Clarifying 21 CFR 212 and 211 – the Evolving Regulatory Landscape

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November 13, 2023

Clarifying 21 CFR 212 and 211 – the Evolving Regulatory Landscape

• Background for differences
• Historical perspective - What did FDA say?
• Other differences needing clarification
• Where are we going?
  (longer half lives, kit-based manufacturing approaches, generator produced PET radionuclides, larger molecules including biologics, and radionuclides with multiple emissions and the potential for therapeutic uses)
• Conclusions
Unique Characteristics of PET Drugs

- **Short shelf life** precludes proliferation of microorganisms
- **Shielding** defines workflow and allows safe handling by operators / healthcare providers
- **Active ingredient** does not cause a pharmacologic effect
- **Limited doses/batch** requires tens of 1000s of batches for national supply
- **100% sample size** for QC testing overcomes sterility test limitations (all vials tested)
- **Closed system** precludes exposure to unclassified air during manufacturing
- **Diagnostic agents** only used a limited number of times in a patient

What did FDA say?

Differences in CGMP Requirements:
PET 21 CFR part 212 vs. part 211

- Simplified organizational requirements
- Streamlined aseptic processing requirements
- Streamline QC requirements for components
- Self-verification, same person oversight for production, QC, and release where appropriate
- Specialized QC verification for sub-batches
Simplified Organizational requirements

- Fewer required personnel with fewer organizational restrictions consistent with the scope and complexity of operations
- Staffing levels
  - Correspond to the size and complexity of the operation
  - Enable the facility to complete all intended tasks in a timely manner before administration of a finished PET drug product to humans.
- We recommend that the responsibilities and assigned duties of all staff be clearly identified in written policies.

Streamlined aseptic processing requirements

- Each batch must be tested, and sterility testing must be started within 30 hours after completion of production (more than 30 acceptable if validated).
- Microbiological monitoring should be performed during sterility testing and aseptic manipulation.
- Media fills are used to simulate aseptic manipulations with operators requalified annually.
Streamlined QC requirements for components

- Organizations with more than one PET drug production facility could store and perform QC testing and approval of components at a centralized facility.
- Acceptance testing: COA with scientific rationale and supporting data as to why ID testing is not necessary for components that yield API.
- When the identity of the F 18 radionuclide is established as part of the finished-product testing, it is appropriate to use the COA without performing identity testing.
- For the production of a PET drug where the finished-product testing does not ensure that the correct components have been used, identity testing must be performed. When specific identity tests exist, we recommend that they be used.
- The inactive ingredients in PET drugs usually consist of a diluent, a stabilizer, and/or a preservative. If a product that is marketed as a finished drug product intended for intravenous administration is used as an inactive ingredient, it is not necessary to perform a specific identity test for that ingredient.

Self-verification, same person oversight for production, QC, and release where appropriate

- Under current CGMP regulations for conventional drug products in part 211, FDA normally requires second-person checks at various stages of production as well as test verification. In a PET drug production facility with only one person assigned to perform production and quality assurance tasks, it is recommended that that person recheck his or her own work.
Specialized QC verification for sub-batches

- **PET drugs that have a very short half-life (e.g., ammonia N 13) can be produced in multiple sub-batches on the same day.** Finished-product testing of the initial sub-batch can be conducted, provided a sufficient number of sub-batches (beginning, middle, and end) have been demonstrated to produce a product meeting the predetermined acceptance criteria. For routine production in this circumstance, the release of subsequent sub-batches can be qualified if the initial sub-batch meets all acceptance criteria. In certain cases, testing each sub-batch for certain attributes prior to release may be appropriate.

Other differences needing clarification

- **Stability testing – long standing FDA policy has been that site specific stability is not required as long as the manufacturing process is the same and uses the same synthesizer.**
  - Recently some reviewer and/or inspectors have been requesting site specific stability annually for each product
- **Annual Product Reviews – not explicitly required in 212.**
- **Does FDA recognize the use of Risk Management for PET Drugs?**
  - Embedded philosophy for 211
- **Aseptic Processing Guidance not designed for PET Drugs.**
- **Other guidance documents (e.g., CMO QA Agreements, etc.) don’t reference applicability to PET Drugs.**
Evolving Landscape of PET Radiotracers

**FDAMA**
- Non-kit based radiotracers (e.g., FDG, NaF, Ammonia)
- Pure positron-emitting radionuclides (i.e., diagnostic “nostic” only)
- Short half life (many small-scale manufacturing facilities needed)

**Today**
- Chelator-based radiotracers (i.e., kit-based)
- Non-pure positron emitters (i.e., therapy “thera” possibilities)
- Biologics
- Longer half life (potential for large-scale manufacturing)
- Kit-based “nostic” only radiotracers with generators (e.g., $^{68}$Ga)

Do we need to think beyond radioactive emissions to determine the appropriate GMPs?

Potential Regulatory Landscape

<table>
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<th>“Nostic” Short T$_{1/2}$</th>
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<th>“Thera” Long T$_{1/2}$</th>
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<td>Yes</td>
<td>212 FDP* 211 kit and “thera”</td>
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*Finished Drug Product
Open Questions

- Stability requirements for various combinations
- Facility qualification requirements
- Should half life be used to determine appropriate regulatory pathway?
- Is it more appropriate to regulate all finished PET drugs/biologics under 212? Too confusing for the industry to comply with separate regulatory pathways.

Unique Characteristics of Investigational PET Drugs

- $^{89}$Zr ImmunoPET
  - Mass of the injected compound plays a role
  - Regulatory guidance on the quality of the antibody precursor material may be needed
  - Production and characterization of conjugated material key intermediate is required
  - Longer final drug product shelf-life

Typical Academic PET Drug Producing Facility

Types of Operations Commonly Conducted
• Manufacture of one or several ANDA/NDA PET tracers.
• Reconstitution of cold $^{68}$Ga kits
• Manufacture of investigational PET tracers for Phase I and II.
• Manufacture of investigational radiotherapeutics for Phase I.

Commonly Shared Characteristics
• Regulatory compliance related experiences are shared freely
• Resources are limited, compared to industry
• Staff perform multiple functions
• Degree of operator scientific knowledge and training is generally higher, compared to industry
• The physical manufacturing process is the same for PET and non-PET, and will require changes should clinical development progress beyond Phase I.
• Investigational product production is sporadic and the number of batches is limited

Which Regulations/Standards may Academic PET Producers Rely On?

- PET:
  - Preclinical Stage: Drug Discovery, Non-Clinical Studies, Protocol Design, Clinical Translation
  - Clinical Investigation Stage: Exploratory IND, Phase I, Phase II, Phase III
  - Marketing Stage: NDA/ANDA
  - USP <823>
  - 21 CFR 212
  - USP <825>

- Non-PET:
  - 21 CFR 312
  - 21 CFR 210/211
  - USP <797>/<825>

- Nuclear Medicine/Pharmacy
  - 21 CFR 2012
Increased Commercial Interest In PET Companion Diagnostics from Pharma

Impactful Points of Discussion During Pharma QA Audits

- Analytical method validation requirements in Phase I
- Complete separation of worker roles
- Collection of retention samples
- Dedicated QMS and training system
- Materials acceptance process
  - COA review versus in-house testing
  - Use of non-compendial grade materials
- Media Fill Testing Study Design
- Equipment Vendor Validation Reports Verification
Conclusions

- The unique difference of PET continues to necessitate separate GMP regulations for PET Drug Manufacturing
- The existing regulatory framework supports new products
- FDA and PET community need to work together to determine applicability (212 vs 211)
- Consider using half life to determine appropriate regulatory pathway
- Path forward needs to be science and risk based (objective vs. subjective)