PET Drug Manufacturing:
Living in an FDA-Regulated World

PET GMP Compliance and Lessons Learned from FDA Inspections

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Introduction: Topics Covered

- cGMP Compliance items in ANDA submissions
- Pre-approval inspection process. (emphasis)
  - hot issues and successful resolutions
- Documents frequently requested by FDA
- Key items to ensure a successful inspection
- PET Drug 483 Observations
- Major Themes in 483 Observations
- Post-approval commitments

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The Process

- Submission of application (eCTD - defined topics: materials, processes, validations; *not* all your SOP's)
- Comments, questions, and requests from area reviewers (chemistry, microbiology, labeling, etc.)
- Responses to reviewers: submission of revisions
- Additional comments and revision as applicable

- ! Decision that application is Approvable - no more review comments, but not approved.

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The Process

- Pre-approval inspection
- Investigator comments/questions on site
- Close out meeting
- Investigator report – the dreaded *FDA Form 483* (it's a process, not a disaster!)
- Responses and amendments addressing 483 comments – correct observed deficiencies
- Followup with Agency
  - Discussion and adjustment of responses as applicable (21 CFR 211 vs. 212)
- !! Final approval of application !!

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The Application

- Contains details of the manufacturer and the process, definition of the product.
- Materials, criteria, tests, COA's
- Manufacturing Processes, Validations
- Quality control procedures, Validation
- Batch records and test results
- Content is well-defined; not much additional to discuss here.

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The Pre-Approval Inspection

- Investigator schedules visit and arrives.
- Investigators are looking for compliance with GMP for PET.
- Content is less well-defined than for the application.
- Investigator ***may*** not have your application or reviewer correspondence; may not know of reviewer agreements.
- Investigators are not all the same.

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Investigators: Hard and Soft GMP

- Concepts presented at previous annual meetings.
- **"Hard" GMP**: Clear objectives "No formal process verification is performed".
  - Easy to identify and anticipate
- **"Soft" GMP**: Interpretive, Subjective "Process Verification Does Not Demonstrate Consistency".
  - Hard to identify and anticipate
- Both types create opportunity for non-compliance allegations.
- Soft comments are most frequent, with greatest potential to cause 'regulation by inspection' and 'regulatory creep'.
- Hope: we can have GMP that is SAFE, needed, and avoid requiring more than is needed. Safety is historically excellent.

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Hot Spots for Compliance

- Environmental monitoring
- Sterility assurance
- Facility Management
- Process verification
- Deviations and OOS Investigations
- Corrective and Preventive Actions

Example: 3D Imaging LLC

- 483 with several observations, all answered, most minor (package variations, procedural details)
- Notably ***environmental monitoring*** of hot cells (touch plates).
  - Hot cells not monitored; synthesis apparatus sealed and fully self-contained.
  - History of operation with good quality products.
  - Written response and conference call with Agency.
  - Result: cell monitoring, but with experimentally determined action levels for hot cell touch plates, based on history and normal levels.

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Example: 3D Imaging LLC

- 483 observations read harshly “you are NOT…” This is a regulatory section-reference. The details are the key. What they mean is “address this item” Don’t panic, just fix it.
- FDA will work with you, they are ***most*** helpful.
- We saw some regulatory creep. Here last year[1] we learned to do daily temperature monitoring of sterility incubators. This year 37 degree *and* ‘room temperature’ incubators were required with continuous temperature monitoring.

Ghosh, K. “PET Drug Inspection” SNMMI Annual Meeting, Baltimore MD, June 9, 2015

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Comment on regulatory creep

- Some requirements are *known* with evidence in proof, to be irrelevant to product quality. (Wash procedure of hot cell enclosure).
- Required ‘safety’ measures because they can be done, not because they are needed.
- Though covered in the application and passed review, the inspection result is different.
- Complied with this regulatory creep because it was easier, but precedent is worrisome.

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Other Notable Examples

- The hot cell lacked air velocity, air changes, and smoke studies.
  - Get report from contractor

  This observation actually mis-applies laminar flow cell concepts to hot cells. Hot cells have a different purpose, to contain radioactive leaks from the sealed system.

  (Dispensing hot cells may be an exception)

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Other Notable Examples

- Observation: need visual inspection validations (clear, colorless, particulate-free).
  - Made standard vials for training – water and water contaminated with hair, septum bits, dye, alumina..

  Other examples as well: There remains a need to work with FDA toward true cGMP for PET – including what is needed and functional.

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Final Example Comment

- Many more examples can be condensed thus:
  - Write what you will do. THINK about this and do not specify details that could need to be adjusted.
  - Then DO what you write!!
  - If you then make changes – justify and record that in writing.

- If the observations catch you not doing what you wrote – do it immediately and keep it that way. Amend your procedures if necessary!!

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Inspection Conclusion

- Conduct a daily wrap-up (if possible) to understand areas of concern

- Take time at final close-out meeting to review Form 483 items:

  - Understand observations, assure their accuracy
  - Understand background to each observation.
  - Discuss any errors in observations, ask questions
  - Demonstrate awareness of regulations
  - Ask questions and understand observations for purposes of formal responses.

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Post Inspection Conclusion

- Respond to 483 formally in writing
  - Required within 15 business days
  - Conference with agency is possible

- Address response letters to District Director or Compliance Officer (as directed) and send a courtesy copy to lead investigator.

- Response may contain reasoned, supported objections to findings and alternatives for compliance.

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Key items for successful inspection

- Staff Preparation
  - Answer questions, ask for clarification/help if needed
- Ensure the site is clean (first impressions)
  - Remove unnecessary items (remove clutter)
- Plan ahead
  - Identify staff to perform key tasks for observation, particularly hotcell cleaning, closure (FPV) assembly and batch release.
- Have overview presentation ready
  - Organizational Structure, Products, Company Info, Quality System

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Key items for successful inspection

- Ensure staff is competent and well trained.
- Have clear SOPs and well-designed forms, and follow them.
- Ensure investigations are thorough and well documented (should address the root cause).

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Key items for successful inspection

- Utilize Corrective/Preventive Action(CAPA) System and meet your CAPA completion commitment dates.
- Have a strong Supplier Quality Program to assure suppliers are continually improving or not regressing.
- Have a strong Internal Audit Program to assure the manufacturing sites are continually improving or not regressing.

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Frequently Requested Items

- SOP Index
- Complaint SOP and Log
- Out of Specification (OOS) SOP and Log
- Deviation/Nonconformance SOP and Log
- Materials Control SOP
- Description of Quality Unit Responsibilities
- Training SOP and staff training records
- Aseptic Qualification SOPs and associated validations
- Process Validation
- Software Validation for Part 11 compliance

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Frequently Requested Items

- Calibration and Maintenance SOP
- Finished Product Specifications
- Batch Release SOP
- Supplier/Vendor Qualification SOP
- Annual Product Reviews
- Batch Records
- Product Test SOPs and records (all release tests)
- Method Validation Documentation
- Media Fill SOP and executed evidence
- Change Control SOP and Change Control Log
- Facility Layout
- Environmental Monitoring SOP and executed evidence

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Major PET Inspection Themes: 483's 2015

FDA Inspection System	# of Observations	Major Themes
Personnel and Resources	3	Inadequate Training ,Lack of resources
Quality Assurance	11	Procedures, change control, Investigations, failure to follow
Facilities and Equipment	5	Facilities, environmental monitoring, LAF Hoods
Components, Closures	2	Improper handling
Production and Process Controls	9	Clothing, Change Control, Process controls, documentation, environmental monitoring
Lab Controls	16	Inadequate Investigation, Procedures (or following them), Equipment, media fill
Finished Drug Product Controls and Acceptance	7	Failure to follow procedures, Inadequate Investigations, Inadequate documentation
Complaints, Distribution, Packaging/Labeling, Records	0	
Total	**53**	

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Don’t forget post-approval commitments

- § 314.80 Adverse Event Reporting
- § 314.81 Other post marketing reports
    - NDA Field Alert Report
    - Annual Report
    - Other (Advertising and Promotion - OPDP)