



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

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# PET Drug GMP

- CGMP regulations for PET drugs can be found at 21 CFR 212
- All PET drug producers must register and list under 21 CFR 207
  - Submit drug establishment and drug listing information through electronic submissions
  - Website for information
    - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default.htm>

# 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.

# Guidance to PET CGMP Regulations

*“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.

# Useful PET CGMP References

## FDA website for PET drugs

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm>

- Federal Register Notice: Final Rule- CGMP for PET Drugs
- [PET Drug Products - Current Good Manufacturing Practice \(CGMP\)](#)
- [Positron Emission Tomography \(PET\): Questions and Answers about CGMP Regulations for PET Drugs](#)
- [Positron Emission Tomography \(PET\): Additional Questions and Answers Based on December 9, 2009 Stakeholder Call](#)
- Media Fills for Validation of Aseptic Preparations for Positron Emission Tomography
- CPGM: PET CGMP Drug Process and Pre-approval Inspections/Investigations
- FAQ Guidance

# 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.

# 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

# 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

# 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**]

# **GMP Systems**

1. Quality system with aseptic sterility controls
2. Facilities and Equipment system
3. Materials system
4. Production system
5. Packaging and Labeling system
6. Laboratory Control system



# Quality System

## 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, facilities and personnel 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.
- Approves change control.
- Oversees complaints, adverse reactions.
- 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.

# 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



# Aseptic Processing & Microbial Controls

## References

CP7356.002P

21CFR212

Guidance for PET Drug CGMP

Media fill for PET drugs

# Holistic Approach to Aseptic Processing Controls

- Personnel training and implementation of aseptic techniques
- Appropriate facility and equipment design
- Process that mitigates risk of contamination
  - *Work flow*
- Environmental controls/ monitoring
- Sterilization process
  - *Filter sterilization*

# Personnel Training

- Aseptic assembly of the bulk product vial (BPV)
- Aseptic manipulations in the hot cell
- Addition of diluents and withdrawal of QC samples

# Facility Design

The design of PET facilities varies:

- Cleanroom design
  - Class 100: Aseptic isolator or LAFW
  - Qualification: normally static
- LAFW and hot cell in separate room or in the same room
- Environmental controls of the surrounding area of the LAFH should be at minimum clean and controlled

# Laminar Air Flow Workbench (LAPW) Production Activities

- Aseptic assembly of BPV (bulk product vial)
- BPV dilution
- Withdrawal of QC samples
- Sterility test
- Subdivision of BPV into multi-dose vials

*\*cleaning and sanitization: use of sterile disinfectant*

# Activities in the Hot Cell

- Chemical synthesis and purification of the PET drug
- Sterile filtration of the drug into the BPV
- Dilution of the bulk drug\*
- Withdrawal of QC samples\*

*\*Preferably be done in LAFW*

## *Environmental control in the hot cell?*

- *While may be unclassified, but should be a controlled and clean area, non-clustered*

# Environmental Controls/ Monitoring

## EM controls:

- Classified
- Clean/ controlled

## EM monitoring:

- Settle plates
- Contact plates
- Active air samplers
- Personnel

\* *When to monitor?*

\* *Frequency?*

# Sterilizing Filters

- Determining the integrity of the membrane filter used for sterilization.
  - Document filter integral for batch production
  - Establish and follow procedures in response to a filter that fails post-filtration testing.

# Aseptic Processing Qualification: Media Fills

- The objective of conducting media fill is to demonstrate that you are capable of producing a sterile drug by aseptic processing.

*FDA Guidance: “The media fill should evaluate the aseptic assembly and operation of the critical (sterile) equipment, qualify the operator, and demonstrate that the environmental controls are adequate to meet the basic requirements necessary to produce a sterile drug by aseptic processing.”*

- Does your media fill simulate routine production process and incorporate all the contamination risk?

# Media Fills, continued

- Simulation of production process includes:
  - Same production personnel
  - Same environmental conditions
  - Same operations, including size of vials; # of vials and volume/batch; dilution; withdrawal of QC samples
- Media used
- Positive controls
- Incubation periods and temperature
- Investigation on failed media fill; contaminant identification

# Qualification of Commercially Available Microbiological Media

- Vendor
  - Qualified by 3 batches
  - Use only qualified vendor
- Periodic qualification
  - Suitable for use
- Incoming commercially prepared media
  - Confirm identity and physical integrity
  - Use within the label's shelf life
  - Store according to label's recommendation

# **Sterility Testing**

## **21CFR 212.70(e)**

- Testing required within 30 hours
- Extension allowed (validation needed)
- Testing samples (individual, not pooled)
- Report sterility failure
- Document sterility failure
- Conduct investigation
- Notify receiving facilities

# Bacterial Endotoxin Testing

- Product conforms to endotoxin specification BEFORE final release
- Reference USP <85> or method established in drug application
- Methods
  - Materials
  - Controls
  - Suitability test



# Facility and Equipment System



## **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.



# Materials System

# 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.
- Use qualified vendors

# Recycling of O18 water

- Establish procedure for the recycling and specification of the recycled O18 water
- Use O18 water of acceptable quality



# Production System

# 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.



# Packaging and Labeling system

# 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.



# Laboratory Control System

# 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.

# Conditional Release – [212.70(f)]

- Conditional release is permitted, if one finished product test<sup>1</sup> cannot be completed due to an analytical equipment malfunction, when the following conditions are met:
  - Prior history demonstrates that the final release of the product will meet the established specifications.
  - The malfunctioning analytical equipment is immediately fixed or replaced.
  - Product identity, purity, and specific activity are verified.
  - No additional batches of product are released until the problem is corrected and the omitted finished product test is reinstated.

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

## 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.

## 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-specification results
  - Distribution and complaints.
- Records: legible and readily available for review and copying by FDA.



# PET Drug Inspection

# PET Drug Inspections

- Pre-approval inspections
  - For new NDAs and ANDAs
- Routine surveillance CGMP inspections of facilities
  - Every 2 years, as resources & priorities allow
- Compliance inspections
  - Follow-up inspections post regulatory actions (e.g. Warning letter)
  - For-cause inspections

# PET Drug Inspections, continued

- The Agency has completed the training of FDA investigators in PET drug CGMP for the inspection of PET drug facilities.
- Inspections to be performed in accordance with the PET drug inspection program (CPGM).
- For the foreseeable future, CDER will closely monitor all PET drug inspections.
- CDER will provide subject matter contacts and guidance to inspectors.
- CDER is responsible to review cases for administrative/regulatory action.

# Inspection Approaches

## System based inspections

1. Quality system with aseptic sterility controls
2. Facilities and Equipment system
3. Materials system
4. Production system
5. Packaging and Labeling system
6. Laboratory Control system

# Selection of Inspection Coverage

- Full inspection (at least 4 systems)
    - Firm has never been inspected
    - Follow up to regulatory action
    - Significant manufacturing changes
    - Microbial contamination or cross-contamination
    - Poor compliance history
    - Biennial inspection
  - Abbreviated inspection (at least 2 systems)
    - Adequate compliance history
    - Firm has been inspected for similar class of product
- \*\*Inspection of quality system and aseptic sterility controls are mandatory for both full and abbreviated inspections*



# PET Inspection Observations

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

# Questions - ?

## FDA Positron Emission Tomography (PET)

Web page -

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

CGMP contacts

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