Regulatory Issues for Radiopharmaceuticals For Positron Emission Tomography--Compounding
USP General Chapter <823>
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US Food & Drug Administration Modernization Act (FDAMA) 1997

- 1997: US Food & Drug Modernization Act (FDAMA) required revisions to Current Good Manufacturing Practice (cGMP) for PET Radiopharmaceutical (RP) production

- FDAMA required a new approval path and separate Current Good Manufacturing Practices (cGMPs) for PET from cGMPs for drugs

- Prior to adoption of final PET cGMP rule, FDAMA requires PET Radiopharmaceutical (RP) production to follow:
  - United States Pharmacopeia (USP) PET RP monographs, if available
  - USP General Chapter <823> for Production of PET RPs
    - USP subcommittee being formed to review

- 2005: PET CGMP Proposed Rule & Guidance published
- 2009: Still waiting for final rule
The proposed 212.5(b) provides that for investigational and research PET drugs, cGMP would be met by producing PET drugs in accordance with USP General Chapter <823> “Radiopharmaceuticals for Positron Emission Tomography – Compounding”.

- PET Drugs produced under Investigational New Drug Application (IND) or
- PET Drugs approved through a Radioactive Drug Research Committee (RDRC)
USP Chapter <823>: Radiopharmaceuticals for Positron Emission Tomography (PET) -- Compounding

- United States Pharmacopeia (USP): National Drug Compendium
- Chapters under 1000 are enforceable—Joe Hung will discuss this
- Chapter <797>: Sterile Compounding of Pharmaceuticals
- Chapter <823>: RP for PET Compounding
- PET compounding involves nonsterile ingredients (high risk), but
- Chapter <823> supersedes Chapter <797> for PET RP compounding
- Upon release of PET RP as finished drug product, further manipulation such as dispensing, contents of Chapter <797> apply
Overview USP Chapter <823>

- Procedures/Process
  - Components, Materials and Supplies
  - Written Procedures
    ✓ Acceptance Criteria
    ✓ Compounding
    ✓ Computers & Automated Equipment
    ✓ Verification (3 consecutive runs) & Stability

- Facilities

- Quality Control
Control of Components, Materials and Supplies

• Establish written specifications
  ✓ Identity, purity & quality of components
  ✓ Appropriate storage

• Log-in each lot of shipments of components; If no expiration date, must assign one

• Determine each batch of components in compliance with written specifications (procedures, tests, and/or certificates of analysis)

• Store components in controlled access area according to established conditions.
Compounding Procedure Verification

1. Written acceptance criteria for identity, purity & quality of each PET drug (If USP monograph exists = minimum acceptance criteria)

2. Written procedures for compounding
   - Master file of Written compounding procedures (Outdated copies retained)
   - Incorporate 0.22 um for parenteral administration; 0.45 um for inhalation
   - Routinely updated at least annually

3. Verification Studies
   - Three consecutive runs are required initially & for any change having potential to alter identity quality or purity
   - Stability testing and expiration dating—meet acceptance criteria at expiry
PET Radiopharmaceutical (RPh) Compounding Process

- Inspect compounding area and equipment before use for cleanliness
- Label final PET RaPh container prior to starting
  - PET drug name and lot number
- Compound PET RaPh according to written, verified procedure with appropriate written batch record
  - Use appropriate components
  - Responsible individual initials—including each critical step
  - Raw analytical data
  - Signature & date of individual assuming overall responsibility
Quality Control Procedures

- Written QC procedures
- Verification of QC equipment and procedures used
- System suitability testing must be confirmed on installation of QC equipment and after repair
  - HPLC, GC, analytic instruments
- Check correct operation on scheduled basis
- Maintenance performed—written scheduled basis
- Dose Calibrators:
  - Assay bulk radioactivity and dispensed dosages
  - Perform applicable tests
Quality Control Requirements

Pre-Release:

- PET RaPh
  - $T_{1/2} \geq 20$ minutes (on Batch); $T_{1/2} \leq 20$ minutes (on QC Sub Batch)
  - Post-filtration integrity test of 0.22 µm sterile filter (e.g. Bubble Test)
  - pH
  - Visual inspection
  - Radiochemical purity/identity ***
  - Radionuclidic identity
  - Specific activity
  - Residual solvent analysis, and other toxic chemicals
  - BET (20 min gel clot, or other recognized procedure)

Post-Release:

Sterility

✓ may inoculate test, within 24 h following preparation
Endosafe PTS® System

- PTS® is a software-driven spectrophotometer for measuring and documenting endotoxin.
- Unique cartridge containing dry, pre-calibrated reagents.
- Each cartridge contains duplicate channels for analysis of sample and positive control.
- PTS® is particularly suited for PET RaPh because test requires
  - ~17-20 minutes
  - Requires < 0.1 mL of diluted product
  - NO preparation of endotoxin standards.
Qualification of Filtration Process

- Sterile Filters:
  - COC examined and maintained for each lot
  - COA obtained from the company listing microbial retention challenge
  - Each lot of filters must be tested for integrity

- After PET drug production, filter tested for integrity pre-release e.g. Bubble Point Test

- The **bubble point** pressure is the pressure at which bubbles first appear from a submerged inlet tube in the receiving vessel.

- Nitrogen gas flow increased until the bubbles appear (e.g. most filters must reach > 50 psi. *)

* Pressure depends on the filter used
Facility Environmental Controls

- Work area is clean
- Aseptic hood located in low traffic area
- Clean laboratory clothing worn
- Aseptic techniques used
- Disinfect final product septum with sterile 70% alcohol
PET RaPh Final Product Vial Assembly Performed In Aseptic Hood

- PET RaPh final product containers must be assembled in Class 100 environment (LFH or Isolator)
- Gloved hands are disinfected before entering hood
- Daily disinfection of surfaces before use
- Microbiological Testing periodically e.g. weekly
  - Contact plate-surfaces
  - Settle plate/dynamic air sampler
  - Airborne, nonviable particle count less often
Aseptic Technique
Training Requirements

- Didactic training: pass written exam
- Training in proper garbing & gloving with documented visual observation audits
- Media-Fill Test Procedures
  - New preparer: Pass 3 separate Media-Fill Procedures
  - Annually for personnel who currently prepare (compound) PET RaPh
Class 100 (ISO Class 5)  
PET Dose Drawing Station

- Upon release of PET RaPh as finished drug product, further manipulation such as *dispensing*, contents of Chapter <797> applies.
Thank-you!

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