USP <797>

Cleanroom Design and Environmental Monitoring

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Objectives

The objectives of this presentation:

• To summarize basic cleanroom concepts and how they relate to USP <797>
• To gain better understanding of the testing and certification requirements of USP <797>
• To discuss possible corrective actions for non-compliant areas
What is USP <797>?

- An enforceable chapter of the U.S. Pharmacopeia – National Formulary
- Defines “best practices” and standards for sterile compounding nationally
USP <797> Purpose

The intentions behind the requirements of USP <797>: 

- Patient Safety – health violations can cause serious injury to patients 
- Drug Sterility – Assure that medication does not become contaminated during preparation
Why is USP <797> in the news lately?

• In September 2012, regulators investigated the NECC in Framingham, MA, in connection with a multi-state meningitis outbreak

• 20 States received tainted steroid injections that were compounded at NECC

• A total of 751 cases of fungal infections linked to the drug, the majority being meningitis and/or spinal infections

• 64 associated deaths

Note: Data collected from CDC website as of 23 OCT 2013 (last update)
Who does it apply to?

USP <797> applies to:
• All persons who perform sterile compounding
• All places where sterile compounding is performed
Enforcement

Who would enforce USP <797>?

- FDA
- State Pharmacy Boards (for approved states)
- The Joint Commission (formerly JCAHO)
- Centers for Medicare and Medicaid Services (CMS)
- State Departments of Public Health
Why Comply?

• Regulation – FDA, Regulations in some states
• Accreditation – Joint Commission
• Best Practices – Proof against liability
• Marketing – Competitive Advantage
• Out of State Compounds
USP <797> Terms

- CSPs – Compounded Sterile Preparations
- PEC – Primary Engineering Control
- Buffer Room – Area where PEC is located
- Ante Room – Transitional area adjacent to Buffer
- Hazardous CSPs – Exposure to these drugs can cause cancer, developmental or reproductive toxicity, or organ damage
- Unidirectional Airflow – Airflow that moves in a single direction, with no dead spots or refluxing, sweeping away particles from clean areas
# ISO Classifications

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Per ISO 14644-1 – Cleanrooms and Associated Controlled Environments
General Concepts

All of the specifications and tests in this presentation serve at least one of the following:

- Product Sterility
- Hazard Containment
PEC Requirements

A PEC is:

• “A device or room that provides an ISO class 5 environment for the exposure of critical sites when compounding CSPs.” Airflow must be HEPA-filtered and unidirectional

Typical examples:

• Laminar Airflow Workbenches – LAFWs (also called Unidirectional Flow Devices or cleanbenches)
• Biological Safety Cabinets – BSC
• Compounding Aseptic Isolators – CAIs (positively pressured)
• Compounding Aseptic Containment Isolators – CACIs (negatively pressured)
Laminar Airflow Workbench

- HEPA filtered air flows over the workspace
- Airflow is unidirectional across workspace
- Recirculated air contributes to room air changes
- Only suitable for non-hazardous compounding
Biological Safety Cabinets

- Offers both contamination control and worker protection
- Airflow from room does not enter work area
- Airflow from work area does not vent into room
- HEPA filtered unidirectional supply air
- HEPA filtered exhaust air
Compounding Isolators

- Isolated from surrounding environment (i.e. no mixture with ambient room air)
- HEPA filtered, unidirectional airflow over work surface
- CACIs provide worker protection (allow for hazardous compounds)
- CAIs do not (non-hazardous compounds only)
Non-Hazardous Compounding Environmental Requirements

Standard Requirements:
• ISO class 7 Buffer Room
• ISO class 8 Ante Room
• At least 0.02 "wc positive pressure to the outside
• At least 30 air changes/hour of HEPA-filtered air
Hazardous Compounding
Environmental Requirements

Same requirements as non-hazardous, with the following exceptions:

• The PEC must provide worker protection (i.e. biological safety cabinet or negative-pressure isolator).
• The PEC should be 100% vented to the outside through HEPA filtration.
• The room must have at least 0.01”wc negative pressure to the outside.
  – Note: Hazardous and non-hazardous compounding are not compliant in same area.
• Requires an ISO class 7 buffer AND ante area.
Hazardous Compounding
Environmental Requirements

Hazardous Compounding Pharmacy

Ante Room
ISO class 7

Buffer Room
ISO class 7

PEC
Cytotoxic Residue Sampling

NIOSH warns that hazardous drugs can cause acute and chronic human health effects, including cancer. USP <797> recommends sampling for hazardous drug residue every six months.

- Common drugs for sampling: Cyclophosphamide, Ifosfamide, Methotrexate, Fluorouracil
- While the literature has not selected any acceptance limits for hazardous drug residue, Cyclophosphamide levels of 1.0 ng/cm$^2$ have been found to result in human uptake.
Cytotoxic Residue Sampling

USP <797> recommends sampling:

- PEC workspaces
- Countertops where finished CSPs are placed
- Areas adjacent to PEC, including floors
- Patient administration areas
Upcoming USP <800>

USP <800> Hazardous Drugs – Handling in Healthcare Settings
The proposed new chapter of USP-NF is still in draft form. Current proposals include:
• Addressing both sterile and non-sterile compounding
• Unambiguously stating the need for a dedicated room
• More information on types of BSCs
• Offering guidance on a variety of room layouts
• Specific instructions for gowning
• Guidelines for cleaning/decontamination
• Hazardous residue sampling will be a requirement
12-hour Beyond Use Date

USP <797> allows an exception to the rule of placing the PEC in an ISO class 7 Buffer area if:

• CSPs are to be administered within 12 hours of compounding, or per physician’s orders, whichever sooner
• CSPs meet the definition of “low-risk” per USP <797>
• Compounding must be non-hazardous
• The PEC is not located near potential contamination (e.g. doors, windows, flow of traffic, food prep)
12-hour Beyond Use Date

Pros:
• No requirements for buffer/ante area ISO classification, HEPA filtration or room pressurization
• May be suitable for older facilities not designed to meet the standard USP <797> specs

Cons:
• Expensive
• Scheduling challenges
Isolator Considerations

USP <797> allows an exception to the rule of placing the PEC in an ISO class 7 Buffer area if:

- The PEC is an isolator (CAI or CACI) that provides isolation from the room and meets ISO class 5 during normal operations, compounding and material transfer.
- Internal procedures are developed to ensure adequate recovery time between material transfer and compounding operations to return to ISO class 5 air quality.
Isolator Considerations

Pros:
• No requirements for buffer/ante area ISO classification, HEPA filtration or (possibly) room pressurization
• Useable in hazardous compounding areas (though the negative pressure requirement still applies)

Cons:
• Expensive
• Reduced production/Worker comfort
Environmental Monitoring

Types of Environmental Monitoring (EM) tests for evaluating compliance with USP <797>:

• Certification of PEC
• Non-viable Airborne Particle Counting
• Certification of HEPA Filters
• Room Air Exchange Rates
• Room Differential Pressures
• Viable Airborne and Viable Surface Sampling
• Cytotoxic Residue Sampling
Certification of PEC

Primary Engineering Controls are required to be certified to the appropriate industry standards at least semi-annually. This includes, but may not be limited to:

• Verification of airflow velocity and direction in accordance with manufacturer’s specifications and/or intended use
• Tested to ISO class 5 within the workspace
• Leak testing of HEPA filters
• Must be performed by a qualified individual
Particle Counting

Particle Counting:
• Is intended to detect non-viable (i.e. non-living) particulate matter that could contaminate CSPs
• Is also a good way to measure the effectiveness of environmental controls
• Is performed semi-annually, or whenever the room/equipment are modified, moved or repaired
Particle Counting

- Tested according to ISO 14644 – Cleanrooms and Associated Controlled Environments
- USP <797> determines which ISO classifications apply to what areas
## ISO Classifications

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Per ISO 14644-1 – Cleanrooms and Associated Controlled Environments
What can be done to prevent high particle counts?

- HEPA-filtration and unidirectional airflow
- Good room isolation and pressurization
- Good gowning practices
- Proper storage of materials
- Restrict traffic through critical areas
- Clean the area regularly to remove dust/debris

For areas that cannot meet ISO class 7:

- Use of an Isolator or low-risk non-hazardous compounding with a 12-hour beyond-use-date
HEPA Filters

- HEPA (High-Efficiency Particulate Air) Filters are 99.97% efficient at removing particles at 0.3µm.
- HEPA-filtered air must be introduced at the ceiling for ISO class 7 areas.
- HEPA filters should be leak tested in accordance with IEST-RP-CC001
ISO class 7 Buffer and Ante Areas require sufficient HEPA-filtered airflow to provide $\geq 30$ air changes per hour (ACPH) for the room.

Room HEPAs only need to provide $\geq 15$ AC/H if recirculated air (e.g. HEPA-filtered air from the PEC) can make up the difference.
Room Pressurization

- Non-hazardous Buffer and Ante Areas require between 0.02 – 0.05 “wc of positive air pressure to the exterior. (i.e. the net flow is out of the room)
- For hazardous Buffer Areas, at least 0.01 “wc negative air pressure to the exterior is required.
Viable Sampling

Viable Sampling is intended to detect living contaminants for both hazardous and non-hazardous areas such as:

- Bacteria and other microorganisms
- Fungal growth

Appropriate areas for Viable Sampling:
- Within the PEC’s direct compounding area
- Devices (e.g. computers & printers), objects (e.g. carts) and work surfaces (e.g. countertops & shelves) within the Buffer and Ante Rooms
Viable Sampling

Media Selection:

- Sampling requires a general-purpose medium that supports the growth of bacteria
  - E.g. Soybean-Casein Digest Medium (aka Tryptic Soy Agar)
- High-risk compounding areas require the use of fungal-selective media
  - E.g. Malt Extract Agar, Rose Bengal Agar, Sabouraud Dextrose Agar
Airborne Viable Sampling:

- Impaction method is preferred, using quantitative air samplers
- Passive settling plates *not* recommended
- 500L samples in rooms, 1000L samples in PECs
- Samples collected on agar plates
Surface Viable Sampling:

- Samples collected on agar contact plates
- “Touch and roll” method
- Clean surface immediately after sampling to remove residue
Viable Sampling

Media Incubation:
- TSA media incubated at 30-35 degrees Celsius for 48 to 72 hours
- Fungal-selective media incubated at 26-30 degrees Celsius for 5-7 days
- Count total number of colony forming units (CFUs)
- USP <797> requires that all air samples demonstrating growth be identified to at least the genus level
# Viable Sampling

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<th>Surface Criteria CFUs/plate</th>
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<td>8 or worse</td>
<td>Ante</td>
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What causes viable growth?

There are several typical sources for viable contamination:

• Human-borne, including organisms carried by skin, breath, mucous, clothing, etc. This is the most common source of contamination for the typical cleanroom.

• Airborne: carried in from the outside or elsewhere in the facility

• Water-borne: can be caused by splashes near sink
What can be done to prevent viable growth?

Utilize good cleanroom techniques:

• Isolate and pressurize the room to keep out external sources of contamination
• Use HEPA filtration to dilute contaminants in air
• Regularly clean critical surfaces with approved disinfectants (e.g. 70% IPA)
• Use good gowning practices to prevent human-borne contamination
What are the corrective actions for viable growth?

TSS recommends a battery of corrective actions when viable samples come back high:

• Verify that no unusual circumstances would have affected the environmental controls
• Review gowning requirements with personnel
• Clean affected area with disinfectant and retest
• Consider identification of organisms (USP <797> requires identification to at least genus level)
  – Note: may be done concurrently with retesting
Questions?

Thank you for attending!

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