MAYO CLINIC

台灣醫用迴旋加速器學會
Taiwanese Society of Medical Cyclotron

Regulatory Updates on USA PET CGMP Compliance Requirements

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Outline

- FDA Inspections
- Hot Cells
- Environmental Monitoring
- Media Fill
- Data Integrity
- OOS (Out-of-Specification) Investigation
- FAR (Field Alert Report)
- Disinfection Efficacy

FDA Inspections

Types of FDA Inspections

- Pre-approval Inspection (PAI)
- Surveillance (Routine) CGMP Inspection
- For-cause (Compliance) Inspection

Pre-Approval Inspection (PAI)

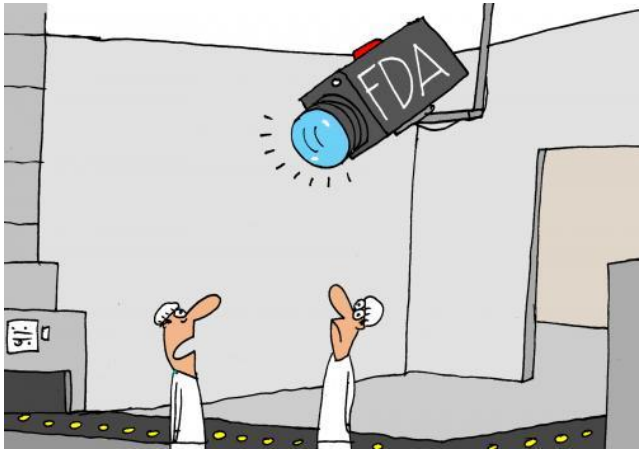
- Occurs at a production facility (establishment) that is named in an Application submitted to FDA after review - but before approval of the Application
  - Typically associated with a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA)
  - Supplement to NDA or ANDA
    - Review clock: 10-month goal date (sANDA)
- Assesses if the facility is capable of manufacture

Pre-Approval Inspection (PAI)

- Overall CGMP evaluation
- Typically unannounced
- Facility is recommended for approval or not by the FDA district office to the review center

Surveillance (Routine) CGMP Inspection

- Routine surveillance
- Most common type of inspection
- May be broad or may cover a specific topic



Surveillance (Routine) CGMP Inspection

- Typically occurs at production facilities that are named in an approved NDA or ANDA
- Periodic, typically unannounced.
  - Every 2 years as resources & priorities allow

For-cause Inspection

- May occur at any production facility at any time
  - Based on a report to the FDA
  - May be triggered by a recall or adverse event
  - Typically focus on the event - but can include anything
  - Most likely unannounced

FDA Inspection – *6 Covered Systems*

- Quality system with aseptic sterility controls
- Facilities and equipment system
- Materials system
- Production system
- Laboratory control system
- Packaging and labeling system

Full Inspections – *at least 4 systems inspected*

- Firm has never been inspected
- Follow up to regulatory action
- Significant manufacturing changes
- Microbial contamination or cross-contamination
- Poor compliance history

Abbreviated Inspections – *at least 2 systems inspected*

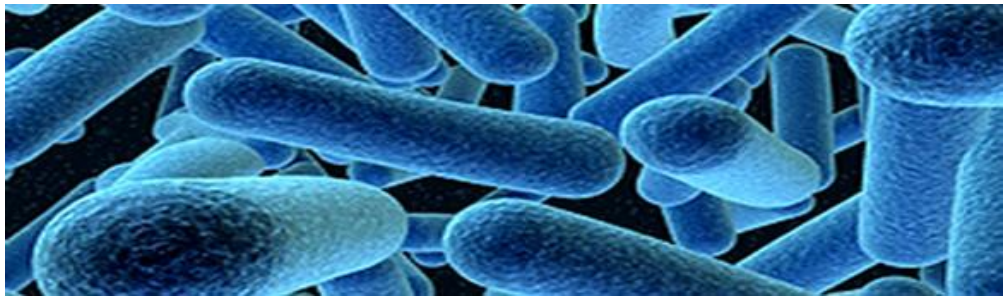
- Adequate compliance history
- Firm has been inspected for similar class of product

Inspection of *quality system with aseptic sterility controls* is mandatory for both full and abbreviated inspections.

Hot Cells

Hot Cells

- Regular hot cells
- Mini hot cells
- Must be clean
  - If the area air is not classified, additional controls and cleaning/monitoring may be required.



Environmental Monitoring (EM)

Environmental Monitoring (EM)

- Viable EM should be conducted in an aseptic workstation *at least once* on each production day
  - Air sampling (active air or settling plate)
  - Personnel monitoring (gloved fingertip sampling)
  - Surface sampling (contact plate)
- Radiation concern should be factored in the EM planning
- 2nd person verification for viable EM results not required

Media Fill

Media Fill – Process Simulation

- Media fill deficiencies typically fail to properly simulate actual production process:
  - Pre-assembly of product vial not simulated
  - Bulk product vial hold: not the worst case
  - Sterile filtration process not simulated
  - Dilution step not simulated
  - Manufacturing process flow not the same
  - Withdrawal of QC samples not simulated
  - No positive control and negative control
  - Media does not come into contact with all interior surface

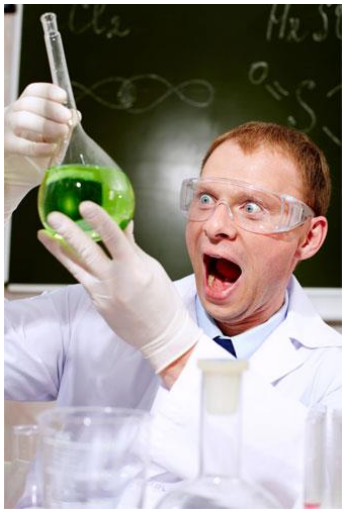
Media Fill Deficiencies – cont'd

- Media fill should be conducted in the same area where aseptic procedures occur
- Not all production personnel participate in media fill

Data Integrity

Data Integrity

- Access controls for computer systems (including GC and HPLC software)
- Not recording activities contemporaneously
- Backdating batch record entries
- Unsupportable data entries - lacking raw data
- Re-running analytical samples without justification
- Copying existing data as new data
- Discarding raw data



OOS (Out-of-Specification) Investigation

OOS Investigation

- Failure to identify as deviation and conduct investigation
- Inconsistency or failure to investigate, unexplained discrepancies and several batch failures
- OOS test averaged to generating passing results
- Cyclotron malfunctions, low yields and synthesis issues with no OOS/corrective actions

FAR (Field Alert Report)

FAR

- For those products that are the subject of approved full and abbreviated new drug applications, regulations require submitting within 3 working days a field alert report (FAR) of information concerning any failure of a distributed batch to meet any of the following specifications.
- So, what specific *failure* constitutes an FAR?

FAR

- *Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.*
- *Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.*

Disinfection Efficacy

Disinfection Efficacy

- Suitability, efficacy, as well as limitations of disinfecting agents & procedures should be assessed
  - Many common disinfectants are ineffective against spores
    - A sporicidal agent should be included in a disinfectant program
  - USP <1072> *Disinfectants and Antiseptics*
    - *Disinfectant Challenge Testing*

Thank you!

Questions & Discussion