



U.S. Food and Drug Administration

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# **Current Good Manufacturing Practices for PET Drugs – Examples of Case Studies**

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# PET Inspections Major Issues

1. Lack of assurance that the drug is sterile
2. Lack of assurance that test results are reliable and accurate
3. Inadequate training and QA oversight



# 1. Lack of assurance of sterility

- Media fills did not simulate production
- Positive controls were not done with media fills
- Deficient sterility test
  - Growth promotion of media not performed
    - Growth promotion need not be performed on each lot provided the vendor has been qualified
  - Inadequate incubation temperature control
    - FTM sterility test exceeded 30–35 °C on 22 of 25 days
    - TSB sterility test exceeded 20–25 °C on 20 of 26 days.



# 1. Lack of assurance of sterility

- Aseptic workstation not suitable for aseptic operations
- Use of non-sterile disinfectant to sanitize aseptic workstation and product contact surfaces
- Frequency of environmental monitoring not reflected in manufacturing operation



## 2. Lack of assurance of reliable & accurate test results

- Production synthesizer & QC equipment
  - Not qualified for use
  - Not calibrated
  - Not properly maintained
- QC Testing Equipment
  - System suitability not performed on analytical equipment (**USP Chapter <621>**)



### **3. Inadequate training and QA Oversight**

- Failure to train personnel to perform media fill simulation
- Failure to conduct investigation of failed batches and deviations
- Release of batches that have not completed all required end-product tests



# PET Inspections — Examples of Case Studies



# PET Inspections - Case

- *Sterility*: *Growth promotion testing is not conducted to verify the suitability of the incoming media used for sterility testing*
  - Growth promotion need not be performed on each lot provided the vendor has been qualified.
- *Media Fill*: *Growth promotion testing is not performed to ensure that media lots are capable of supporting growth*
  - *Positive controls were not included with each media fill conducted to qualify your operators in the aseptic process.*



## PET Inspections - Case

- *No media fill simulation studies were performed to qualify the process and the persons during sterile operations.*
- *The media fill simulation for F-18 product is not representative of actual production and is limited to the assembly of the bulk product vial onto a sterile vial of Tryptic Soy Broth, from which the QC samples are withdrawn and for which all steps are conducted in the Laminar Flow Hood.*



# PET Inspections - Case

- *Routine environmental monitoring (microbiological testing) of the firm's sterile area (laminar flow hood), where aseptic product manipulations take place, were not performed or recorded.*



# PET Inspections - Case

- *The firm lacked documentation of the notification of sterility failures of PET drug product to the nuclear pharmacy.*
- *The firm lacked follow up to determine if complaints or adverse experiences had been reported to the nuclear pharmacy.*



# PET Inspections - Case

- *Failure to conduct all finished product quality control testing on PET drug product to ensure that batch meets the acceptance criteria for purity and quality*
  - *A residual solvents test was not conducted prior to release of several lots produced due to malfunctioning of the gas chromatograph (GC).*
  - *Prior to each day of use, a system suitability test of the GC should be conducted to ensure its proper functionality.*



# PET Inspections - Case

- *There are no procedures related to training.*
- *There is no documentation of training or qualification of employees performing particular duties (drug production, testing, preparation etc).*



# Thank you for your attention.

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