You Submitted Your NDA/ANDA to the FDA; Now What?

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Almost

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How did we get here?

- Section 121(c)(1)(A) of the FDA Modernization Act of 1997 (Modernization Act) directed FDA to establish appropriate approval procedures and CGMP requirements for PET drugs.
- Sept. 2005 FDA published a proposed rule to establish CGMP requirements for PET Drugs.
- Final rule (21 CFR 212 (212 CGMP)) published Dec 10, 2009 - NDAs and ANDAs for PET drugs are required to be submitted by December 12, 2011
- Final Guidance published at the same time.
Timeline Challenges

• Community Meeting with the FDA March 2011

• Bracco Rb Generator Voluntary Recall
  – July 2011
  – Shift to $^{13}\text{NH}_3$ for MPI
  – Early discussions with FDA
    • Verbal agreement to postpone $\text{NH}_3$ NDA/ANDA submission

• FDA had received requests, from PET Drug producers attempting to comply, to extend the application deadline
The Latest News

• On December 6, 2012 FDA issued the following statement:
  – For the next six months, until June 12, 2012, FDA does not intend to take enforcement action against a PET facility currently producing PET drugs for clinical use for a failure to submit a new drug application by December 12, 2011, provided that the facility complies with all other FDA requirements, including current good manufacturing practices (CGMPs). FDA will not exercise enforcement discretion after June 12, 2012.

• Total compliance by December 15, 2015

• All studies covered by RDRC/ IND/ ANDA/ NDA
Post Submission

- Changes in equipment or facilities
- Inspections
- Fees
Changes in Equipment/Facilities

• Add or replace production equipment described in the application before NDA/ANDA approval
• Add an additional production facility before NDA/ANDA approval
• Add or replace production equipment under an approved NDA/ANDA
• Add an additional production facility under an approved NDA/ANDA
Add/Replace Equipment Before PAI

• Equipment identical
  – No application supplement needed
  – Validation data audited during inspection

• Equipment different – no formulation/strength change
  – Amend application describing new equipment, procedures and validation data
  – May initiate production for clinical use while application is pending
Add/Replace Equipment Before PAI

• Equipment and procedures are different with a change in strength or formulation
  – Cannot change formulation or strength in ANDA
  – May change exception excipients (buffers, preservatives or antioxidants)
    • Amend application, describe equipment, procedures, excipient changes with validation data
    • May initiate production for clinical use while application is pending
  – Change in formulation from the RLD requires a new NDA/ANDA
  – Change in strength requires NDA or suitability petition and new ANDA
Add New Facility Before PAI

- Equipment identical or Equipment different – no formulation/strength change
  - Amend application
  - Describe new facility
  - New CMC data for drug produced
  - May initiate production for clinical use while application is pending
Add New Facility Before PAI

• Equipment and procedures are different with a change in strength or formulation
  – Cannot change formulation or strength in ANDA
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Add/Replace Equipment After Approval

• Equipment identical
  – No application supplement needed
  – Validation data audited during inspection
  – Provide information in annual report

• Equipment different – no formulation/strength change
  – Submit supplement (21 CFR 314.70) describing new equipment, procedures and validation data
  – May not begin production for clinical use until the supplement has been approved
Add/Replace Equipment After Approval

• Equipment and procedures are different with a change in strength or formulation
  – Submit supplement (21 CFR 314.70) describing new equipment, procedures and validation data
  – May not begin production for clinical use until the supplement has been approved
Add New Facility After approval

- Equipment identical or Equipment different – no formulation/strength change
  - Submit supplement (21 CFR 314.70) describing new production facility
  - Provide new CMC for the drug produced
  - May not begin production for clinical use until the supplement has been approved
Add New Facility After Approval

• Equipment and procedures are different with a change in strength or formulation
  – Submit supplement (21 CFR 314.70) describing new production facility
  – Provide new CMC for the drug produced
  – May not begin production for clinical use until the supplement has been approved
Inspections

• Training of FDA inspectors in PET drug CGMP has been completed

• PET drug inspection program (CPGM) has been written to guide the inspectors
Compliance Program Guidance Manual

FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM GUIDANCE MANUAL

PROGRAM 7356.002P

CHAPTER 56 - DRUG QUALITY ASSURANCE

SUBJECT:
POSITRON EMISSION TOMOGRAPHY (PET)
CGMP DRUG PROCESS AND PRE-APPROVAL INSPECTIONS/INVESTIGATIONS

IMPLEMENTATION DATE
12/12/2011

COMPLETION DATE
12/11/2014

REF: 7356.002 (2/01/2002) and 7346.832 (5/10/2010)

DATA REPORTING

<table>
<thead>
<tr>
<th>PRODUCT CODES</th>
<th>PROGRAM ASSIGNMENT CODES</th>
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<tr>
<td>All PET Drugs</td>
<td>56002P Drug Process Inspections (PET)</td>
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<tr>
<td>Industry code: 65</td>
<td>46832P Positron Emission Tomography (PET) Pre-Approval Inspections/Investigations (NDA)</td>
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<td>Profile Class code: PET</td>
<td>52832P Positron Emission Tomography (PET) Pre-Approval Inspections/Investigations (ANDA)</td>
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Types of Inspections

• Pre-approval inspections

• Routine surveillance CGMP inspections of facilities
  – 2 year frequency

• Compliance inspections
  – Follow-up inspections post regulatory actions (e.g. Warning letter)
  – For-cause inspections
Inspection Systems

• Quality system with aseptic sterility controls
• Facilities and Equipment system
• Materials system
• Production system
• Packaging and Labeling system
• Laboratory Control system
Full/ Abbreviated Inspection

• Full inspection
  – At least 4 systems reviewed
  – Initial site inspection
  – Regulatory action followup
  – Significant manufacturing changes
  – Microbial contamination
  – Poor compliance history
  – Every 2 years

• Abbreviated inspection
  – At least 2 systems
  – Adequate compliance history
  – Previous inspection for similar drug product

• All inspection include quality system and aseptic sterility
Initial Inspection Findings

• Lack of assurance that the drug is sterile and non-pyrogenic

• Lack of microbiological controls

• Lack of assurance that test results are reliable and accurate

• Inadequate training and QA/QC Oversight

• Inadequate documentation
Sterile and Non-pyrologic Assurance

- No simulated media fills performed
- Growth promotion not done for media fills
- Deficient sterility test
  - Hold time not validated
  - Growth promotion of media not performed
  - Inadequate storage of media
  - Inadequate incubation temperature control
  - Automatic re-test without investigation

- Inadequate endotoxin test
  - Shorter time of gel clot assay without prior validation

FDA PET Drug Webinar January 2012
Lack of Microbiological Controls

• Aseptic workstation not suitable for aseptic operations
• Use of non-sterile disinfectant to sanitize aseptic workstation and product contact surfaces
• Frequency of environmental monitoring does not reflect the intensity of manufacturing operation
Lack of assurance of reliable & accurate test results

- Production synthesizer & QC equipment
  - Not qualified for use
  - Not calibrated or maintained

- System suitability not performed on QC analytical equipment

- Inadequate reference standards used
Inadequate training and QA/QC Oversight

- Failure to train personnel to perform assigned tasks
- Failure to conduct investigation of failed batches and deviations
- Failure to audit at a regular basis and update procedures
- Allowing release of
  - failed and questionable batches
  - batches that have not completed all required USP end-product tests
Fees

• PDUFA
  – Prescription Drug Users Fee Act
• GDUFA
  – Generic Drug Users Fee Amendments Act
PDUFA

- First enacted in 1992
- Renewed every 5 years
- Current version: PDUFA IV signed Sept. 2007
- Allows FDA to collect fees from drug manufacturers to fund the new drug approval process
- PDUFA V in Congress now
  - Includes language about application submissions
    - Require all applications in eCTD format
    - IND/ANDA/NDA
    - Need to educate everyone so we can comply
    - Cost?
PDUFA (2)

- **Basic Fee Structure for PET Drug Manufacturers**
  - NDA requiring clinical data: $1,841,500
  - NDA not requiring clinical data: $920,750
  - Establishment Fees: $86,685
    - 1/6\(^{th}\) full fee
  - Product Fee: $98,970

- **Waivers available**

- **ANDAs are exempt from fees**
• Generic Drug User Fee Amendments of 2012
• Statutory Language 1/12/12
  – Submission of an application for a positron emission tomography drug or active pharmaceutical ingredient for a positron emission tomography drug shall not require the payment of any fee under this section. Facilities that solely produce positron emission tomography drugs shall not be required to pay a facility fee as established in subsection (a)(4). Facilities that produce positron emission tomography drugs or active pharmaceutical ingredients of such drugs are required to be identified pursuant to subsection (f).
Where do we go from here?

• The review process has started.
  – One site has already been contacted by the FDA to answer some questions
  – Initial feedback
    • Applications look different
    • Content seems OK
• More guidance documentation to arrive soon from FDA
  – IND
  – Q&A for items raised in March 2011
• If you are using FDG or NaF produced by another manufacturer for any studies – make sure that the manufacturer has submitted a NDA/ANDA or holds a NDA/ANDA
Coalition for PET Drug Approval

http://coalitionforpetdrugapproval.org/

Janette Merrill
Hey, everyone! I think I found the bottleneck!