Cleanroom Workshop: Negotiating Regulatory Management with Real-World Experience

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Disclosure

- All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
Objectives

- Define key elements and processes to achieve sterile compounding compliance using citations.
- Assess what compliance readiness means for compounding practices.
- Evaluate findings from other arenas (e.g., GMP) and discern what can be highlighted in your work areas.
- Given a scenario, discuss and incorporate best practices into the cleanroom workflow.
Self-Assessment

Which of the following is an indicator of a facility that is under a state of control?

a) Performance Qualification
b) Installation Qualification
c) Operational Qualification
d) Environmental Monitoring
e) a, b, and c
Self-Assessment

- The most common citation in FDA audits (FY16 and FY17) were procedures?  
  – True or False
Self-Assessment

- What guidance document can be used as a reference to generate an Environmental Monitoring plan?
  a) USP 795
  b) USP 797
  c) USP 800
  d) ISO 14644, Table 2
  e) EPA P-Listed Products
Self Assessment

- Regulations are developed to ensure patient safety.
  – True or False
The Challenge of Modern Pharmacy

- Regulatory agencies are discussing the intersection between manufacturing/large batch compounding (503b) and cleanrooms (503a)
- Insanitary conditions are being enforced by the US Food and Drug Administration to health-system (503a) pharmacies
- Lack of didactic courses on cleanroom management

The challenge is to learn from the principles of large batch production and apply it to a prescription of one
Are you a 503a or a 503b

503a
- Compound according to prescriptions...
- ...for a specific patient...
- ...under USP guidelines...
- ...and does not produce a large batch.

503b
- Compound in large batches...
- ...with or without a prescriptions...
- ...that can be sold to end user...
- ...are subject to cGMP requirements...
- ...and must be registered with FDA.
...FDA investigators will make a preliminary assessment of whether such entities are compounding their human drugs in accordance with certain conditions of section 503a...

...the investigator will not include observations that represent deviations solely from FDA’s current good manufacturing practice (CGMP) requirements unless it appears, based on the investigator’s preliminary assessment, that the firm compounds drugs that do not qualify for the exemptions under section 503a.

...503a does not provide an exemption from the prohibition on insanitary conditions...[the FDA]...will continue to include observations...that appear to constitute insanitary conditions...

Insanitary Conditions

- Construction within the cleanroom
- Exposed skin in the ISO5
- Leaning into the ISO 5 hood
- Wood or other porous surfaces that can collect debris
- Drop tiles in the ceiling
- Pets in the pharmacy
- Employees leaving in gowning and then returning
- Not using a sporicidal agent regularly
- Mold, insects, foreign matter in the facility
- Water is your worst enemy
The Three P’s of Cleanrooms

- Plant
- Process
- People
- Patient
FY 2016 Inspection Observation Summaries

- The ten most common citations of 483s that translate to pharmacy are:
  1. Procedures not in writing, fully followed (147 occurrences)
  2. Absence of written procedures (85 occurrences)
  3. Environmental Monitoring System (78 occurrences)
  4. Calibration/Inspection/Checking not done (76 occurrences)
  5. Procedures for sterile drug products (70 occurrences)
  6. Cleaning/Sanitizing/Maintenance (65 occurrences)
  7. SOPs not followed/documenting (49 occurrences)
  8. Equipment design, size, and location (48 occurrences)
  9. Training—operations, GMPs, written procedures (44 occurrences)
 10. Clothing appropriate for duties performed (39 occurrences)

https://www.fda.gov/ICECI/EnforcementActions/ucm531890.htm#Drugs
FY 2017 Inspectional Observation Summaries

- Top five common citations of 483s that translate to pharmacy:
  1. Procedures not in writing, fully followed (185 occurrences)
  2. Investigations of discrepancies, failures (100 occurrences)
  3. Absence of written procedures (91 occurrences)
  4. Written procedures not established/followed (68 occurrences)
  5. Training – operations, GMPs, written procedures (51 occurrences)

https://www.fda.gov/ICECI/Inspections/ucm589892.htm#Drugs
Plant: Facility Design and Consideration

- Cleanroom foundations have five basic documents
- User Requirements Specifications (URS) and Basis of Design (BOD)
- Validation of process is broken down into four phases:
  - Design Qualification (DQ)
  - Installation Qualification (IQ)
  - Operational Qualification (OQ)
  - Performance Qualification (PQ)
- Should have the documents ready for an auditor
- Should reside with the QA Manager and updated regularly with new information as data is generated
Plant: Facility Design and Consideration

- Cleanroom must not be designed like office spaces and need to be designed for singular purposes
- Designed with containment in mind (USP <797>/<800>) with increasing levels of sterility increasing as you approach ISO 5 space
- Built with a redundancy of systems and fail safes
- Cleanable and can withstand sporicidal agents
- Spread out of HEPA filters and returns around the room
- Separate by function and allow for cleaning/maintenance during normal operations
Plant: Environmental Monitoring

- Air visualization studies (AVS) of the cleanroom and hoods
  - Goal of AVS in the hood vs the room
  - AVS should be conducted prior to initiating Environmental Monitoring Performance Qualification (EMPQ), but can be used to troubleshoot
  - Identifies the following:
    - Rooms are working properly and can help troubleshoot future problems
    - Identifies areas of stagnant air/eddies in the air
    - Ensures design criteria are functioning properly (doors seals, wall returns)
    - Identifies how items in the hood are impacting first air
  - Must be done under static and dynamic conditions
Plant: Environmental Monitoring

- Environmental Monitoring Performance Qualification (EMPQ)
  - Goal is to assure the building, after conducting a DQ/IQ/OQ/PQ can establish a state of control for producing medications
  - Must meet non-viable particulate and viable particulates (bacterial and fungal)
  - Completed once in a state of rest (no operations) and triplicate in dynamic conditions (performing normal duties)
  - Helps establish environmental monitoring plan

<table>
<thead>
<tr>
<th>Area of cleanroom (m²)</th>
<th>Minimum number of location to be tested (NL)</th>
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Equation A: \( N = 27 \times \frac{\text{Area}}{1000} \)
Plant: Facility Cleanliness and Operations

- No insanitary conditions to ensure protection of the patient
- Ensure every surface is cleaned regularly
- Create a checklist and place in your cleanroom management solution (including light fixtures, examination of the surfaces)
- Document all regular cleaning tasks and issue remediation when not completed
Activity: Design a cleanroom

- At your table, please take a paper and create cleanroom design given your experiences based on the random geometric shapes.
- Must have six LAF, four BSC, and two Genetherapy Rooms with unidirectional flow (10 minutes)
- Rotate one table and provide recommendations (5 minutes)
Practice Reflection

- What did you learn from this activity that you will take back to your practice?
- What “big idea” can you take back and apply immediately?
Process: Policy and Documents

- **IMPORTANT**: Write, train, test, and audit policies
- Conduct a USP 797/800 assessment
- Conduct a gap assessment for each area and ensure answers are appropriate for each area
- Review all policies as a part of the gap assessment
- Regularly query staff and observe
- Conduct ongoing assessments of the staff is essential to ensure a state of readiness for regulatory bodies
Process: Daily Controls

- Utilize a technology solution to evaluate daily tasks that need to be completed
- Automate responses to send emails to phones when not completed
- Take the checklist of daily activities and conduct daily QA of all activities expected in the area
- Document all audits and QA activities in your Quality Management System
Activity: Cleanroom Learnings

- At your table, please take a paper and list all the lessons learned from your own cleanroom experience (10 minutes)
- Use tick marks to vote and identify the top three impactful lessons
- Select a spokesperson to present the three highest rated lessons learned from your table (5 minutes)
Practice Reflection

- What did you learn from this activity that you will take back to your practice?
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People: Employee Training

- Staff are the variable to manage
- Staff follow the policies
- Proposed USP <797> training qualification
  - Initial triplicate qualification for media fill and glove finger samples
  - Quarterly qualification retesting
- Establish regular rounds for visual inspection and understand the challenges staff encounter
- Consider having an outside consultant come evaluate the operations
People: Garbing

- Provide hospital-laundered scrubs and ensure new scrubs are replaced daily
- Upon leaving the facility, staff must be wearing an overcoat on top of their scrubs
- Keep water out of the ISO 8, consider dry gowning
- Do not use air hand driers
- Gel after washing, before gloves
- Utilize sterile gloves and sleeves in the ISO 5 spaces
- Provide a mirror for self evaluation, hair and skin not showing
Essential Roles in the Pharmacy Department

- **IV Supervisor** *(should not be a shared responsibility)*
  - Required by USP <797>
  - Reviews all reports, trends, and examines operations

- **IV Shift Leads**
  - Responsible for upholding the integrity of the daily operations
  - Need to be in the space working with the team AND able to observe regularly

- **IV Quality Assurance**
  - Ensures compliance with relations and conducts regular audits
  - Ensures ongoing Quality Management System Development
  - Utilize a microbiologist to review and trend environmental monitoring data
Activity: Cleanroom Learnings

- Four groups
- Open your bags and follow the instructions
Practice Reflection

- What did you learn from this activity that you will take back to your practice?
- How can a process be circumvented?
Cleanroom management is about managing the three P’s
- Plant
- Process
- People

Regulation was born out of necessity
- Failures that impacted patient care necessitated a regulation
- Not a checklist – it is patient safety

Remember to examine areas outside of your pharmacy where medications may be inappropriately mixed

We should never lose sight of the goal of what may seem as extra steps...the patient
The Three P’s of Cleanrooms

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- Process
- People
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Key Takeaways

- Our cleanrooms need to be evaluated from the three P’s
  - Run through each of these in your system
  - Work them backwards from the process and review SOPs
- Our staff’s engagement is the best solution to running a compliant cleanroom
- *Writing* policy for a process vs *showing* a process for a policy are two different things
Self-Assessment

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