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
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.
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 !!
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.
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.
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.
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.
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 year¹ we learned to do daily temperature monitoring of sterility incubators. This year 37 degree *and* ‘room temperature’ incubators were required with continuous temperature monitoring.

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.
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)
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.
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!!
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.
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.
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
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).
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.
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
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
## Major PET Inspection Themes: 483’s 2015

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