FDA Inspections: Commercial Perspective

Speaker: Keith Bowen, Avid@ Lilly

Industry Perspective on Commercial Site Inspections In Relation to cGMPs

Discuss Opportunities to Clarify GMP Expectations For Manufacturer & Inspection Success

PURPOSE
A proactive approach to clarify GMP expectations for manufacturer and inspection success

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FDA and PET Drug Manufacturing Industry Partnership

ACHIEVE

2. FDA Public Meeting – PET Drugs: Submitting An Application for PET Drugs Currently in Clinical Use, March 2, 2011
3. FDA 21 CFR PART 212 - CURRENT GOOD MANUFACTURING PRACTICE FOR POSITRON EMISSION TOMOGRAPHY DRUGS
4. FDA 21 CFR PART 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS
5. FDA POSITRON EMISSION TOMOGRAPHY (PET) CGMP DRUG PROCESS AND PRE-APPROVAL INSPECTIONS/ INVESTIGATIONS PROGRAM 7356.002P; 11 Sep 2015.
6. FDA Oversight of PET Products – Questions and Answers; Dec 2012
7. FDA Guidance - PET Drugs - Current Good Manufacturing Practices; Aug 2011
8. FDA Guidance – Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography (PET) Drugs; Apr 2012
9. FDA Sterile Drug Products Produced by Aseptic Processing; Sep 2004

REFERENCES
REFERENCES

10. FDA Inspection Observations | FDA: FY 2022 Excel File
11. USP-NF 40, <1116> Microbiological Control and Monitoring of Aseptic Processing Environments
13. ISO14644-7:2004; Cleanrooms and associated controlled environments. Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini environments)

OTHER REFERENCES

15. Product Quality Assurance: Microbiological Regulatory Perspective; Laura R. Wasil, Ph.D. WEB LINK: PET Drugs Workshop Presentations Part II (fda.gov)
16. Microbiological Safety of Positron Emission Tomography Drugs; David Hussong, PhD and Henry VanBrocklin, PhD. WEB LINK: PET Drugs Workshop Presentations Part II (fda.gov)
What is a PET Drug?

- A medical imaging modality involving the use of a unique type of radiopharmaceutical drug product that contains a positron emitting isotope.

- Intended for diagnostic use and are not intended to provide a therapeutic effect; however, many PET drugs provide their diagnostic effect by binding to receptors, which is a type of pharmacological activity.

PET Drug GMP Scope

- All operations to the point of final release of a finished dosage form (commonly a single multi-dose vial).

- Not covered,
  - Dispensing of the patient unit doses from a multidose vial
    - Does not apply if manufacturer’s marketed product is a unit dose vial
  - Use of a PET drug product after receipt by a receiving facility
### COMMERCIAL SITE INSPECTION

#### OBSERVATION METRICS

<table>
<thead>
<tr>
<th>21 CFR 212.20(e) Written QA procedures established, followed</th>
<th>0 1 2 3 4 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 CFR 212.30(a) Orderly handling, prevention of mix-ups, prevention of contamination</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>21 CFR 212.30(b) Equipment procedures</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>21 CFR 212.50 Adequate controls (general - production and process controls to ensure the consistent production)</td>
<td>0 1 2 3 4 5</td>
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<tr>
<td>21 CFR 212.20(c) Specifications and processes</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>21 CFR 212.20(d) Determination need for investigation</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>21 CFR 212.40(c) Each lot identified and tested</td>
<td>0 1 2 3 4 5</td>
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#### Recurring Themes
1. Written procedures
2. Adequate controls

#### 21 CFR PART 212 - FDA INSPECTION OBSERVATIONS - FY22

16 Total Observations
Procedures not in writing, fully followed
Investigations of discrepancies, failures
Absence of Written Procedures
Scientifically sound laboratory controls
Equipment Design, Size and Location
Computer control of master formula records
Cleaning / Sanitizing / Maintenance
Testing and release for distribution
Procedures for sterile drug products
Written procedures not established/followed
Calibration/Inspection/Checking not done
Environmental Monitoring System
Validation lacking for sterile drug products
Control procedures to monitor and validate performance
Lack of written stability program
Written record of investigation incomplete
SOPs not followed / documented
Cleaning System
Training—operations, GMPs, written procedures
Microbiological testing

ALL DRUG INSPECTIONS – FY22

INDUSTRY INSPECTION PERSPECTIVES

2,126 Total Observations
Recurring theme – Procedures not established/in writing, followed
Industry Inspection Perspectives

• Mostly pre-announced

• *Manufacturing sites have “fewer personnel”¹,²,³,⁵* to manufacture product. Requires Admin/Corporate resources to host inspections.

Industry Inspection Perspectives

• 7356.002P - POSITRON EMISSION TOMOGRAPHY (PET) CGMP DRUG PROCESS AND PRE-APPROVAL INSPECTIONS/INVESTIGATIONS was established for PET Drug Manufacturing inspections, Impl. 09/2015

• Additional guides employed,
  1. 7346.832 - Preapproval Inspections, Impl. 2010
Industry Perspectives Survey

A change could also mean a difference in interpretation

There are several unique features of PET drug products, and many common GMP expectations

Source: Academic and commercial PET drug manufacturers conducted by the Coalition of PET Drug Manufacturers (the Coalition) in September 2023 (18 Responders)

Various Industry Interpretations

Why would almost 12% believe there are no Action Limits?

PET Drug cGMPs state “ISO 5”, “Class 100”
What risk-based expectations should apply to “Closed Vial Systems”? 

Alert/Action Limits stated in FDA Sterile Drug Products Produced by Aseptic Processing; Sep 2004

Scope: 21 CFR 210 and 211, Supplementary to 21 CFR Parts 600, 680

Turbulent airflow can be allowed for “Closed Isolator Systems”

Source: Academic and commercial PET drug manufacturers conducted by the Coalition of PET Drug Manufacturers (the Coalition) in September 2023 (18 Responders)
Industry Inspection Perspectives

• A [PET drug] Recall consists of,
  – notifying the receiving facility, the pharmacist, and the patient’s physician, if known.
  – When the receiving facility disposes of the recalled drug, the PET drug producer can obtain a notification from the receiving facility confirming the recalled drug has been disposed of and describing the manner in which it was disposed. 

If no inventory exists, should a recall checklist per current guidance & 21 CFR 7.40 be employed?

Industry Inspection Perspectives

• **Annual Product Reviews** - strongly recommended
Industry Inspection Perspectives

Annual stability testing strategy

...under discussion

FDA Public Meeting – March 2, 2011

PET Drugs: Submitting An Application for PET Drugs Currently in Clinical Use
Stability. Release and stability, three batches at the upper range of proposed radio concentration should be provided. We are not looking for site-specific stability. So as long as your manufacturing process is the same, uses the same synthesizer, the data from that site should be okay. You don't need to generate stability data at each site.

Industry Perspective Application Reviews

– a Phase 1 Laboratory investigation cannot be initiated to evaluate/invalidate original test results. Any OOS result should result in a rejected batch.
Industry Perspective
Application Reviews

• Differing facility/product change mgmt. filing strategy recommendations

Industry Perspectives

• Feb 2020 - PET Industry & FDA Workshop on Inspections Management and Regulatory Considerations
  – Highlighting differences in cGMP interpretations
  – Action to develop training materials for site inspectors. SNMMI drafted material issued
What Could be Causing This?

INDUSTRY LED CGMP ASSESSMENT
Final Rule: We further stated that the proposed CGMP regulations were designed to be sufficiently flexible to accommodate not-for-profit, academically oriented institutions as well as larger commercial producers.¹

Guidance documents issued to better understand FDA’s thinking concerning compliance - Resources, Procedures, and Documentation for production facilities, academic and commercial.⁵

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PET Drug GMP Origins
FDA Public Meeting (Dec. 2009)
Current Good Manufacturing Practice for Positron Emission Tomography Drugs

- In consideration of the unique nature of PET drugs and PET drug production, the proposed CGMP requirements for PET drugs differed in many significant ways from the CGMP requirements for non-PET drugs found in our regulations in parts 210 and 211 (21 CFR parts 210 and 211).¹

- The proposed PET CGMP requirements included differences concerning personnel; aseptic processing; quality control of components; self-verification of production steps; same-person oversight of production, batch record review, and authorization of product release; and labeling requirements.¹
Industry Feedback on the New Regulation

How can they allow these different requirements?

Differences of PET Drug Product Manufacturing Potentially Enabling Risk Based GMPs

• Mostly single use materials and components, many pre-sterilized
• Very small or No production hold times
• Identical automated equipment, electronic manufacturing sequences, & procedures across manufacturing networks
• Single produced batch vial (“100% batch QC sampling”)
• Patient dose administration within minutes, hours, to a few days
Closed isolator systems

Should the Laminar Flow Hood require ISO 5 / Class 100 & Non-Turbulent conditions?

Should the GMPs focus on guidance for aseptic practices, LFH sanitization, Sanitization and aseptic handling of the pre-sterilized vial

What Should We Do?
Industry led cGMP Assessment Initiative

• MITA Quality and Regulatory Team

<table>
<thead>
<tr>
<th>Team Members</th>
<th>Organization</th>
<th>Job Title</th>
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<tbody>
<tr>
<td>Stacie Aman</td>
<td>Novartis</td>
<td>Director, Federal Policy, Global Public Affairs</td>
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<tr>
<td>Keith Bowen</td>
<td>Eli Lilly</td>
<td>Associate Vice President, Quality Assurance, Avid @Lilly</td>
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<tr>
<td>Sue Bunning</td>
<td>Medical Imaging &amp; Technology Alliance (MITA)</td>
<td>Managing Director, Positron Emission Tomography</td>
</tr>
<tr>
<td>Anne Butterworth</td>
<td>Lantheus</td>
<td>Vice President, Quality Assurance</td>
</tr>
<tr>
<td>Christopher Ignace</td>
<td>Cardinal Health</td>
<td>Vice President, Scientific Affairs and Strategic Partner Management, Nuclear &amp; Precision Health Solutions</td>
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<td>Lynn C. Mendonca</td>
<td>Lantheus</td>
<td>Associate Director, Regulatory Affairs</td>
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<td>Ashley Mishoe</td>
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<td>Michael Nazerias</td>
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<td>Daniel Yokell</td>
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Industry Led PET cGMP Assessment

<table>
<thead>
<tr>
<th>GMP Area</th>
<th>Examples of Clarity Needed</th>
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<tbody>
<tr>
<td>1 Annual Stability Strategy</td>
<td>Manufacturer’s producing the same product on the same automated radiosynthesizer, same manufacturing sequence at different manufacturing sites</td>
</tr>
<tr>
<td>2 Aseptic Processing</td>
<td>EM alert/action limits, Risk based approach when using closed vial systems</td>
</tr>
<tr>
<td>3 Annual Product Reviews</td>
<td>Strongly recommended</td>
</tr>
<tr>
<td>4 Electronic/Computer Systems and CSV, Data Integrity/True Copy</td>
<td>What parts of the PET Drug manufacturing operation are in scope?</td>
</tr>
<tr>
<td>5 Recalls</td>
<td>Should a Recall be conducted when there is no finished product inventory?</td>
</tr>
<tr>
<td>6 Handling OOS investigations (sterility and analytical QC )</td>
<td>Currently discussed for sterility testing and non-conforming rejected product. Can PET manufacturers conduct Phase 1 Laboratory investigations?</td>
</tr>
<tr>
<td>7 GMP/Science Based Principals to Risk Management</td>
<td>What standards are needed, What details are missing for PET drug manufacturers? How should it be applied in PET drug manufacturing environments?</td>
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Industry Perspective on 21 CFR Part 212 & PET Guidance

- “Relatively new”
- Fundamental (common) GMP Expectations across product types
- Unique Features designed into cGMPs
- Possible to enhance cGMPs using scientific and risk-based principals?

Conclusion

- An enhanced risk-based approach could result in an opportunity to clarify GMP expectations

A partnership with FDA could create a balanced approach to applying risk management principles leading to manufacturer and site investigator success