



Current Good Manufacturing Practice for PET Drugs - CGMP 21 CFR 212

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PET Drugs Regulatory Framework

- PET CGMP regulation is effective December 12, 2011.
- Starting on this date, FDA will require the submission of a new drug application (NDA) or abbreviated new drug application (ANDA) for any PET drug product in clinical use (as opposed to research or investigational) in the United States.



History of PET CGMP Rule

- Public meeting.....February 19, 1999
- Preliminary draft regulations.....September 21, 1999
- Public meeting.....September 28, 1999
- Preliminary Draft Proposed Rule.....April 1, 2002
- Draft Guidance PET Drug Product-CGMP.....April 1, 2002
- Public meeting on PET CGMP.....May 21, 2002
- Issuance: Proposed Rule/Draft Guidance.....Sept 20, 2005
- CGMP Final Rule.....December 10, 2009



What are CGMPs for PET drugs?

Current good manufacturing practices for PET drug products are the minimum requirements for the methods to be used in, and the facilities and controls used for, the production, quality control, holding, or distribution of a safe and effective PET drug product intended for human use.



PET CGMP Regulations

- Exceptions:
 - Provisions of USP Chapter <823> apply when PET drugs are produced under,
 - Investigational New Drug Application (IND)
 - Radioactive Drug Research Committee (RDRC)
 - Option to follow the requirements in part 212 **or** to produce PET drugs in accordance with USP Chapter <823> “Radiopharmaceuticals for Positron Emission Tomography— Compounding,” (USP 32/NF 27) (2009)
 - IND and RDRC holders are not required to register and list PET drugs.



PET CGMP Regulations , continued

FDA also announced in the Federal Register of December 10, 2009 (74 FR 65409) the availability of a guidance entitled,

- “PET Drugs—Current Good Manufacturing Practice (CGMP)”
- Intended to help PET drug producers better understand FDA’s thinking regarding compliance with the new PET CGMP requirements.



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



Objectives in developing CGMP for PET Drugs

- Safeguards to assure safety, identity, strength, quality and purity of PET drugs
- Quality built into production process
- Sufficiently flexible to accommodate all PET production, without unreasonable regulatory burden
- Mechanisms to proactively identify potential problems, eliminate them, and promote continuous improvement



Major Elements in PET Drug CGMPs

1. Personnel and Resources **[212.10]**
2. Quality Assurance **[212.20]**
3. Facilities and Equipment **[212.30]**
4. Control of Components, Containers, and Closures **[212.40]**
5. Production and Process Controls **[212.50]**



Major Elements, continued

6. Laboratory Controls **[212.60]**
7. Drug Product Controls and Acceptance criteria **[212.70]**
8. Packaging and Labeling controls **[212.80]**
9. Distribution controls **[212.90]**
10. Complaint Handling **[212.100]**
11. Record keeping **[212.110]**



Personnel and Resources – [212.10]

- Sufficient number of qualified and trained personnel to perform their assigned tasks.
 - Facilities where few individuals are employed, one individual can be assigned to perform both production and quality assurance tasks.
- Sufficient resources including equipment and facilities to produce a quality PET drug.



Quality Assurance – [212.20]

- Person or organizational element responsible for the duties relating to quality control.
- Oversees production operations to ensure that a quality PET drug is produced.
- Examines and approves or rejects components, containers, closures and the finished PET drug.
- Approves or rejects procedures and/or specifications.



Quality Assurance, continued

- Reviews production records for accuracy & completeness.
- Ensures that investigations have been conducted and corrective action taken.
- It's possible for a certain part of the QA function to be at a centralized off-site location, however batch release must be signed off on-site by a responsible QA individual.



Facilities and Equipment – [212.30]

- Equipment: clean, suitable for its intended purposes, properly installed and maintained.
- Facilities: adequate to assure the orderly handling of materials and equipment, prevent mix-ups and contamination of equipment and the PET drug.



Control of Components, Containers, and Closures – [212.40]

- Procedures for the handling of components.
- Establish appropriate specifications, and examine each lot upon receipt with established specifications.
- Each lot must meet all established specifications to be used in production.
- Instead of full testing, a certificate of analysis (COA) may be accepted provided the PET center establishes the reliability of test results.



Production & Process Controls – [212.50]

- Ensure consistent and quality production
- Establish written procedures, master and batch production and control records.
- Include inspection of the production area and all equipment for suitability and cleanliness before use.
- Process verification results must be documented when the production batch is not fully verified through finished product testing.



Production & Process Controls, cont.

- Prepare batch production and control record for each batch of PET drug produced.
- Batch record should include the critical production steps and test results
- Deviations from established procedures must be investigated and documented
- The process must be validated.



Laboratory Controls – [212.60]

- Follow written procedures and document each laboratory test results.
- Analytical methods should be suitable, sensitive, specific, accurate, and reproducible.
- Control the identity, purity and quality of reagents, solutions and supplies used in testing procedures.
- All testing equipment must be suitable for its intended purpose and capable of producing valid results.



Laboratory Controls, cont.

- Test records
 - a complete description of the sample received
 - a reference to the method used
 - raw data: including charts, graphs and calculations
 - results: pass or fail acceptance criteria
 - initials or signature of the person performing the test
- Program to assess the stability a PET drug, including suitable storage conditions, use of reliable and specific test methods, and expiration dates/ times.



Drug Product Controls and Acceptance Criteria – [212.70]

- Sterility testing must be performed but need not be completed prior to drug product release.
 - Must begin < 30 hrs after completion of PET production
- Establish procedures for release:
 - complete laboratory testing and review data
 - release authorized by designated person
- Each batch must meet its established acceptance criteria prior to release.
 - If product does not meet acceptance criteria: reject product; conduct investigation and take action to correct any identified problems.

DP Controls: Conditional Release – [212.70(f)]

- Conditional release applies, if one finished product test¹ cannot be completed due to an analytical equipment malfunction, when the following conditions are met:
 - Prior history must demonstrate that the final release of the product will meet the established specifications.
 - Immediate corrective action of the malfunctioning analytical equipment.
 - The performance of the product identity, purity, and specific activity must be verifiable
 - No addition batches of product can be released until the problem is corrected and the omitted finished product test is reinstated.

¹All other finished product acceptance criteria must be met. Document all actions that justify the conditional release of product.



Packaging & Labeling Controls – [212.80]

- Packaging and shipping containers should protect against damage during storage, handling, distribution, and use.
- In part, the label should also contain the product name, strength, batch number, date/time prepared, expiration date/time.
- Operations should be controlled to prevent mix-ups.
- Labels must be legible.



Distribution Controls – [212.90]

- Drug products should be shipped in accordance with labeling conditions.
- Establish and follow procedures if the drug is distributed or shipped.
- Keep adequate distribution records
 - The chain of distribution of each batch of drug product must be readily determined to permit its recall if necessary.

Complaint Handling – [212.100]

- Establish procedures to handle complaints pertaining to the quality and labeling, or possible adverse reactions.
 - A written record of each complaint, the investigational findings, and follow-up must be maintained.
 - A drug returned due to a complaint must be destroyed.
 - Corrective action should be taken immediately if there is reason to believe that an adulterated drug was implicated in the complaint.
- Written complaint records must include:
 - drug name, strength
 - batch number
 - date and nature of complaint
 - response to complaint
 - findings of investigation, follow-up



Record Keeping – [212.110]

- Maintain records at location that is reasonably accessible.
- Keep records for 1 year from the date of drug product release.
- Records to include:
 - Composition and quality,
 - Production operations, batch records, and out-of-specifications
 - Distribution and complaints.
- Records: legible and readily available for review and copying by FDA.



PET Drug Inspections

- Pre-approval inspections
 - For new NDAs and ANDAs
- CGMP inspections of facilities
 - Every 2 years, as resources & priorities allow
- For-cause inspections



PET Drug Inspections, continued

- The Agency will have an inspectorate cadre of trained investigators in PET CGMPs by 2011.
- District Offices will have a trained investigator.
- Inspections performed by an established program.
- CDER will endeavor to increasing inspection coverage as we approach 2011 and thereafter on a more routine, biennial basis after 2011.
- CDER will maintain subject matter contacts to give guidance and to review cases for administrative/regulatory action.



PET Inspection Outstanding Issues

1. Lack of assurance that the drug is sterile and non-pyrogenic
2. Lack of microbiological controls
3. Lack of assurance that test results are reliable and accurate
4. Inadequate training and QA/QC Oversight
5. Inadequate documentation

1. Lack of assurance of sterility

- 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



2. 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

3. 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

4. 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



5. Inadequate Documentation

- Inadequate batch records
- Inadequate QC records



Drug Registration and Listing of PET Drug Producers

- All PET drug producers are required to register/list now.
- Submit drug establishment and drug listing information through electronic submissions
- Website for information
 - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default.htm>



Questions - ?

FDA Positron Emission Tomography (PET)

Web page -

[http://www.fda.gov/Drugs/DevelopmentApprovalProcess/
Manufacturing/ucm085783.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm)

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