Current and Future USP Initiatives for Radiopharmaceuticals

Steve Zigler, Ph.D.

June 24, 2018
Disclosures

• Employee of Siemens PETNET Solutions
• Volunteer member of USP committees and panels associated w/ radiopharmaceuticals
  - Currently serving in third five-year cycle
  - Served on and/or chaired various panels for revision of general chapters and monographs for radiopharmaceuticals

This presentation is not endorsed by Siemens or the USP, nor does it represent the views or opinions of either organization
Acknowledgements

USP Staff and Executives
James Austgen
Domenick Vicchio
Ravi Ravichandran
Jaap Venema

USP EC Volunteer
Jim Ponto

The USP for permission to use copyrighted material
Topics

• Background on radiopharmaceuticals and USP
• Recent USP activities and milestones
• How to get involved and why to get involved
What does the USP do?

Develops public standards for identity, strength, quality and purity of medicines, food ingredients, and dietary supplements.
What exactly is a “public” standard?

- Public provides input to the USP through:
  - Volunteers on Expert Committees and Expert Panels (ECs and EPs)
  - Data supplied by sponsors (typically NDA/ANDA holders)
  - Comments and publications in the Pharmacopeial Forum (PF)
What exactly is a “public” standard?

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We are the “public” in USP public standards.
Background on Radiopharmaceuticals

- Radiopharmaceuticals = radioactive drugs
- Radiopharmaceuticals contain:
  - A radionuclide with emissions used for diagnostic or therapeutic purposes
  - A drug moiety to provide localization of the radiation
- Employ very small mass quantities, so minimal to no pharmacologic effects
  - Act as ‘tracers’ of biologic functions
  - Adverse reactions extremely rare
USP Standards Must...

...reflect the attributes of radiopharmaceuticals
  e.g., some QC testing can't be completed before use
...support all formats for radiopharmaceuticals
  - Manufactured dosage forms ready to use
  - Prepared from non-radioactive kit and radioactive solution (generator concept)
  - Prepared in small batches (one vial = one batch)
...allow for safe handling by operators, transporters, users
USP and Radiopharmaceuticals

• USP played a key historical role in development of radiopharmaceuticals
USP and Radiopharmaceuticals

• > 60 monographs for radiopharmaceuticals
• Four general chapters focus on specific topics related to radiopharmaceuticals
• Expert Committee (EC) and 2 Expert Panels (EPs)
  - EC: oversight / ballot authority (Ponto / Zigler)
  - EP 1: charged with radiopharmaceutical monographs
  - EP 2: charged with preparation of <825>
Advocacy – Munir Ghesani, MD, FACNM, FCR

Educating policymakers about how the nuclear medicine and molecular imaging field can improve patient outcomes

- Working with peer organizations to raise visibility and improve understanding of nuclear medicine with regulatory agencies and the legislature
- Advocating for better approval, coverage and reimbursement decisions for NM/MI drugs, devices, diagnostic procedures, and therapies
- Improving understanding among those developing new radiopharmaceuticals of the different types of evidence the FDA and CMS require
- Getting appropriate coding and reimbursement for NM/MI procedures, and educating members and their staff on how to file accurate claims
- New resources focused on advocating for nuclear medicine at the state level
- Continuing to address compounding issues with the FDA and the U.S. Pharmacopeia (USP), which is drafting a new chapter on compounding radiopharmaceuticals
- Working to ensure the integrity of the isotope supply chain
USP General Chapters

**<1821> Radioactivity – Theory**
- Types of emissions
- Decay
- Carrier
- Radiochemical ID/Purity
- Radionuclidic ID/Purity
- Counting / Instrumentation
- Nomenclature for radionuclides

**<821> Radioactivity**
- Training and documentation
- Instrument qualification and performance
- Radionuclide identification and assay
- Etc.

**<1823> PET Drugs – Information**
- Unique properties of PET drugs
- Production techniques
- Analytical methods
- Validation
- Development stages
- Quality attributes

**<823> PET Drugs – Compounding, Investigational and Research Uses**
- Personnel
- Facilities and equipment
- Quality assurance
- Periodic testing / OOS
- Etc.
USP and Radiopharmaceuticals

• > 60 monographs for radiopharmaceuticals
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Panel established early 2016

Charter:
- Review existing radiopharmaceutical monographs
- Determine relevancy of monographs based on regulatory expectations and industry practices
- Determine if a monograph should be revised, modernized, or omitted from USP-NF
# EP 1: Members

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Corinne Bensimon</td>
<td>Health Canada</td>
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<td>Jonathan Fitzsimmons</td>
<td>Brookhaven National Lab</td>
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<td>Umesh Gangadharmath</td>
<td>Optimal Tracers</td>
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<td>Adrian Nunn</td>
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<td>David Pipes</td>
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<td>Jim Ponto</td>
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<td>Kara Weatherman</td>
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<td>Martin Williamson</td>
<td>Consultant, EC Member</td>
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<tr>
<td>Steve Zigler</td>
<td>PETNET Solutions, EC Member</td>
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EP 1: Achievements to Date

- Completed revisions for two PET radiopharmaceutical monographs
  - Fludeoxyglucose F 18 Injection
  - Ammonia N 13 Injection
- Proposed revisions published in May 2017
- All public comments reviewed / addressed by EP
- EP recommended approved to supervising EC
- Balloted and approved by EC
- Revisions become official December 1, 2018*
EP 1: Monograph Template

- TITLE
- DEFINITION
- IDENTIFICATION
- ASSAY
- PURITY
- IMPURITIES
- SPECIFIC TESTS
- ADDITIONAL REQUIREMENTS
Recent Ammonia N 13 Revision

• TITLE
  - e.g., Ammonia N 13 Injection

• DEFINITION
  - Chemical name, etc.
  - Other important characteristics (e.g., sterile)
  - Amount (e.g., NLT 90% and NMT 110% of the labeled amount expressed in MBq (mCi)/mL at the time of calibration)
  - Added substances (e.g., buffering agents, preservatives, stabilizing agents, or sodium chloride)
  - Specific activity (e.g., does not contain added carrier)
Recent Ammonia N 13 Revision

• IDENTIFICATION
  - Radionuclidic Identity (cite <821>)
    • Analysis (approximate half-life)
    • Acceptance Criteria (9.5 – 10.5 min)
  - Radiochemical Identity
    • Analysis (TLC Rf comparison to non-radioactive standard)

• ASSAY (cite <821>)
  - Radioactivity Concentration (Strength)
    • Analysis (e.g., determine MBq (mCi)/mL)
    • Acceptance Criteria (90% - 110% at the time indicated on the label)
• PURITY
- Radionuclidic Purity (cite <821>)
  • PET drugs cannot typically be differentiated by emission spectroscopy, so Radionuclidic Purity is performed post-release after decay
  • Analysis (e.g., collect emission spectrum, decay-correct each radionuclide to expiration time)
  • Acceptance Criteria (NLT 99.5% corresponds to the intended radionuclide)

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Recent Ammonia N 13 Revision

PURITY

Change to read:

• RADIONUCLIDIC PURITY

(See Radioactivity (821), 5. Identification of Radionuclides, 5.2 Gamma-Ray Spectrometry.)

[NOTE—This may be a periodic quality indicator test. The injection may be distributed and dispensed prior to completion of this test.]

Analysis: Determine the purity of ammonia N 13 in the portion of injection taken for the Radionuclidic Impurities test:

\[
\text{Result} = [1 - \left( \frac{C_t}{C_i} \right)] \times 100
\]

- \( C_i \) = sum of the concentrations of all longer-lived radionuclides, decay corrected to the expiration time from the Radionuclidic Impurities test (Bq/mL) or (\( \mu \)Ci/mL)

- \( C_t \) = sum of the concentrations of all long-lived radionuclides and ammonia N 13, all decay corrected to the expiration time from the Radionuclidic Impurities test (Bq/mL) or (\( \mu \)Ci/mL)

Acceptance criteria: At the time of expiration, NLT 99.5% of radionuclides in the injection correspond to \( {^{13}}\text{N} \).
Recent Ammonia N 13 Revision

• PURITY
  - Radiochemical Purity
    • Analysis (e.g., HPLC, TLC, or other method)
    • Acceptance Criteria (NLT 95%)
Recent Ammonia N 13 Revision

- IMPURITIES
  - Radionuclidic Impurities
  - Radiochemical Impurities
  - Identified Chemical Impurities

- SPECIFIC TESTS
  - Appearance and pH
  - Bacterial Endotoxins Test
  - Sterility Test

- ADDITIONAL REQUIREMENTS
  - Packaging and Storage
  - Labeling
  - USP Reference Standards (ethanol and ammonium)
EP 1: Monograph Template

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- ASSAY
- PURITY
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- SPECIFIC TESTS
- ADDITIONAL REQUIREMENTS

USP General Chapters

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Ammonia N 13 Monograph

• First monograph to employ "sub-batch" concept
• A group of sub-batches collectively forms a batch
• Addresses challenge of QC tests the require more time than half-life
• See <1823> PET Drugs – Information
PET Radiopharmaceuticals – Next Steps

• In process revisions
  - Sodium Fluoride F 18 Injection
  - Choline C 11 Injection

• Will complete modernization of PET monographs to reflect NDAs and ANDAs that ensued after 1997 FDA Modernization Act
EP 1: Beyond PET Monographs

• Nearly all SPECT monographs need to be modernized to reflect current standards
• Review each radiopharmaceutical for marketing status in U.S. and other countries
• Identify sponsors for monographs to be maintained
• Recommend omission of monographs for products that are no longer relevant
  - Revisions published in Pharmacopeial Forum for comment
EP 1: Challenges

• USP not licensed for radioactive materials, so must depend on data from the manufacturers
• Limited data available from manufacturers
• Older products may lack complete data package
• Dedication of resources toward <825>
EP 1: Potential for New Monographs

• Prompted by FDA request to update a Tc-based monograph, EP recognized potential need for monographs for non-radioactive kits

*Basis:* FDA approved product is the non-radioactive kit, but USP monographs only exist for the finished radiopharmaceutical
Potential Kit Monographs – What's Next

• EP drafted stimuli article to describe rationale
• Article will appear in upcoming issue of *Pharmacopeial Forum*
  - Availability will be announced on USP website
• Public outreach to solicit comments
  - SNMMI / APhA / others?

*Nothing will happen until USP hears from the public*
Why should I get involved??
...because it matters!!
Fall 2016 – SNMMI COR developed a white paper addressed to USP

Three recommendations:

- Establish an EP to delineate "compounding" practices
- Create a general chapter for the preparation, compounding, and dispensing radiopharmaceuticals
- Reinstate an expert committee dedicated to all standards for radiopharmaceuticals [i.e., chapters and monographs]
What can I do?
Advocacy – Munir Ghesani, MD, FACNM, FACR

Educating policymakers about how the nuclear medicine and molecular imaging field can improve patient outcomes

- Working with peer organizations to raise visibility of nuclear medicine with policymakers
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Background – Radiopharmaceutical EC

• **1960**: first dedicated Expert Committee for radiopharmaceuticals

• **2010**: eliminated EC

• Relied on Expert Panels for additional expertise as needed
Challenges with Expert Panel Approach

• Expert Panel members are "one and done"
• Difficult to maintain continuity / consistency over long term
• Expert Panels lack voting authority
• *Expertise diluted during interactions between EPs and ECs*
SNMMI Develops USP Recommendations for Compounded Sterile Radiopharmaceuticals

December 14, 2016

SNMMI has developed USP recommendations for compounded sterile radiopharmaceuticals. The recommendations aim to address certain common practices in the field of nuclear pharmacy that are not adequately defined by generally accepted practice standards. The society believes there is confusion in the field of nuclear pharmacy, which threatens the availability and safe usage of radiopharmaceuticals in the U.S. The recommendations are a response to these challenges. The recommendations were developed by SNMMI’s Committee on Radiopharmaceuticals (COR) and approved by SNMMI’s Board of Directors. The COR worked with several professional organizations and trade associations in an attempt to rectify the situation. Our efforts to date have met with some success, but have still fallen short of realizing suitable standards that are generally accepted for common practices in nuclear pharmacy.

The COR believes that the USP, as the world’s leading organization for the development and maintenance of public standards, can play a critical role in the resolution of these challenges. The three recommendations from the white paper are:

- **Recommendation 1.** Establish an expert panel to delineate common practices that are defined as sterile compounding within the practice of nuclear pharmacy.
- **Recommendation 2.** Create a public standard for the preparation, compounding, and dispensing of sterile radiopharmaceuticals with the practice of nuclear pharmacy.
- **Recommendation 3.** Reinstate an expert committee dedicated to all standards for radiopharmaceuticals.

On September 29, SNMMI President Sally Schwarz sent the letter to the USP, where it is currently under consideration. Further details will be provided as they become available.

Access SNMMI’s full white paper »
Five Years of Effort

Dear Dr. Williams,

As members of the GC-PA and SM4 Committees (EC) it is our responsibility to improve communication and oversight throughout the LSP. In conclusion, the formation of a new EC will simultaneously eliminate tasks that dilute the efforts of existing EC’s and improve collaboration among LSP volunteers and staff members with expertise in radionuclides and contrast imaging agents. In turn, this will leverage LSP’s ability to maintain leadership and quality standards in this specialized area for decades to come. We hope the new EC can be included in the 2015-2020 cycle. Thank you for your consideration. We look forward to working with you and the LSP to realize these goals.

On behalf of the members listed below:

Jennica Lewis (SM4), Steve Ziegler (SM4), James Portin (GC-PA), Sally Schwarz (GC-PA)

Steve Ziegler
SM4 Expert Committee Member
1. Comment

2. Volunteer
If we don't stand together, we will fall apart