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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 Updates

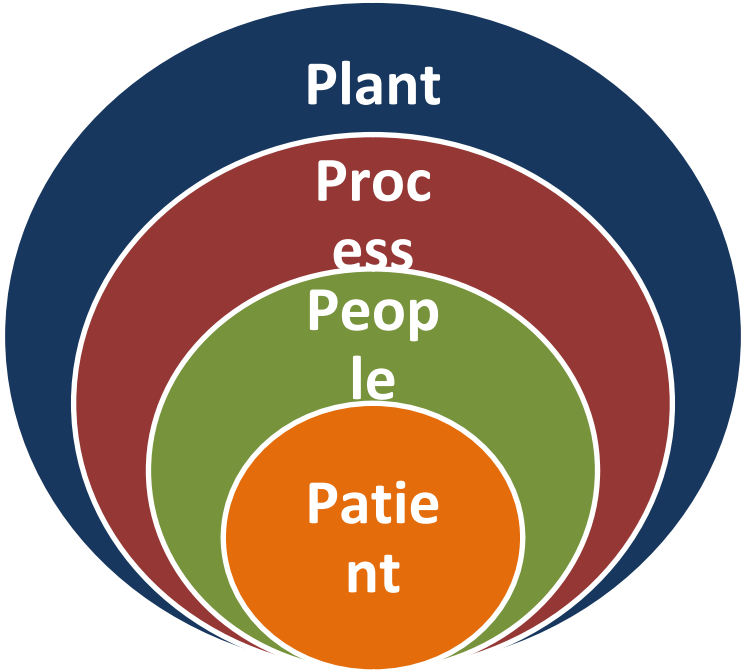
- …FDA investigators will make a preliminary assessment of whether such entities are compounding their human drugs in accordance with certain conditions of section 503a...
- …the investigator will not include observations that represent deviations solely from FDA's current good manufacturing practice (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…

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm510684.pdf

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



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/documented (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

Area of cleanroom (m^2) Less than or equal to	Minimum number of location to be tested (NL)
2	1
4	2
6	3
8	4
10	5
24	6
28	7
32	8
36	9
52	10
56	11
68	12
64	13
72	14
76	15
104	16
108	17
116	18
148	19
156	20
192	21
232	22
276	23
352	24
436	25
500	26
1000	27
>1000	Equation A

Equation A ----- $N = 27 \left[\frac{\text{Area}}{1000} \right]$

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

PLANT

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)

PLANT

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

PROCESS

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)

PROCESS

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

PEOPLE

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

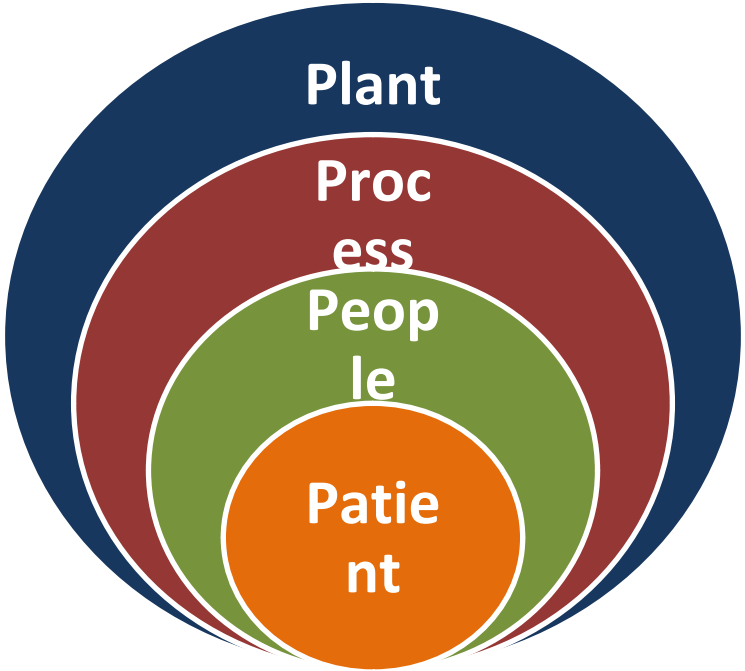
- What did you learn from this activity that you will take back to your practice?
- How can a process be circumvented?

PATIENT

Patient Safety

- 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



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

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