Facility Evaluations in Applications and Pre-approval Inspections

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**Presentation Outline**

- **New draft Guidance**
  - Use of Alternate tools for Facilities Assessment, *September 2023*
  - Use of Remote Interactive Evaluation for application, *October 2023*

- **Key Topics with recommendations:**
  - Application vs Post Market Stability study requirements and reporting
  - Identity Testing requirements for PET drug Precursors and drug substance
  - Data Integrity topics and recommendations
Risk-based facility assessment for Application Approvals

Facility Risks
- Compliance history/status
- Competency to manufacture the product under evaluation
- FDA 483 Observational Trends

Process Risk - *Risks with execution of manufacturing process design and control strategy?*
- Inherent process complexities
- Unique process characteristics
- Application concerns – Manufacturing and Micro

Product-specific Risk Factors - *Risks related to drug product characteristics*
- Radiopharmaceuticals/ PET Drugs
PET Drug Facility Assessment
Application Approvals during COVID-19

• **Same Quality Standards** using **risk-based** assessment of product, process and facility risks to determine inspection need

• **Successful use of “Alternative Tools” used during facility assessment of PET drug applications during COVID-19**
  - Relying on Mutual Recognition Agreement (MRA) (EU and UK)- For Identification of risks
  - Information using 704(a)(4) of the FD&C Act in lieu of inspection
  - Remote Interactive Evaluations (RIEs) - *No PET drug RIE’s were conducted*

• **Four (4) 704(a)(4) desk reviews** were conducted between 2020 March to 2021 Dec for application approvals

• **We completed 12 Pre-approval inspections** of PET drugs between 2020 March and mid 2023 for application approvals

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Use of Alternate tools
Assessment of Manufacturing Facilities

Draft Guidance issued **September 2023** describing how facility assessments will be conducted utilizing alternate tools for original and supplemental applications

a. NDA
b. ANDA
c. BLA

This guidance does not apply to other drug inspection programs:

- ✔ Post Approval Inspection
- ✔ Surveillance Inspection
- ✔ Follow up and compliance inspection
- ✔ Bioresearch Monitoring facilities
Use of Remote Interactive Evaluation

- Draft Guidance issued **October 2023** describing what to expect when FDA performs “remote interactive evaluation”
- RIE means any interaction with a facility other than inspection or a record request (704(a)(4) of the FD&C Act)
- T-cons, livestreaming video of facility/ops, screen-sharing of records/info, disclosing records, etc.
- Records Requests and RIEs may be used in lieu of inspections **to make application decisions**
- **Voluntary**: a facility is not obligated to participate
- RIE will **support an application approval**

1. Stability study requirements and reporting
Product Stability Requirements
For Application Approval

- The stability protocol and post market stability commitment in an original NDA/ANDA is reviewed as described in FDA's Manual of Policy and Procedures (MAPP) 5200.14 Filing Review of Abbreviated New Drug Applications

- Stability studies should be performed at the highest radioactive concentration, and the whole batch volume should be stored in the intended container/closure

- At least 3 batches for each configuration (vials, syringes etc.) and each process (e.g., Cyclotron vs Generator or different synthesizers) should be tested for a period equal to the labeled shelf life of the PET drug product

- Stability studies performed at one of the PET drug facility is acceptable with PET producers with a network of facilities submitted in the 356h form for application approval only

- Network of facilities should be under the same Quality system (e.g., same procedures, equipment's, methods and manufacturing processes etc.)

Appropriate parameters should be evaluated to establish and document the stability of PET drug under proposed storage conditions.

- Examples of stability parameters: radiochemical identity and purity, appearance, pH, stabilizer or preservative effectiveness, and chemical purity (impurities)

- Use stability–indicating methods that can distinguish degradation products and impurities (e.g., radiolysis phenomenon generates byproduct, and detection mechanisms will vary based on chemistry, being unique to each product and approved in the application)
Importance of Post Approval Stability Studies

There may be continued variations in the PET Drug production process after an application approval:

- Personnel
- Raw material lots/controls
- Change in Suppliers
- Manufacturing and testing equipment/ upgrades
- Software/firmware upgrades
- Facility related controls- Environmental factors

It is imperative that stability studies are not limited only to initial three production batches produced to support application approval, but a portion of annual production batches are to be subjected to an ongoing stability program at each production facility.

This is consistent with FDA’s recommendation to manufacturers of drug products regulated under 21 CFR 211 described in FDA’s inspection technical guide *Expiration Dating and Stability Testing for Human Drug Products* (2014).

Stability Program and CGMP requirement

- 21 CFR Part 212 CGMP requirements are applicable to all finished dosage PET drug production facilities listed and approved in an application
- Establishment of a stability program at each production facility is a requirement under 21 CFR Part 212.61
- FDA requires a PET drug producer to establish, follow, and maintain a written testing program to outline how it will implement the stability protocol and any post approval stability commitment they submit to FDA in each PET drug application (21 CFR 212.61(a))
- Annual stability studies aligned to post market stability protocol should be conducted at each PET drug production facility including PET producers with a network of facilities
- PQIT tests submitted and approved in an application should be included as part of annual stability testing program
Post Market Stability Study
Execution and Reporting

- **Regulatory Application Requirement**: FDA requires that PET drug producers submit the stability test results in an annual report (21 CFR 314.81(b)(2)(viii)) from all manufacturing sites.

- **Applications with one facility**: Acceptable executing and reporting. Annual Stability study is executed and annually reported on a minimum of one batch based on the Post Approval Stability Protocol for each packaging configuration and process as applicable.

- **Some applications with multiple production facilities**: *Gaps identified* in annual study execution and reporting:
  - Post approval annual stability study is **executed only at one facility** and **stability report from one facility** is submitted in annual report.
  - **PET drug producers need to conduct annual stability study from at least one batch for each of the PET Drug production facilities** listed in the 356h form in the application.
  - Sponsors may choose to adopt an abbreviated format of annual stability studies data reporting for **large number of additional facilities only**.

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**Post Market Stability Study Reporting**

Example of an Abbreviated format for annual stability results from network of facilities:

- Name/location and FEI#
- Confirmation regarding date of annual stability study execution at each listed facility
- Confirmation of meeting all approved specifications in the application
- Any failure of stability studies should be reported with full test results, failure investigation details and root cause identification

Each PET drug producer should store the stability study results, reports, data etc. at the respective facilities and make it available during inspections.
Stability Testing Program
Example: FDA 483

21 CFR 212.61(a)
There is no written testing program designed to assess the stability characteristics of drug products. Specifically,

You failed to establish a formal written stability program including reliable, meaningful, and specific test methods with approved protocols, reports, and raw data to support stability conclusions in your final report.

2. Precursor and drug substance IDENTITY (ID) testing
Control of Components – 21 CFR 212.40(c)

- 21 CFR 212.40(c)(1)(ii)
  - If finished product testing of a PET drug product can not ensure that the correct components have been used, you must conduct identity testing on each lot of a component that yields an active ingredient and each lot of an inactive ingredient used in that PET drug product.
    - (e.g., this is applicable for precursors)
  This testing must be conducted using tests that are specific to each component that yields an active ingredient and each inactive ingredient.

Why a precursor will require ID Testing

- Precursor is the last intermediate that can be tested directly for correct structure and quality of the API
  - TLC or HPLC based identity tests are not specific to the precursors/API and do not conclusively confirm that the correct precursor has been used (e.g., identity of the precursor).
  - A precursor may have stereochemical center, which may have an impact on safety or efficacy – simple TLC or HPLC is unlikely to confirm this.
  - Since API is produced in-situ, upstream control of the precursor is necessary.
  - Only approved suppliers (as filed in application) should be used.
  - Precursor/API manufacturers are inspected under ICH Q7 standards
Control of Components – 21 CFR 212.40(c)

• 21 CFR 212.40(c)(1)(ii)
  • For any other component, such as a solvent or reagent, that is not the subject of finished-product testing, you must determine that each lot complies with written specifications by examining a certificate of analysis provided by the supplier; if you use such a component to prepare an inactive ingredient on site, you must perform an identity test on the components used to make the inactive ingredient before the components are released for use.
    • [E.g., preparation of sodium chloride solution instead of purchasing 0.9% Sodium Chloride Injection, USP, would require an identity test on components used to make sodium chloride]
  • However, if you use as an inactive ingredient in a product that is approved under section 505 of the act (21 U.S.C. 355) and is marketed as a finished drug product intended for intravenous administration, you need not perform a specific identity test on that ingredient.
    • [E.g., purchasing commercially available 0.9% Sodium Chloride Injection, USP or Ascorbic Acid Injection, USP, an identity test would not be required]

Identity Testing Summary

A specific identity test is not required for:
• Components that are themselves finished products
• Components whose identity is confirmed through finished product testing
• Components that are not active or inactive ingredients

Regardless of whether a specific identity test is required for a component, the producer must confirm that the component meets written specifications.
3. Data Integrity Topics

Data Integrity and PAI Objectives

1. Determine whether the establishment has a quality system that is designed to achieve sufficient control over the facility and commercial manufacturing operations

2. Verify that the formulation, manufacturing or processing methods, and analytical (or examination) methods are consistent with descriptions contained in the CMC section of the application for the Exhibit batches (and other clinical batches, when applicable)

3. Audit the raw data in analytical and manufacturing equipment, hardcopy or electronic, to authenticate the data submitted in the CMC section of the application. Verify that all relevant data (e.g., stability, Exhibit batch data) were submitted in the CMC section

4. Commitment to Quality in Pharmaceutical Development (New Objective)
Data Integrity and PET Drug Manufacturing

“Data Integrity and Compliance With Drug CGMP Questions and Answers Guidance for Industry” December 2018

- Access controls for computer systems [212.60(a) – 212.60(g), 212.30(b)]
  - Changes to programs and methods must be controlled
- Shared login unacceptable – [212.50(c)10]
  - Actions must be attributable to individuals
  - Deficiencies may be found in Electronic Batch Records where steps are executed electronically
- Production and testing areas must have restricted access controls to authorized personnel – [212.40(d), 212.50]
- Document Control system [212.50, 212.60 & 212.70]
  - Lack of control of blank forms can result in data manipulation
  - Issuance of electronic batch record should be restricted to limited individuals

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Data Integrity and PET Drug Manufacturing

- Audit trails and review [212.60(g)(3) “complete records”; 212.50(a)]
  - Activation of all audit trails is required (exceptions for legacy systems)
  - Frequency of review should be based on risk
- Maintenance and storage of electronic records [212.110(b) “stored to prevent deterioration or loss”]
  - Metadata must be secured
  - Dynamic records must be maintained as originally obtained (e.g., HPLC and accompanying metadata)
  - Static records (e.g., printout from a balance)
- Raw test data (e.g., chromatograms, spectra) and any calculations need to be preserved [212.60(g)(3)]
- Personnel should be trained to prevent and detect data integrity issues [212.10]

*Reference: FDA Guidance for Industry — Reference: Data Integrity and Compliance With Drug CGMP, Questions and Answers, Dated December 2018*
Audit Trail Review
21 CFR 212.60(a)

- Audit trails are considered part of the associated records.

- Audit trails that capture changes to critical data...should be reviewed by firms:
  - A reasonable frequency of review for audit trails should be based on risk
  - This review should be ideally be performed by someone other than the person capturing the data

- Not every batch release requires audit trail review. Firms may be able to demonstrate a reasonable frequency of review

- Equipment exemptions for audit trails are applicable for legacy systems
  - Without an audit trail for legacy systems, operational and procedural controls should be established to ensure the reliability of the electronic data
  - Electronic data should still be reviewed for unexplained retesting, unjustified reprocessing, or unreported data

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Raw Data Access Controls
FDA 483

21 CFR 212.60(a)
Each laboratory used to conduct testing of PET drug products does not have and follow written procedures for the conduct of each test and the documentation of the results. Controls have not been established to restrict user access and data file access for the following:

- The Microsoft Excel spreadsheet is used for raw data entry (half-life parameters) and calculations. This spreadsheet is accessible to anyone with access to the network drive and has no restrictions to prevent alteration of cells containing formulas.

- The radionuclidic purity data generated by HPGe detector, has no controls. In addition to QC personnel, the equipment and software are used by university students with no access controls established.

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Loss of Raw Data
FDA 483

21 CFR 212.110(b)
All records including those not stored at your inspected establishment are not stored to prevent deterioration or loss. Electronic records are used, but there is no assurance they are complete. Specifically:

- When computers were updated from Windows 7 operating system to Windows 10, electronic data from the #### and #### software, which captured endotoxin test data for several batches of final drug product Injection, were lost.

- Additionally, the ###### software is incompatible with the Windows 10 operating system, so it can no longer be used.

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Some Closing Remarks…

- We are in a post COVID-19 era and the successful implementation of flexible regulatory frameworks during COVID-19 phase has helped us to evolve rapidly
- Alternate tools and best practices published as draft guidance will help the agency to facilitate efficient facility evaluations and approvals during application review
- We have observed great improvements in implementation of 21 CFR Part 212 regulations, but the changing landscape with newer PET drugs (e.g., PET drug kits and generators) may need additional controls and standards to ensure product quality
- Lack of Identity testing as an incoming acceptance test has been identified during pre-approval inspections in several PET drug facilities and it requires immediate corrective action by PET producers
- Clarifications on application related stability study requirements vs post approval annual stability studies and meeting CGMP requirements at each production facility will help PET drug producers to address the existing compliance gaps
- Data Integrity principles and its applicability during any manufacturing operations is one of the key objectives for pre-approval as well as surveillance inspections

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