



U.S. PHARMACOPEIA
*The Standard of Quality*SM



Proposed Revision of USP General Chapter Radiopharmaceuticals for Positron Emission Tomography— Compounding <823>

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Agenda

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Rationale for the revision of Chapter <823>
 - 21st Century PET Environment
 - Gaps in current chapter
 - USP's approach and actions
- Overview of the proposed revision
 - Major concepts
 - Proposed changes
 - Revision Process
 - FAQs (available online)
- Stakeholder participation
 - Submit comments to revised chapter
 - Communicate to constituencies
 - Identify potential USP Instructional offerings
- Next steps
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- Questions



Rationale for Revision of General Chapter <823>

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- First published in 1998 in USP 23
- Has not been modified since original publication
- However, the production environment for PET drugs has changed dramatically
- Most PET drug production facilities were associated with research institutions
- Since then, commercial suppliers have evolved to serve larger patient populations
- Also, numerous efforts underway to develop new commercial imaging agents
- Thus, PET drugs are used in discovery, research, clinical development and routine diagnostic imaging
- The USP must support the evolution of PET drugs



USP's Approach to <823> Revision

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

1. Understand technological, market place, and regulatory changes that have occurred in PET since the original publication of Chapter <823>
2. Jointly sponsor two symposia with the Society of Nuclear Medicine (SNM) in 2008 and 2009
3. Perform gap analysis on Chapter <823>
 - Form Expert (Advisory) Panel charged with drafting a revision of Chapter <823>
 - Panel members from academia and commercial PET production companies
 - Consensus driven approach to revision process



Recommendations of the Advisory Panel

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

1. Change the title to Positron Emission Tomography-Drugs for Compounding, Investigational and Research Uses <823>
2. Create a Definitions section for technical terms
3. Provide necessary flexibility needed for investigational and research uses
4. Reorganize the contents into sections similar to the outline of FDA's PET GMP's (published in Dec 2009)



Recommendations of the Advisory Panel

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

5. Consolidate key standards and requirements from general chapter Automated Radiochemical Synthesis Apparatus <1015>
6. Create an informational general chapter <1823> to describe the concepts, technologies and procedures currently used by the PET drug community
7. Revise all USP monographs for PET drugs based on revised <823>



1. Prepared a revision of <823> based on the Advisory Panel recommendations
2. Submitted the proposed revision to the 2005-2010 Expert Committee for further action
3. Recommended the preparation of a stimuli article to explain the reasons for the proposed revision of <823>
4. Published stimuli article and proposed revision of <823> in Pharmacopeial Forum 37(1)
5. Launched a Hot Topics section on USP website for information on the revision of <823>



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- New name in the proposed revision
 - “Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses”
- Consolidate key standards from Chapter <1015>
- Changes summarized in stimuli article
- Some information in the existing <823> will be added to a new informational Chapter <1823>

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STIMULI TO THE REVISION PROCESS
 Stimuli articles do not necessarily reflect the policies
 of the USPC or the USP Council of Experts

Pharmacopeial Forum
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**Revision of USP General Chapter Radiopharmaceuticals for Positron
 Emission Tomography—Compounding <823>**

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Change to read:

~~<823> RADIOPHARMACEUTICALS
 FOR POSITRON EMISSION
 TOMOGRAPHY—COMPOUNDING~~

▲ POSITRON EMISSION TOMOGRAPHY
 DRUGS FOR COMPOUNDING, INVESTI-
 GATIONAL, AND RESEARCH USES ▲^{USP35}



Sections for Proposed Revision Chapter <823>

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

1. Definitions
2. Adequate Personnel and Resources
3. Quality Assurance
4. Facilities and Equipment
5. Control of Components, Materials, and Supplies
6. Process and Production 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



1. Definitions

- The proposed revision of <823> contains a definitions for the following terms:
 - Active Pharmaceutical Ingredient
 - Batch vs. Lot
 - Conditional Final Release
 - PET Drug
 - Production vs. Compounding
 - PET Drug
 - Quality Assurance vs. Quality Control (QC)
 - Strength
 - Validation vs. Verification



2. Adequate Personnel & Resources

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Sufficient number of personnel with appropriate education, training and experience
- Number depends on size and complexity of operations
- Training should include:
 - Radionuclide production
 - Materials and components
 - Synthesis and purification techniques
 - Quality control testing
- Training should also include aseptic operations:
 - Assembly of sterile components including techniques and equipment
 - Media simulations required in triplicate to qualify a new operator



3. Quality Assurance

- Quality assurance (QA) and quality control (QC) are important elements in the production and testing of PET drugs
- The proposed revision separates these functions
 - QA consists of oversight activities
 - QC consists of execution activities
 - Personnel at the facility may perform both QA and QC functions



4. Facilities & Equipment

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Environmental controls
 - Aseptic workstation
 - Microbiological testing
- Equipment
 - Installation (IQ, OQ and PQ)
 - Calibration
 - Preventative maintenance
- Cleaning
- Day of use checks
- System suitability for QC equipment



Cleaning of Production Equipment

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Before used in production, equipment should be cleaned to ensure that the resulting PET drug meets established specifications for identity, strength, quality, and purity
- Once cleaned, equipment should be maintained in a state of cleanliness before use
- Equipment may be used to make multiple batches with cleaning between batches
 - Documented studies should demonstrate cleaning effectiveness



System Suitability of QC Equipment

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- System suitability ensures that QC equipment and analysts function properly as a system
- Existing <823> refers to Chapter <621> for tailing factor, replicate injections and resolution
- Number of injections required in <621> is inappropriate due to short half-life and number of different products prepared at typical academic or commercial facilities
- Proposed revision of <823> describes two alternative system suitability approaches



5. Control of Components, Materials & Supplies

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Identity test for precursors (e.g. melting point or other appropriate identity test)
 - Alternatively, use COA for acceptance of precursor if finished-product testing is performed
- Deleted requirement for new incoming lots of membrane sterilizing filters to be integrity tested
- Added requirement for growth promotion testing
 - Perform GPT with a single organism
 - Alternatively, use positive control during sterility test



6. Process and Operational Controls

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- A key ***process control*** is a master formula and associated procedures
- Should describe:
 - Components, materials and supplies
 - Process and synthesis steps
 - Formulation, including strength, buffers, stabilizers, carrier, impurities, etc.
 - Calculations used in yield and purity determinations
 - Quality control tests and schedules
 - Sterile filtration (parenteral PET drugs)
 - Particulate filtration (inhalation PET drugs)
 - Cleaning procedures for equipment & facilities

- A key operational control is a ***batch record*** used to document routine production
- A batch record is a subset of the master formula and should document:
 - Lot numbers of components
 - Execution of procedures and initials assuring that critical steps and processes were completed
 - Calculations for key parameters (e.g., yield,)
 - Final product labeling
 - QC test specifications, results and initials of analyst
 - Date, time of release, signature of individual releasing
 - Documentation of out-of-specification (OOS) results and process deviations

Aseptic techniques—

- Wear clean laboratory clothing, forearm sleeves, hair cover, beard & mustache cover (as appropriate), sanitized gloves
- May prepare multiple final product vials at once
- Perform sterility test consistent with personnel radiation exposure requirements
 - Screw-cap media tubes, perform in ISO Class 5
 - Septum-cap media tubes, perform in shielded area (does not require HEPA filtered area)

- PET drugs must meet acceptance criteria at expiry when stored according to proposed conditions
- Stability indicating assays are: radiochemical purity, appearance, pH, and stabilizer or preservative effectiveness (as appropriate)
- Stability should be demonstrated at the highest radioactivity concentration in intended container
- Three batches should be tested for stability
- Does not require that stability studies be performed at all locations in a network of facilities



8. Controls and Acceptance Criteria for PET Drugs

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Compendial QC tests—

- Do not require validation
- Suitability requires verification under actual conditions of use

Non-compendial QC tests—

- Should be reliable and specific

Tests that must be performed—

- Radiochemical purity and ID for all dosage forms
- pH for parenteral dosage forms
- Bacterial endotoxin test for parenterals
- Sterility test for parenterals

Endotoxin and Sterility Tests—

- After a record of successful tests is established for a particular PET drug, it is only necessary to test the first batch prepared each day
- Proposed revision eliminates requirement for a 20-minute in-process endotoxin test
- Proposed revision requires that samples for sterility must be inoculated within 30 hours

Two New Concepts in <823>—

- Periodic Quality Indicator Tests (PQIT)
 - Examples include non-critical attributes like radionuclidic purity or tests for Class 3 residual solvents
- Conditional Release—
 - Allows conditional release in event of equipment malfunction
 - Only appropriate under certain conditions

Out of specification (OOS) QC results—

- When a QC result does not meet predetermined specifications, the result is OOS
- Must determine if the OOS result is due to an analytical error or a true product failure
- Thus, an OOS result does not necessarily mean that the batch fails and must be rejected
- If the OOS result is due to a true product failure, the batch must be rejected



10. Reprocessing

- PET drugs that do not meet QC specifications may be reprocessed
- Some examples of reprocessing include:
 - pH adjustment
 - Refiltration in the event of a failed filter integrity test
 - Second passage through a purification column to remove an impurity
- Reprocessing procedures must be described in written procedures
- Reprocessed batch must be tested to ensure it meets specifications



11. Labeling and Packaging

- Delineates labeling information on the final product vial vs. the shielded container
- Consistent with personnel radiation exposure concerns and operational workflow



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Stakeholder Participation

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- First, who are the stakeholders?
- Companies having INDs for PET drugs
- Organizations involved research using PET drugs
- Research institutions having IND for PET drugs

- Access PF 37(1) [Jan-Feb 2011]
 - As of Jan 3, 2011 PF is freely available
 - Visit <http://www.usp.org/USPNF/pf/pfRedesign.html>
 - Registration required
- Review the <823> revision proposal and Stimuli article
- Submit comments to USP no later than **31 March 2011**
- Inform your interested colleagues about the revision
- Encourage your colleagues to submit comments
- Provide feedback to USP about continuing education in the area of PET drugs especially <823>



1. USP collects and reviews comments, shares with Expert Panel
Comment period ends on March 31, 2011
2. Expert Panel submits reviews all comments
3. If comments received are minor which do not require significant text changes the Expert Panel will recommend the Advancement of the PF37(1) to June 2011 ballot for USP 35-NF 30
4. . If comments received warrant significant changes to the revised text in PF37(1), the Expert Panel will recommend the republishing of the revised text in PF for public comments



Advance to June 2011 ballot for USP 35-NF 30

- General Chapters Physical Analysis Expert Committee approval required
- USP 35-NF 30 official date in 1 May 2012
- USP will work with FDA to update the reference to USP32 in the final rule to reflect revised version of <823>
- Until this update happens FDA will continue to enforce the current version of <823> in USP32

Questions