performance Evaluation Program

Equipment

It is necessary that equipment, apparatus, and devices used to compound a CSP be consistently capable of operating properly and within acceptable tolerance limits.

Compounding facilities must have at least the following written procedures for verifying the correct identity and quality of CSPs before they are dispensed and administered:

1. That labels of CSPs bear correct names and amounts or concentrations of ingredients; the total volume; the beyond-use date; the appropriate route(s) of administration; the storage conditions; and other information for safe use.
2. That there are correct identities, purities, and amounts of ingredients by comparing the original written order to the written compounding record for the CSP.

3. That correct fill volumes in CSPs and correct quantities of filled units of the CSPs were obtained. When the strength of finished CSPs cannot be confirmed to be accurate, based on the above three inspections, the CSPs must be assayed by methods that are specific for the active ingredients.

Storage and Beyond-Use Dating

Determining Beyond-Use Dates

Monitoring Controlled Storage Areas

Controlled temperature areas in compounding facilities include the following:

<table>
<thead>
<tr>
<th>Area</th>
<th>Range (ºC)</th>
<th>Mean Kinetic Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room</td>
<td>15 - 30</td>
<td>25</td>
</tr>
<tr>
<td>Refrigerator</td>
<td>2 – 8</td>
<td>--</td>
</tr>
<tr>
<td>Freezer</td>
<td>≤ 10</td>
<td>--</td>
</tr>
</tbody>
</table>

Additional Temperature Storage Comments

A controlled temperature area should be monitored at least once daily and the results documented on a temperature log.

Pharmacy personnel should note the storage temperature when placing the product into or removing the product from the storage unit in order to monitor any temperature aberrations.

If the pharmacy uses a continuous temperature recording device, pharmacy personnel should verify at least once daily that the recording device itself is functioning properly.

Additional Sections in the document include:

- Verification of Compounding Accuracy and Sterility
- Personnel Training
- Packaging, Handling, and Transport
- Use and Storage
- Readying for Administration
- Redispensed CSPs
- Education and Training
- Packing and Transporting CSPs
- Patient Monitoring and Adverse Events Reporting
- Verification of Automated Compounding Devices
- Accuracy
- Precision
- Inspection of Solution Dosage Forms and Review of Compounding Procedures
- Physical Inspection
- Compounding Accuracy Checks
- Sterility Testing
- Bacterial Endotoxin (Pyrogen) Testing (High Risk Compounding Only)
- Identity and Strength Verification of Ingredients

Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACD</td>
<td>Automated compounding devices</td>
</tr>
<tr>
<td>ACPH</td>
<td>air changes per hour</td>
</tr>
<tr>
<td>ALARA</td>
<td>as low as reasonably achievable</td>
</tr>
<tr>
<td>ASHRAE</td>
<td>American Society of Heating, Refrigerating and Air-Conditioning Engineers</td>
</tr>
<tr>
<td>BSC</td>
<td>Biological safety cabinet</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>CAI</td>
<td>compounding aseptic isolator</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CETA</td>
<td>Controlled Environment Testing Association</td>
</tr>
<tr>
<td>cfu</td>
<td>colony-forming units</td>
</tr>
<tr>
<td>CSPs</td>
<td>compounded sterile preparations</td>
</tr>
<tr>
<td>CSTD</td>
<td>closed-system vial-transfer devices</td>
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<td>DCCA</td>
<td>direct and contiguous compounding areas</td>
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<td>EU</td>
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<td>FDA</td>
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<td>FPM</td>
<td>feet per minute</td>
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<td>HEPA</td>
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<td>HICPAC</td>
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<td>HPLC</td>
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<td>NBS</td>
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