Design and Construction of an Investigational Drug Service Compounding Pharmacy

Agenda

• Overview of USP Compounding Chapter Revisions – Elaine Strauss
• Project Overview – Charles Gaziano
• Architectural Considerations – Sandy Cohn
• Lessons Learned – Everet Simmons
Learning Objectives

• Discuss the recent revisions to chapter USP <797> and publication of <800> and their impact on pharmacy cleanroom engineering systems.
• Describe additional facility and engineering considerations for compliance with clinical trial sponsor requirements.
• Analyze the phases of a pharmacy cleanroom construction project and proactive measures for success.
• Review the outcomes and lessons learned from a pharmacy cleanroom construction project.

Abbreviations

• USP: United States Pharmacopeia
• RH: relative humidity
• PEC: primary engineering control (i.e. biological safety cabinets)
• CAI: compounding aseptic isolator
• CACI: compounding aseptic containment isolator (i.e. glove boxes)
• CSP: compounded sterile product
• ISO: International Standards Organization
• SCA: segregated compounding area
• ACPH: air changes per hour
• HEPA: high efficiency particulate air
• EM: environmental monitoring
• C-SEC: containment secondary engineering control (i.e. mix room)
• C-PEC: containment primary engineering control
• HD: hazardous drug
Abbreviations

- **BSC**: biological safety cabinet
- **BUD**: beyond use date
- **IND**: Investigational new drug
- **IDS**: Investigational drug service
- **PPE**: personnel protective equipment
- **DP**: differential pressures
- **HVAC**: heating ventilation and air conditioning
- **UPS**: uninterruptible power supply
- **MEP**: mechanical, engineering, plumbing
- **DX**: direct expansion air conditioning unit
- **FRP**: fiberglass reinforced panels
- **EVS**: environmental services
- **GC**: general contractor

Moffitt Cancer Center

- Mission: to contribute to the prevention and cure of cancer
- Only NCI Designated Comprehensive Cancer Center in Florida
- No. 8 US News & World Report Best Cancer Hospital
- Ranked in top 10 since 1999
- Over 2 Million square feet
- 205 Patient Beds
- 20 OR's
- 4 Compounding Pharmacies
- $2.1 Billion Economic Impact for Florida
Introduction to USP Compounding
Chapter Revisions

Elaine Strauss

Compounding Standards Updates

• Official date for compliance with new and revised USP Compounding standards is December 1, 2019
• USP<795> Pharmaceutical Compounding Nonsterile Preparations
• USP<797> Pharmaceutical Compounding Sterile Preparations
• USP<825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging
• USP<800> Hazardous Drugs – Handling in Healthcare settings
USP Chapters <797> and <800>

- **USP 797**: prevent harm, including death, to patients that could result from compounded sterile preparations from microbial contamination, excessive bacterial endotoxins, variability in intended strength of the product, unintended chemical and physical contaminants, or ingredients of inappropriate quality.

- **USP 800**: practice and quality standards for handling hazardous drugs in healthcare settings; promote patient safety, worker safety, and environmental protection; minimize the exposure to hazardous drugs in healthcare settings.

Updates to USP <797>
USP <797> Updates

• Facilities and Engineering Updates
  − Temperature < 20°C/68°F
  − Humidity < 60%; Risk of mold at RH > 60%.
  − Placement of primary engineering controls (PECs)
    − Compounding Aseptic Isolator (CAI) and Compounding Aseptic Containment Isolator (CACI) must be placed in a cleanroom suite with an ISO 7 buffer room and ISO 8 Ante room to prepare Category 2 CSPs.
    − Isolators must be placed in ISO 8 air to compound Category 2 CSPs

USP <797> Updates

• Facility Design Updates
  − “Should” minimize dust collecting overhangs, “must” be easily cleaned
  − Pass-through doors “should” be interlocking
  − No tacky mats in classified areas
  − Access doors “should” be hands-free
  − Smoke studies “must” demonstrate proper placement of PEC and compounder ability to maintain first air in the direct compounding area
USP <797> Updates

• **Facility Design: Segregated Compounding Area (SCA)**
  - Unclassified area with no ante-room or buffer room
  - “Must” be away from unsealed windows, doors to outside, traffic flow
  - “Must” be located away from environmental control challenges
  - “Must” have a visible perimeter to establish SCA boundaries
  - Only for Category 1 CSPs

USP <797> Updates

• **Ante-room and placement of sink**
  - 2008: Ante-area “may contain a sink”
  - 2019: sink is “either inside or outside the ante-room”
    - Outside ante-room: must be in a clean space to minimize the risk of bringing in contaminants into the ante room
    - Inside ante-room: sink may be on clean or dirty side of ante-room
    - SCA: at least 1 meter away from PEC
  - No water sources inside buffer room
USP <797> Updates

- Air Exchange Requirements

<table>
<thead>
<tr>
<th>COMPOUNDING AREA</th>
<th>ACPH REQUIREMENT</th>
</tr>
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<tbody>
<tr>
<td>Unclassified SCA</td>
<td>No requirement</td>
</tr>
<tr>
<td>ISO Class 7</td>
<td>≥ 30 ACPH</td>
</tr>
<tr>
<td>ISO Class 8</td>
<td>≥ 20 ACPH</td>
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</tbody>
</table>

- Total ACPH must maintain ISO Class 7 or 8 during dynamic operating conditions
- At least 15 of total ACPH from HEPA ceiling-mounted filters
- Returns low on walls unless verified by a smoke study

USP <797> Updates

- Environmental monitoring (EM)

<table>
<thead>
<tr>
<th></th>
<th>2008 USP &lt;797&gt;</th>
<th>2019 Revised USP &lt;797&gt;</th>
</tr>
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<tbody>
<tr>
<td>Viable Air</td>
<td>6 Months</td>
<td>6 Months</td>
</tr>
<tr>
<td>Surface Sampling</td>
<td>Periodic</td>
<td>Monthly</td>
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- Continuous pressure, temperature, humidity monitoring with daily documentation
Summary of USP <800> Facilities and Engineering Updates

- Sterile HD Compounding Suite (C-SEC) Ante room
  - ISO 7 air quality
  - ≥ 30 ACPH of HEPA-filtered air
  - May be a non-hazardous buffer room
  - Positive pressure 0.02” w.c. to adjacent unclassified areas.
  - Transition personnel and materials from uncontrolled areas into cleaner controlled space
USP <800> Designated Areas

• Sterile HD Compounding Suite (C-SEC) Buffer Room
  - ISO 7 air quality or cleaner (ISO 8 if using isolator)
  - Contains C-PEC
  - > 30 ACPH
  - Pressure gradient of -0.01 to -0.03" w.c. to adjacent areas
  - Protects both product and compounder (C-PEC)
  - Exhaust air vents to the outside
  - Enter C-SEC through an anteroom
  - If the C-SEC is entered though non-HD buffer room: Line of demarcation in C-SEC for garbing / de-garbing

USP <800> Designated Areas

• Containment Segregated Compounding Area (C-SCA)
  - Meets cleanroom structural requirements but not air quality requirements
    • Temperature 20º C/68º F, humidity <60%
    • Contains a C-PEC
    • Category 1 (Immediate Use) CSPs only
    • At least 12 ACPH of HEPA filtered air
    • Externally vented through HEPA filtration
    • Negative pressure between 0.01 and 0.03” w.c.
    • Sink placed ≥ 1 meter from C-PEC
**USP <800> Updates**

**Ante-room Design For HD Cleanroom**
- Wet vs Dry Ante Room. De-couples viable generating activity from offset balancing air supplying negative pressure areas.
- Order of garbing and hand hygiene depends on placement of sink

**Wet Ante-room**
- Staff don shoe covers, hair cover, face mask
- Staff perform hand hygiene
- Staff don gown/gloves

**Dry Ante Room**
- Storage of sterile garb and clean supplies
- HD gown/gloves

**Staff enter buffer room**

**USP <800> Designated Areas**

**Receipt and unpacking of HD**
- Neutral or negative relative to surrounding areas

**Storage**
- Antineoplastic HD’s: Externally vented, negative pressure room with > 12 ACPH
- Non Antineoplastic (reproductive risk only) or FINAL dosage forms of antineoplastic HD's can be stored with other inventory if permitted by entity policy
- Refrigerated antineoplastic HD’s stored in a dedicated refrigerator in a negative pressure area with > 12 ACPH
- If refrigerator placed in the negative pressure buffer room, exhaust adjacent to the refrigerator compressor and behind refrigerator should be considered
USP <800> Engineering Controls

• C-PEC
  - All C-PEC – externally vented
  - Must operate continuously for sterile compounding
  - For most known HD’s: Class II BSC Type A2 offer simple and reliable integration with ventilation and pressurization requirements of C-SEC
  - Class II B2 BSC reserved for volatile
  - C-PEC must be placed in a Class 7 buffer room with Class 7 ante room or C-SCA (unclassified)
    • If in C-SCA, BUD must be limited to category 1

USP <800> Engineering Controls

• HD Non-sterile Compounding
  • C-PEC only used for nonsterile compounding does not require unidirectional airflow because the critical environment does not need to be ISO classified
  • C-PEC must be externally vented
  • C-SEC must be negative pressure
  • > 12 ACPH
  • Surfaces must be smooth, impervious, free from cracks, non shedding
Pharmacy Project Overview

Charles Gaziano

Project Overview

• Investigational Drug Services (IDS) compounding pharmacy
• Compliance with upcoming USP <797> and <800> requirements, as well as specific storage and use requirements described in IND documentation associated with experimental drug products
• Combination of hazardous, non-hazardous, and experimental therapies
• Accommodate anticipated future growth in compounding volumes and IND product storage volumes
User Requirement Specifications

• Regulatory platforms
• Research grant requirements
• Clinical trial study sponsor requirements
• Drug products used

Operational Considerations

• Present/future daily compounding volumes (HD, Non-HD, sterile and non-sterile)
• Operating hours/number of shifts
• Pharmacist/technician head count in compounding space per shift
• Method of pharmacist verification used
• PEC devices: types, quantities, sizes
Operational Considerations (cont.)

- **Incoming materials flow:** sources, packaging, delivery point, unboxing, inspection, transport, storage, transport into compounding areas
- Storage/compounding space adjacencies
- **Finished compound material flow:** out of compounding area, transport to patient care areas
- **Personal protective equipment:** risk analysis, equipment, donning and doffing procedures
- Personnel movement within the clean spaces

Operational Considerations (cont.)

- **Cleaning protocols:** equipment requirements and chemical selections
- Environmental requirements:
  - Temperature
  - Relative humidity
  - Room differential pressures (DP)
  - DP map of adjacent spaces
  - Air changes per hour
- Phasing plan and provisions for compounding during construction period
Operational Considerations (cont.)

- HVAC/cooling system redundancy requirements (patient care, and revenue protection)
- Emergency/UPS power requirements
- Environmental monitoring, local and remote alarm strategy
- Alarm response protocols

Equipment Selections

- Cooling sources
- Heating sources
- Emergency power sources
- Existing building automation system
- Campus standards (type, manufacturers)
Design Packages

- Schematic design:
  - Preliminary floor plan
  - Adjacencies
  - Workflows
  - Pressure relationships
  - MEP narrative
  - User group review and approval

Design Packages (cont.)

- Design development:
  - Typical package
  - Demolition and phasing
  - Major equipment selected (e.g., air handler)
  - Budget estimate from contractors/reconciliation
  - 100% construction documents
  - Owner and subject matter expert review and sign off
  - Finalize pricing
Construction Considerations

- Careful review of submittals
  - Miscommunication
  - Unapproved substitutions

- Installation quality control
  - Actual materials delivered
  - Product installation requirements
  - Work area restrictions

- Clean construction protocols once installation completed

Post-Construction Testing and Certification Timeline
Architectural Considerations

Sandy Cohn
MCC Ground Floor

MCC Third Floor

Current IDS Compounding Pharmacy Location.

New IDS Compounding Pharmacy Location
Optimal Concept Pharmacy Diagram

- HD Holdg. 12 ACPH Neg. Pressure
- HD Buffer Rm. ISO 7 30 ACPH Neg. Pressure -.01 to .03 w.c.
- Ante Rm. ISO 7 30 ACPH Poss. Pressure .02 w.c. min.
- Non-HD Buffer Rm. ISO 7 30 ACPH Poss. Pressure .02 w.c. min.
- Garbing ISO 7 30 ACPH Poss. Pressure .02 w.c. min.
- ISO 8 20 ACPH Poss. Pressure

Direction of airflow
Pass Thru w/ Interlocking doors

IDS Pharmacy Layout

- Pickup Vest.
- Oral Drug
- Receiving
- HD Holding
- HD Buffer
- Non-HD Buffer
- Garbing
- Ante Room
- Workroom
IDS Pharmacy Axon

Garbing & Ante Room Plan
Garbing & Ante Room Axon

HD Buffer Room Plan
HD Buffer Room
Axon

HD Holding Room Plan
HD Holding Room Axon

Minimum Environmental Standard

• Must maintain above required minimum environmental standards
  • Remember, first day of operation is the best day

• ISO Class 7 rooms require minimum 30 ACPH
  • Design for 20% more or 36 ACHP

• USP <797> and <800> require ≤ 68 degrees at ≤ 60% RH
  • 65 degrees at 50% RH is recommended
A/E Elements

• Mechanical Elements –
  • Dedicated air handling unit serving the classified spaces
  • Existing chilled water systems are not always enough. Use supplemental DX system to lower off coil temperature
  • Static vs. dynamic HVAC system
  • HEPA filters at the ceiling of all classified spaces
  • Consider fan filter units in ceiling of these spaces
  • Non-HD IV buffer room can use laminar flow hoods for part of the required ACPH
  • All ISO classified spaces require low side wall returns or exhaust. This includes HD buffer, Non-HD buffer, ante room and garbing/ante room

A/E Elements (cont.)

• Architectural Elements –
  • Limit amount of fixed/built-In equipment
  • Eliminate or limit ledges
  • No porous materials in classified spaces
  • Epoxy vs. FRP – all finishes cleanable
  • Ceilings either drywall or sealed clean room ceiling tiles
    • Eliminate or limit serviceable items above ceilings
  • Consider paperless drywall
A/E Elements (cont.)

- Electrical Elements –
  - Emergency Power – minimum refrigerators, freezers, biological safety cabinets and exhaust fans
  - Lighting fixtures, cleanable and sealed

Outcomes and Lessons Learned

Everet S. Simmons
Desired Outcome

- First Time Quality
- First Time Compliance
- Prepared to Operate
- Maintaining compliance
- Interconnection to EVS, Facilities, and Pharmacy Operations

Lessons Heard

- GC Quality Non Compliance
- Support Services Preparedness
- Design with Environmental Monitoring in Mind
Lessons Learned

- Where is the Subject Matter Expert
- Construction Deficiencies
- Current Project Status

Top Ten Lessons Learned

1. Eliminate single ante room at HD buffer entrance; major contributor for failed EM
2. Minimize fixed elements (i.e. shelving, counters vs rolling tables and carts)
3. Fixed elements (i.e. hoods) have adequate clearance around for cleaning
4. Chemical compatibility of building materials with cleaning agents
5. Eliminate non-cleanable items (i.e. keyboards, monitors, label makers) in compounding rooms
Top Ten Lessons Learned

6. Avoid locating negative pressure HD buffer room adjacent to “dirty” rooms (i.e. break rooms, restrooms, food prep)
7. Interlock air handler units/exhaust fans/fan filter units together
8. Confirm ceiling heights appropriate for all equipment; clearance to connect hoods to exhaust systems
9. Confirm equipment travel paths through ante rooms into buffer rooms
10. Eliminate pass-through refrigerators into clean spaces (likely source of contaminants)

**BONUS LESSON:** Avoid pneumatic tube stations into clean rooms

Questions?