PET Surveillance Inspections and Training Update

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Positron Emission Tomography Product Quality Regulatory Submissions, Facility Inspections, and Benefit-Risk Considerations
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Outline

Surveillance Inspections
Recent 483 Examples
Investigator Training
Inspection Protocol
Surveillance Inspections

PET Drug Surveillance inspections monitor conformance to 21 CFR 212 Regulations, which represent the minimum CGMP requirements. These systems-based inspections follow Compliance Program (CP) 7356.002P and will always include coverage of Quality System with Aseptic Sterility Controls, with additional system(s) as described in the CP for abbreviated and full inspections.

Some Key Points on Surveillance Inspections

- Compliance Program and electronic Inspection Protocol are based on conformance with 21 CFR 212 Regulations.
- Inspections are generally scheduled with a firm in advance due to limited operational staff, except in the case of “For Cause” assignments.
- The cyclotron is not typically physically inspected due to potential hazards, but maintenance records may be encompassed in the inspection (e.g., target maintenance, frequency of window replacement)
Some Key Points on Surveillance Inspections

- As with other inspection types, the collection of electronic records to facilitate faster, more thorough data review may be performed and is outlined in the Investigations Operations Manual.
- Collection of photographs has routinely been utilized on FDA inspections to document deficiencies or better describe an operation and is supported by case law.
- The FDA-483 is not a final Agency determination and voluntary firm response is considered if received within 15 business days.

PET Surveillance Inspections 2020-2023

- 31 Total Surveillance Inspections:
  - 2020: 10 inspections
    • (5 VAI, 5 NAI)
  - 2021: 11 inspections
    • (2 OAI, 4 VAI, 5 NAI)
  - 2022: 4 inspections
    • (2 VAI, 1 NAI)
  - 2023: 7 inspections
    • (1 OAI, 5 VAI, 1 NAI)
704(a)(4) Record Requests 2020-2023

- Approximately 19 record requests conducted for surveillance of PET facilities since 2020 under FD&C Act Section 704(a)(4)
- Starting July 2021 and going forward, findings are being communicated to firms in writing

Recent 483 Examples

The following summarizes the Top FDA 483 Citations utilized for inspections of PET Facilities between 2020 and 2023, among both Surveillance and Pre-Approval assignments.
Top PET 483 Citations – 2020-2023

<table>
<thead>
<tr>
<th>CFR Citation</th>
<th>Short Description</th>
<th>Number of Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>212.30(b)</td>
<td>Equipment procedures</td>
<td>10</td>
</tr>
<tr>
<td>212.20(d)</td>
<td>Determination need for investigation</td>
<td>8</td>
</tr>
<tr>
<td>212.20(e)</td>
<td>Written QA procedures established, followed</td>
<td>8</td>
</tr>
<tr>
<td>212.50</td>
<td>Adequate controls (general)</td>
<td>8</td>
</tr>
<tr>
<td>212.30(a)</td>
<td>Orderly handling, prevention of mix-ups, prevention of contamination</td>
<td>8</td>
</tr>
<tr>
<td>212.60(b)</td>
<td>Lab sampling and test procedures</td>
<td>3</td>
</tr>
<tr>
<td>212.60(c)</td>
<td>Analytical methods</td>
<td>3</td>
</tr>
<tr>
<td>212.70(b)</td>
<td>Before implementing new procedure establish and document accuracy etc.</td>
<td>3</td>
</tr>
<tr>
<td>212.30(c)</td>
<td>Contact surfaces</td>
<td>2</td>
</tr>
<tr>
<td>212.71(c)</td>
<td>Correction of problems</td>
<td>2</td>
</tr>
<tr>
<td>212.40(a)</td>
<td>Written procedures for control of components, containers, and closures</td>
<td>2</td>
</tr>
</tbody>
</table>

Most Common 483 Citations – 212.30(b) Equipment Procedures

You did not [implement procedures] [document your activities in accordance with your procedures] to ensure that all equipment is [cleaned] [suitable for its intended purposes] [properly installed, maintained, and capable of repeatedly producing valid results] that could reasonably be expected to adversely affect the identity, strength, quality, or purity of a PET drug, or give erroneous or invalid test results when improperly used or maintained. Specifically, ***
Most Common 483 Citations – 212.30(b) Equipment Procedures

• “[Nuclear Pharmacist placed] his head, which included his exposed neck and facial skin, directly within the ISO 5 vertical Laminar Flow Hood (LAFH) during cleaning...immediately prior to sterile preparation and assembly of empty product vials”
• “...failed to apply the appropriate contact time for a sporicidal cleaning agent...as outlined by the manufacturer’s instructions”
• “...do not disinfect the ISO 5 rated hot cell with sporicidal agents on a routine basis...[and there] is no documented cleaning procedure for the ISO 5 rated hot cell or the non-rated QC lab where the hot cell is located.”

Most Common 483 Citations – 212.20(d) Determination Need for Investigation

When errors occurred or a production batch or any component of the batch, failed to meet specifications, you did not [determine the need for an investigation] [conduct an investigation] [take appropriate corrective actions] when necessary. Specifically, ***
**Most Common 483 Citations – 212.20(d) Determination Need for Investigation**

- “Two operators...continued to manufacture sterile drugs...when their media fill re-qualification was expired.”
- “...failed to adequately investigate and assess potential product impact...from the failure of the container closure system...”
- “(OOS) results...obtained during endotoxin analysis of five (5) batches...retested a single time and the passing result was considered valid...no detailed investigations to determine the root cause(s) of these events.”

**Most Common 483 Citations – 212.20(e) Written QA Procedures Established/Followed**

You did not [establish] [follow] written quality assurance procedures. Specifically,**

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Most Common 483 Citations – 212.20(e) Written QA Procedures Established/Followed

- “Pharmacy Technician quickly and lightly touched the agar plates...as opposed to slowly rolling each fingertip and thumb on the agar surface with adequate pressure to ensure recovery of potential microbes as per SOP...”
- “QA personnel did not ensure all GMP records are complete and accurate” (e.g., facility maintenance and sanitization log not documented, glove fingertip testing, environmental monitoring results not reviewed)
- “…failed to establish procedures...in the event that there are system suitability failures of the...(TLC) instrument...”

Most Common 483 Citations – 212.50 Adequate Controls (General)

Your firm lacks adequate production and process controls to ensure the consistent production of a PET drug that meets the applicable standards of identity, strength, quality and purity. Specifically,...
Most Common 483 Citations – 212.50 Adequate Controls (General)

• “Operator replaced the dirty mop head...and did not sanitize their gloved hands before taking out a sterile clean mop head from the packet...”
• “…gloves used during aseptic manipulation of components, in-process materials, and finished drug products...within the ISO 5 rated hot cell were non-sterile.”
• “non-sterile [mop] covers [are used for] cleaning the inside ISO 5 surfaces of the Hot Cell.”

Most Common 483 Citations – 212.30(a) Orderly Handling, Prevention of Mix-Ups, Prevention of Contamination

Your facilities are not adequate to ensure [the orderly handling of materials and equipment] [the prevention of mix-ups] [the prevention of contamination of equipment or product by substances, personnel, or environmental conditions] that could reasonably be expected to have an adverse effect on product quality. Specifically, ***
Most Common 483 Citations –
212.30(a) Orderly Handling,
Prevention of Mix-Ups, Prevention of
Contamination

• “…sterility test failure classified as a ‘false positive’…attributed to a contaminated septum…consistent recovery of microorganisms from the ISO 5 laminar flow hood, gloves, and…inside Hot Cell [above alert and action levels that include] spore-forming bacteria…and multiple too numerous to count (TN TC) results.”
• “…failed to label the mini cell housings containing chemistry modules with on-going batch manufacturing status and cleanliness status to avoid…contamination, errors, and mix-ups…”
• “robotic arm grabbers [not included] in your environmental monitoring program…come into direct contact with final product vials when performing aseptic manipulations”

PET-Specific
Investigator
Training

Updated comprehensive training was delivered in 2021 to FDA Investigators focusing on the 21 CFR 212 Regulations for PET Drug Manufacturing, highlighting differences from the 211 Regulations.

Training targeted to Investigators already performing inspections of sterile drug manufacturers, to elucidate key differences in PET products and their associated controls. Also encompassed use of PET Inspection Protocol and Basic Radiation Safety.
PET Inspection
High-Level Training Topics

- Introduction to PET Drugs, Brief History of Production, and 21 CFR 212 Regulations
- Unique Aspects of PET Drug Production and Regulations
- Manufacturing Traditional PET Drugs & Production Technologies
- Systems-Based Surveillance and Pre-Approval Inspectonal Coverage as Outlined in CP 7356.002P
- Emphasis of Differences Between 21 CFR 211 and 21 CFR 212 Regulations Throughout

PET Inspection Protocol

Inspection Protocol specifically designed for PET Drug facilities is currently being used for Surveillance Inspections conducted under Compliance Program 7356.002P.

The protocol may be executed on a tablet or laptop computer by FDA Investigators and was specifically created for systems-based coverage and aligns with 21 CFR 212 Regulations.
PET Inspection Protocol

• Leads to more efficient and consistent inspections that align with 21 CFR 212 Regulations
• Modernize inspections through collection of structured data that can be analyzed over time:
  – Quantitate the state of pharmaceutical quality
  – Accelerate the pace of making informed, data-driven decisions supporting areas such as:
    • Application approvals
    • Resource allocation
  – Identify policy and outreach opportunities across the industry

Thank You!

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