FDA Inspectional Observations and Corrective Actions

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Summary of Presentation

- Background
- FDA 503A and 503B inspections
- Inspectional observed deficiencies and expected corrective actions

FDA Inspections

- Inspections focus on CGMP requirements and/or insanitary conditions (facilities in compliance with section 503A are exempt from CGMP requirements)
- FDA investigators:
  - Visually inspect condition of the facility and product in inventory,
  - Review records and other documents, and
  - Observe compounding operations in their entirety.
- Once inspection completed, findings are reviewed and evaluated by compliance officers for significance and potential risk to product quality.

Inspectional Observations & Corrective Actions

- Lack of routine surface, personnel, and viable and nonviable air count air monitoring.
- The “so what?”
  - Sterility tests are not statistically reliable to ensure sterility of products.
  - Firms need to be able to demonstrate that they can control and maintain their environment to minimize risk of contamination.

Lack of Routine Surface, Personnel, and Viable and Nonviable Air Count Air Monitoring

- Corrective actions, what's needed:
  - Environmental/personnel monitoring SOPs that address equipment and supplies needed, methods used and frequency of performance
    - CGMP: Daily monitoring required
    - 503A: *USP* <797> recommends regular monitoring; minimal every 6 months
  - Invoice of equipment and supplies needed
  - Training records
  - EM logs

Non-representative or Biased Environmental Monitoring

- For example:
  - Not performing EM under dynamic/operational conditions – no compounding has occurred that day
  - Locations of samples not significant
  - Cleaning and disinfecting occurs before sampling
  - Growth media do not contain “neutralizers” to residue of previous cleaning and disinfecting
  - Growth media not demonstrated to be growth promoting
  - Incubation not performed under temperatures that promote growth.

Non-representative or Biased Environmental Monitoring

- Corrective actions, what's needed:
  - Revised environmental/personnel monitoring SOPs that address the conditions and location in which EM is be performed
  - Invoice of equipment and supplies needed
  - Training records
  - EM logs
  - May also want to observed revised procedure in action (repeat inspection)

Cleaning and Disinfecting Issues

- Examples:
  - Use of non-sterile cleaning agents, including wipes, and/or disinfectants in an ISO-5 area.
  - No routine use of sporicidal disinfectant.
  - Inadequate contact time for disinfectant.
  - Failure to clean and disinfectant from clean to dirty.
  - Failure of aseptic operators to frequently disinfect gloves during aseptic manipulations.
  - Failure to adequately disinfect supplies and equipment entering from non-classified areas to ISO-5 area.
- The “so what?” – microbial contamination is brought into the cleanrooms through personnel and supplies. The amount of microbes present needs to be controlled and minimized.

Cleaning and Disinfecting Issues

- Corrective actions, what's needed:
  - Revised SOP that addresses deficiencies.
  - Invoices of needed supplies.
  - Training material and training records.
  - May also want to observed revised procedure in action (repeat inspection) .

Gowning Issues

- Examples:
  - Non-sterile gowning items:
    - Insanitary condition guidance and *USP* <797>: sterile gloves required
    - CGMP: all outer gowning items sterile on donning
  - Exposed skin
    - Insanitary condition guidance and USP <797>: no exposed wrist or arm skin
    - CGMP: no exposed skin anywhere
  - Contaminating sterile gowning items during donning
- The "so what?" – personnel are the primary source of microbial contamination in a pharmacy cleanroom and represent the principal risk to product. That risk needs to be reduced.

Gowning Issues

- Corrective actions, what's needed:
  - Revised gowning SOPs that address the observed conditions
  - Invoice of supplies needed
  - Training material and records
  - Recertification records
  - May also want to observed revised procedure and activity in action (repeat inspection)

Qualification of the ISO-5

- ISO-5 unit (e.g. hood, BSC, glovebox) has not been demonstrated to produce unidirectional airflow under dynamic/operational conditions
  - Smoke study not performed
  - Smoke study performed, but not under dynamic conditions
  - Requirement of CGMP, insanitary conditions guidance and *USP* <797>
  - The “so what?” – sterile drug products, open to the environment, are protected from microbial contamination by the supply of “clean” unidirectional airflow sweeping across the opening (no turbulence, no areas of stagnation)

Qualification of the ISO-5

- What does “dynamic conditions” mean
  - ISO-5 unit contains all equipment and supplies that are used in aseptic processing during the study
  - The maximum number of personnel allowed in cleanroom are present during the study
  - All aseptic operations and manipulations are simulated
  - All of the above are capable of disrupting unidirectional airflow within IS0-5 unit

Qualification of the ISO-5 – Smoke Studies

- Corrective actions, what's needed:
  - Revised SOP that addresses the observed deficiency (e.g. lack of smoke studies, inadequate smoke study)
  - Certification/recertification of IS0-5 performed under dynamic conditions and supporting documentation
    - Documentation includes certificate and, preferably, video

The Importance of Smoke Study Video

- “A picture is worth a thousand words”
- A video is worth 1,000 pictures (or 1,000,000 words)
- Smoke study videos are a CGMP recommendation, not a requirement
- If a written document is only provided, a simple statement that the smoke study was performed under dynamic conditions is not adequate
  - The document needs to give a detailed summary of what equipment and supplies present, the number of personnel present and all activities simulated.

Videos of Smoke Studies

- Advantages – regulatory agencies are able to make their own assessment
- Observed deficiencies from smoke study videos
  - Generated “smoke” is not robust, widespread, or continuous over the critical areas – non-informative
  - “Passing” smoke studies show non-uniform airflow or slow moving or stagnant air in critical areas.
  - May also show poor aseptic behavior of operators

Aseptic Technique Issues

- Examples:
  - Disruption of unidirectional airflow by aseptic operator.
  - Touching with gloved hands the container closure surfaces that come into direct contact with the drugs
  - Inadequate media fills/qualification of aseptic operator – not performed under the most stressful or challenging conditions.
- The “so what?” – aseptic operators’ poor practices are frequently the major contributor to sterility failures.

Aseptic Technique Issues

Disruption of unidirectional airflow by aseptic operator.

Aseptic Technique Issues

- Corrective actions, what's needed:
  - Revised SOP that addresses the deficiencies
  - Invoice of supplies needed
  - Training material and recertification records
  - May also want to re-inspect to observe aseptic operators.
    - Appropriate cleanroom behavior of personnel is both a conscious awareness and a habit

New Resource for States

Inspectional observations and corrective actions chart

Observations relate to insanitary conditions that can cause drugs to be contaminated or rendered injurious to health. Federal prohibitions on insanitary conditions are applicable to all compounding facilities. In addition, where indicated, certain observations relate to current good manufacturing practice (CGMP) requirements, which apply to outsourcing facilities and to compounding pharmacies that do not operate in compliance with section 503A .

Observations	Common Corrective Actions to Look For
Environmental Monitoring	
Lack of routine surface, personnel, and viable and nonviable air count air monitoring	SOPs and environmental monitoring logs are kept that reflect adequate and routine surface and air monitoring. Invoices reflect the acquisition of appropriate equipment and supplies if necessary (e.g. air particle counters, and appropriate plates for surface sampling).
CGMP: Lack of daily surface, personnel, and viable and nonviable air count air monitoring.	SOPs and environmental monitoring logs are kept that reflect daily surface and air monitoring. Invoices reflect the acquisition of appropriate equipment and supplies if necessary (e.g. air particle counters, and appropriate plates for surface sampling).
Failure to conduct environmental monitoring under dynamic conditions, i.e. conditions	SOPs stipulate environmental monitoring under dynamic conditions, and these practices are directly

Questions or Comments?

Thank you!