Issues Related to PET Radiopharmaceutical Monographs & General Chapters

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Agenda

- Some milestones for PET and the USP
- PET monographs
- General chapters for PET
- Topics not addressed in USP monographs
- Problems with PET monographs
- Pitfalls with certain QC tests
- Potential solutions
Some Milestones for PET and the USP

- First monograph for a PET article published in 1989 (Fludeoxyglucose F 18 Injection)
- First commercial PET production facility in the US opened in 1990
- More monographs published in 1990’s
- General compounding chapter for PET radiopharmaceuticals published in mid-1990’s (Chapter <823>)
- FDA Modernization Act (FDAMA) passed by Congress in 1997
  - Required that PET radiopharmaceuticals be compounded according to USP monographs and chapters until FDA establishes PET GMP’s
Some Milestones for PET and the USP

Today—

- USP maintains 12 PET monographs and 2 general chapters associated with PET
- FDAMA and the USP have provided a legal and regulatory framework for the establishment of the commercial PET distribution business in the US
- Approximately 1.5 million doses are commercially supplied each year in the US
- A wide variety of PET products are in use at numerous academic and research institutions for clinical, investigational and research purposes
- Monographs and chapters support and must continue to support research and commercial production environments
USP Monographs for PET

**Carbon-11**
- Sodium Acetate C 11 Injection
- Methionine C 11 Injection
- Raclopride C 11 Injection
- Flumazenil C 11 Injection
- Mespiperone C 11 Injection
- Carbon Monoxide C 11 Injection

**Fluorine-18**
- Fludeoxyglucose F 18 Injection
- Sodium Fluoride F 18 Injection
- Fluorodopa F 18 Injection

**Nitrogen-13**
- Ammonia N 13 Injection

**Fluorine-18**
- Fludeoxyglucose F 18 Injection
- Sodium Fluoride F 18 Injection
- Fluorodopa F 18 Injection

**Oxygen-15**
- Water O 15 Injection

**Rubidium-82**
- Rubidium Chloride Rb 82 Injection

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USP Monographs for PET

- Describe quality standards for identity, strength, quality and purity, including:
  - Appearance
  - pH
  - Radiochemical ID/purity
  - Radionuclidic ID/purity
  - Chemical purity
  - Residual solvents
  - Specific activity
  - Bacterial endotoxins
  - Sterility
USP General Chapters for PET

- Radiopharmaceuticals for PET — Compounding <823>
- Automated Radiochemical Synthesis Apparatus <1015>

A note concerning numbers for USP general chapters

- If the number is less than <1000>, compendial articles must comply with the standards, procedures, etc. in the chapter
- If the number is greater than <1000>, the chapter is intended for informational purposes
Other Relevant General Chapters

- Injections <1>
- Sterility <71>
- Bacterial Endotoxins <85>
- Residual Solvents <467>
- Chromatography <621>
- pH <791>
- Pharmaceutical Compounding – Sterile Preparations <797>
- Radioactivity <821>
- Validation of Compendial Methods <1225>
- Plus many others...
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Topics not Addressed in USP Monographs

- Test frequency
- Timing of QC test completion relative to product release
- Membrane filter integrity determination
- Out-of-specification (OOS) investigations
- Quantitative analysis
Test Frequency

- USP monographs do not address frequency of testing
- However, it is possible to release a batch without performing QC tests to confirm every USP specification
- Addressed in the Front Matter of the USP
  - Based on process validation data, final product QC tests may be omitted
  - In-process testing may be used instead of final product QC tests

Potential solutions—
- Define test frequency on a test-by-test basis in each monograph or
- Include recommendations in chapter <823> or
- Include reference to Front Matter in each monograph
Timing of QC Test Completion Relative to Product Release

- USP monographs do not address the timing of QC test completion relative to batch release
  - Exceptions: sterility testing and the 20-minute endotoxin test discussed in chapter <823>
- Using the same logic described for the frequency of testing, completion of QC tests after product release is possible if supported by process validation data

Potential solutions—
- Define product release criteria on a test-by-test basis in each monograph or
- Include recommendations in chapter <823> or
- Include reference to Front Matter in each monograph
Membrane Filter Integrity Determination

- Injectable PET articles must be passed through a membrane sterilizing filter to produce a sterile solution
- The integrity of the membrane filter must be verified to ensure a successful filtration
- Filter integrity test is more important than the sterility test to ensure patient safety
- Integrity testing is not addressed by USP

Potential solutions—
- Define filter integrity test criteria in each monograph or
- Include recommendations in chapter <823>
Out of Specification Investigations

◆ When the result of a final product QC test is out of specification (OOS), an investigation is required to determine if the result is an analytical error or a true product failure

◆ OOS protocols are well-established in traditional pharmaceutical manufacturing, but they don’t apply to short-lived products

*Potential solution*—

◆ Explore development of a new USP general chapter to address PET OOS investigations
Quantitative analysis requires calibration of analytical instruments
A good calibration curve must bracket the range of values expected in routine testing
Some PET monographs imply the use of a single-point calibration as part of each analysis

Potential solutions—
Explore potential of including calibration data in each PET monograph or
Include recommendations in chapter <823> or
Explore development of a new USP general chapter to address calibration
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Problems with PET Monographs

- Inaccuracy of analytical methods in certain PET monographs
- Use of outdated analytical methods in certain PET monographs
- Availability of USP reference standards described in PET monographs
- Inclusion of system suitability parameters in PET monographs
Inaccurate and/or outdated analytical methods create challenges for certain PET monographs

Addressed in the front matter of the USP
  - Compliance of an article may be determined by use of alternate methods for purposes of accuracy, sensitivity, precision, selectivity...
  - Alternative methods must be validated

Potential solutions—
  - Include corrections and updates in the upcoming monograph revision process
  - Explore independent verification of PET methods
  - Use validated alternative methods as necessary
Availability of Reference Standards

- Some USP reference standards have been unavailable from the USP
- Today, the USP does not propose new monographs until materials are available for any reference standards required in the monograph

**Potential solutions—**
- USP is addressing availability of reference standards
- Standards from other sources must be used in interim
• Certain PET monographs contain system suitability parameters (e.g., tailing, resolution, theoretical plates) for chromatographic methods
• Not included in all monographs

**Potential solutions**—
• Include system suitability parameters in the upcoming monograph revision process
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Pitfalls with Certain QC Tests

- Appearance
- pH determinations
- Radionuclidic identity and purity
- Limit of chlorodeoxyglucose in FDG
Appearance—

- Visual assessment of the product must be performed through leaded glass
- Difficult to determine color

pH Determination—

- The use of pH paper strips is not included in the monographs
Appearance and pH Determination

Potential solutions—

- Include wording in monographs to address appearance

- Include use of pH strips in monographs and state minimum specifications for strips
Radionuclidic Identity and Purity

Radionuclidic identity—

- Specifies half-life measurement to determine radionuclidic identity
- Does not specify a time interval for the measurement

Radionuclidic purity—

- Specifies use of gamma-ray spectrometry
- It is not possible to differentiate positron emitters by their energy spectrum
- It is not possible to detect low levels of long-lived radionuclides produced in target
Radionuclidic Identity and Purity

Potential solutions—

- Specify a time interval for the half-life measurement and include in the upcoming monograph revision process.
- Specify the periodic use of gamma-ray spectrometry on decayed samples to test for long-lived radionuclides.
Chlorodeoxyglucose Levels in FDG

- Chlorodeoxyglucose is a by-product in the production of FDG
- The USP limit is 1 mg/batch
- Based on the assumption that a batch may be administered to a single patient
- The vast majority of FDG administered in the US is drawn from a multi-dose vial

Potential solution—
- Change the specification of Cl-DG to 1 mg per injected dose
Summary

- USP has played a key role in the establishment of PET in the US
- Monographs and chapters have supported research and commercial uses
- PET remains a dynamic discipline with a truly unique production environment
- The USP must continue its instrumental role in order for PET to realize its full potential in molecular medicine
Numerous participants and contributors to the development and maintenance of PET chapters and monographs in the USP

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Thank You