USP Chapter 823

USP 32 (old) vs. USP 35 (new)

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Why USP Chapter <823>?

- FDA has allowed USP Chapter <823> to constitute CGMP standards for investigational and research PET drugs to “allow more flexibility during the development of these drugs”

- Provisions in <823> are generally less specific and explicit than the requirements in Part 212

- Provisions in <823> are “adequate to ensure that investigational and research PET drugs are produced safely under appropriate conditions”

- “…appropriate CGMP requirements for the investigational and research stage of development”
Why are Research/Investigational PET Radiopharmaceuticals Treated Differently?

- Majority of investigational and research PET radiopharmaceuticals (IND and RDRC regulated PET drugs) do not have commercial potential

- It is not necessary to subject these radiopharmaceuticals to the stipulations of Part 212 which are more appropriate for approved or late investigational phase PET radiopharmaceuticals
“To Market…”

• Once a PET radiopharmaceutical producer intends to seek marketing approval for their PET drug or a new indication, an NDA or ANDA will be required.

• Investigational radiopharmaceuticals under IND Phase 3 studies should be in compliance with Part 212
Better Compliance is the Goal of the FDA

- For this reason the FDA permits producers of investigational and research PET to choose Chapter <823> or Part 212 for meeting CGMP requirements.

- The FDA specifically mentions that because “most PET drug producers are very familiar with the requirements in Chapter <823>, allowing producers to meet the CGMP requirements for investigational and research PET drugs by following Chapter <823> should greatly facilitate producers’ compliance with the CGMP requirements.”
USP Chapter <823> Revision

Old Title
- CHAPTER <823> RADIOPHARMACEUTICALS FOR POSITRON EMISSION TOMOGRAPHY—COMPOUNDING

New Title
- CHAPTER <823> POSITRON EMISSION TOMOGRAPHY DRUGS FOR COMPOUNDING, INVESTIGATIONAL AND RESEARCH USES
Scope of the Chapter

- Production & compounding of PET drug products for human administration
  
  (a) according to state-regulated practice of medicine & pharmacy
  
  (b) IND (21 CFR 312)
  
  (c) RDRC (21 CFR 361.1)

- Scope of the does not include dispensing
Chapter <823> Revision

- Proposed Chapter <823> released 11/24/10
- Public comment period was 11/24/10 to 3/31/11
- Final Revision published 9/2011 on USP hot topics page

- www.usp.org/hottopics/uspGeneralChapter823.html

- Revised Chapter <823> becomes effective May 1, 2012

- USP has petitioned FDA for rulemaking to amend 21 CFR Part 212 to refer to general chapter <823> in *USP 35-NF 30*
Why revise Chapter <823>?

- Technology, marketplace, and regulatory changes have occurred since the original publication.

- Chapter has been revised in entirety to represent current compendial thinking about the preparation of PET drugs as well to reflect FDA 21 CFR Part 212.
Revision Goals

• To provide more flexibility in the production of PET drugs for investigational and research uses

• Appropriate provisions have been written in the revised Chapter <823> to ensure drug identity, strength, quality, purity, and patient safety
Chapter 823

- The revised chapter 823 is organized into sections that reflect organization of 21 CFR Part 212

- The changes will serve the needs of patients, research subjects, medical institutions, clinical researchers, pharmaceutical companies, commercial PET drug producers, and all members of the PET community
Future Enhancements

• Future potential changes in general chapters will provide additional information—descriptions of certain concepts, technologies, and procedures related to PET drugs e.g. addition of Chapter <1823> Radioactivity, and revision of Chapter <821> Identification & Assay of Radionuclides
Revised Chapter <823>
Positron Emission Tomography Drugs For Compounding, Investigational, And Research Uses

Sections reflect organizational layout of 21 CFR 212

1. Definitions
2. Personnel
3. Quality Assurance
4. Facilities and Equipment
5. Control of Components, Materials, and Supplies
6. Process and Operational Controls
7. Stability
8. Controls and Acceptance Criteria for Finished PET Drug Products
9. If a PET Drug Does Not Conform to Specifications
10. Reprocessing
11. Labeling and Packaging
DEFINITIONS

• Line Clearance: segregation and cleaning of different processing and work areas to avoid cross-contamination

• Manufacturer’s Certification: includes (but not limited to) COA, COC, COQ...describes quality characteristics

• Strength: amount of radioactivity per volume at the time of calibration (e.g. mCi/mL [MBq/mL])
Number of Personnel:
Number and size depends on complexity

Training Requirements:

1. Personnel trained before they begin to make and test PET drug products
2. Training can be performed by various methods…
   ✓ Live instruction, audio-video, publications
   ✓ Radionuclide production techniques
   ✓ Materials, components, reagents, stock solutions
   ✓ Synthetic and purification methods
   ✓ Quality control (QC) methods
   ✓ Equipment & computers for synthesis and QC
   ✓ Aseptic operations

3. Training must be documented
Aseptic Operations Training

- Include aseptic manipulations as well as techniques & equipment used to achieve ISO Class 5 environmental conditions

- Include all manipulations required for the aseptic assembly of PET drug vial assembly (vial, filter, syringe assembly & filtration)
Aseptic Operations Training

- Evaluate periodically by observation &
- Microbiological Tests (aseptic simulations)
  - Include all manipulations required for assembly of final product vial assembly
  - Represent worst-case scenarios
  - New operator: Pass 3 separate aseptic simulation procedures
  - Annually for personnel who currently prepare (compound)
  - Any time procedures are changed significantly
  - If aseptic simulation results in microbial growth, reinstruct personnel & re-evaluate
QUALITY ASSURANCE (QA)

• QA is a broad concept that covers all matters that influence identity, strength, quality & purity of a PET drug product. Quality Control (QC) is a subset of QA.

• QC functions
  ✓ Evaluate each lot of incoming material
  ✓ Evaluate each batch of a PET drug product to ensure the batch meets its established specifications

• QA functions
  ✓ Review and approve
  ✓ Investigate problems
  ✓ Handle complaints
  ✓ Conduct audits

• Personnel may perform both QA and QC functions
FACILITIES AND EQUIPMENT

1. Facilities must be adequate
2. Work area organized to prevent contamination or mix-ups
3. Work area periodically cleaned
4. Requirements described in written procedures AND execution should be documented
Environmental Control for Parenteral PET Drug Products

**Aseptic Workstation**

1. Primary environmental control–ISO Class 5 HEPA filtered environment (e.g. laminar airflow workstation [LAW])
2. Aseptic workstation located in low traffic area
3. Certification at inception & at least annually
4. Clean & disinfect using disinfectants that are sterile filtered or those certified sterile from the manufacturer
Microbiological Testing

1. Air Quality: periodically
   - asses by settling plates or active air-sampling device
   - (e.g. every 6 months)

2. Surfaces: after each use
   - Swabs or contact plates for surfaces (work surfaces or fingertips)

3. Testing for non-viable particles performed during annual certification

4. Alert and action limits should be established
   - Typical alert levels set at
     - 3 colony-forming units (cfus) per plate
   - > 3 cfus require corrective actions
Installation of New Equipment

- Production and QC equipment should be qualified before use
- Qualification should be at an appropriate level of detail based on complexity
- Qualification should be documented, including the date and the name of the person who performed the qualification
- Consists of three phases:
  - Installation Qualification (IQ)
  - Operational Qualification (OQ)
  - Performance Qualification (PQ)
Cleaning Equipment & Components

- Equipment used in production must be cleaned before use
- Written procedures should describe line clearance & cleaning between batches of different PET drugs
- Equipment may be used to make multiple batches with cleaning between batches
  - Documented studies should demonstrate the effectiveness of the cleaning process between batches
Day-of-Use Checks

• Ensure proper equipment function
  – Written procedures should check key parameters
  – Examples: temperature, pressure integrity, gas supply, vacuum supply, proper delivery line selection, …radiation monitors
System Suitability for QC Equipment

- Used to verify the resolution & reproducibility of QC system
- Written procedures established & results documented
- Tests required include tailing factor, replicate injections & resolution

**Two acceptable approaches**—

- Create a calibration curve from a range of standards
  - Routine system suitability is a single standard injection
  - Tailing factor and resolution (or column efficiency) determined from the same chromatogram.

- Create a single-point calibration from two standard injections
  - Average used as calibration factor for subsequent injections
  - Tailing factor and resolution (or column efficiency) determined from one of the two chromatograms
System Suitability for QC Equipment

Other QC equipment:

1. **Dose Calibrator**—constancy check with a suitable high-energy radionuclide source

2. **Radio-TLC Scanner**—uniformity, positional accuracy, detector linearity & resolution should be assessed with a suitable radionuclide source

3. **MCA**—constancy check with a suitable high-energy radionuclide source
CONTROL OF COMPONENTS, MATERIALS AND SUPPLIES

• Establish written specifications for each PET drug component
  ✓ Identity, purity & quality
  ✓ Appropriate storage
• Log-in each lot of shipments of components; if no expiration date specified, must assign one
• Determine each batch of components is in compliance with written specifications (procedures, tests, and/or certificates of analysis)
• Store components in controlled access area according to established conditions.
Control of Components…

Raw Materials Specifications:
Receipt & Release (green sticker)

Quarantine Refrigerator

Lab Supplies

Controlled Storage

Production
CONTROL OF COMPONENTS, MATERIALS AND SUPPLIES

• **Precursors**: identity test or COA if final testing of PET drug to ensure that correct precursor received.

• **Reference standards**—requires suitable documentation of purity & identity

• **Media used in sterility testing**
  – Obtained from commercial sources
  – Growth-promotion testing that employs a suitable single species or organism should be performed on initial qualification of the supplier and periodically (e.g. quarterly) thereafter
PROCESS & OPERATIONAL CONTROLS

Process Controls: The following process controls should be established & summarized in a master formula for the PET drug.

1. Written acceptance criteria
2. Written procedures for preparation each PET drug
   a) Parenteral PET drug—0.22 µm sterile filtration
   b) Inhalation PET drug—0.45 µm particulate filtration
   c) Cleaning procedures for equipment & facilities
   d) Describe components, materials & supplies
   e) Describe process & steps to make PET drug
   f) Describe formulation
   g) Describe calculations (e.g. yield, specific activity)
   h) Describe QC tests & schedule
Operational Controls: batch record should establish & summarize:

1. Execute suitable line clearance procedures
2. Lot numbers of components
3. Description of procedures
4. Initials or signature of individual assuring steps completed
5. Percent yield
6. Raw data
7. Labeling
8. Calculations performed for key parameters
9. QC test results and initials of analyst & met specifications
10. Date, time of release, signature of individual releasing
11. Documentation of process deviations
12. Entries made immediately after each activity performed
PROCESS AND OPERATIONAL CONTROLS

• Complete batch records and associated documentation should be maintained for one year after batch release.
Aseptic Operations: should adequately ensure a sterile PET drug

The final product vial (FPV) assembled from pre-sterilized, commercially available components

All aseptically prepared PET drugs should be filtered through sterile 0.22 μm filter or sterilized

PET Drug FPV assembly—performed in an ISO Class 5 environment

Aseptic Techniques—aseptic operators should wear appropriate laboratory attire (Clean laboratory clothing, forearm sleeves, sanitized gloves & hair cover)

Storage conditions for assembled FPVs based on aseptic simulations
Aseptic Operations:

*Sterility Test Inoculations*—Performed in a manner consistent with radiation exposure requirement. For media tubes with screw-cap, inoculate in aseptic workstation. Tubes with septum cap can be inoculated in shielded area without a HEPA filter.
STABILITY

- Written specifications for storage and expiration time
- Establish conditions and time for each PET drug
- Stability Test – must be performed at highest strength of PET drug in the intended final vial
- Must be performed on at least 3 batches of the PET drug
- PET Radiopharmaceutical must met acceptance criteria for radiochemical & chemical purity, appearance (color & clarity), pH and stabilizer effectiveness
CONTROLS & ACCEPTANCE CRITERIA FOR FINISHED PET DRUG PRODUCTS

• Written specification for each PET drug
• Written QC procedures
• Accept or reject PET drug
Quality Control Tests

Pre-Release on PET drug Batch or QC sub-batch:
1. Visual inspection for color & clarity
2. pH
3. Radiochemical purity / identity
4. Chemical Purity
5. Radionuclidic identity
6. Strength determination
7. Specific activity—if appropriate
8. Residual solvent analysis, and other toxic chemicals
   ✓ Periodic Quality Indicating Testing (PQIT) may be appropriate
   ✓ Class 3 residual solvents & radionuclidic purity testing
Microbiological Tests for Sterile PET Drugs

**Pre-Release:**

- Determine the integrity of membrane filter
- Bacterial endotoxin test (BET)**

**Post-Release:**

- Sterility test: The samples can be inoculated immediately after membrane filtration, or can be allowed to decay in a shielded area for as long as 30 hours before inoculation. Can extend the time by appropriate testing using a suitable indicator organism
**Bacterial Endotoxin Test**

- Should be initiated on PET drug before release of each batch for human administration
- If very short half-life, complete on QC sub-batch before release
- After a record of successful BET (and sterility) tests for a particular PET drug, it is necessary to test only the first batch prepared each day for that PET drug product
Determine the Integrity of Membrane Filter

1. Increase Pressure
2. Bubbles Observed
IF A PET DRUG PRODUCT DOES NOT CONFORM TO SPECIFICATIONS

• If PET drug does not meet established acceptance criteria
• Perform an Out of Specification (OOS) investigation
• Investigate the failure
• It may be possible to reprocess the PET drug
REPROCESSING

If PET drug is rejected, it may be reprocessed according to established procedures-- examples include:

• pH adjustment

• A second passage through a membrane filter in the event of a failed filter integrity test

• A second passage through a purification column to remove an impurity
**LABELING**

**Final Container**
- Name of the PET drug product, including the dosage form
- Assigned batch number
- Any required warning statements or symbols (e.g., investigational use, radioactive)

**Shielding**
- All the above
- Date and time of calibration
- Total radioactivity or strength (mCi/mL or MBq/mL)
- Expiration
- Added substances (e.g. stabilizer)
- Producer, name and address
Revised USP Chapter 823 was posted 9-2011

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Becomes official May 1, 2012
Thank-You!