# USP Standards for Radiopharmaceuticals

**June 12, 2017**

**10:00 – 11:30**

Organizers: Ravi Ravichandran, PhD, Jim Ponto, MS, RPh, BCNP, Steve Zigler, PhD

Moderator: Ravi Ravichandran, PhD

Sponsor: Coalition for PET Drugs

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Historical Role of the USP in Radiopharmaceuticals

Steve Zigler, Ph.D.
SNMMI Annual Meeting
June 12, 2017
Disclosures

- Employee of Siemens PETNET Solutions
- Volunteer member of USP committees and panels associated with 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 the USP, nor does it represent the views or opinions of the USP.
Topics

• Brief background
• Historical involvement of the USP in radiopharmaceuticals
  – Monographs and products
  – General chapters
  – People
• Applying lessons from the past
What it is not...

History of nuclear medicine
History of nuclear pharmacy
History of FDA regulation in nuclear medicine
If you don’t know history, then you don’t know anything. You are a leaf that doesn’t know it is part of a tree.

- Michael Crichton
Acknowledgements

USP Staff
Geeta Tirumalai
Eli Begoun
Domenick Vicchio
Ravi Ravichandran

USP EC Volunteers
Bob Wolfangel  Jim Ponto
(served from 1985-2005)  (current)

The USP for permission to use copyrighted material
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
  – Data supplied by sponsors (typically NDA/ANDA holders)
  – Comments on publications in the *Pharmaceutical Forum (PF)*
What exactly is a “public” standard?

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  - Data supplied by sponsors (typically NDA/ANDA holders)
  - Comments on publications in the *Pharmaceutical Forum (PF)*

*We are the “public” in USP public standards*
What was the first USP monograph for a radiopharmaceutical?

Sodium Iodide I\(^{131}\) solution

“Sodium radio-iodide (I\(^{131}\)) solution”
15th Revision of the USP (1955)
SODIUM RADIO-IODIDE (I\(^{131}\)) SOLUTION

Radioactive Iodine Solution

Sodium Radio-iodide (I\(^{131}\)) Solution is a solution containing iodine-131 suitable for either oral or intravenous administration. Iodine-131 is a radioactive isotope of iodine processed in the form of sodium iodide from the products of uranium fission in such manner that it is essentially “carrier-free” and contains only minute amounts of naturally occurring iodine-127. Sodium Radio-iodide (I\(^{131}\)) Solution contains a suitable bacteriostatic agent.
Sodium Radio-Iodide (111) Solution contains not less than 95 per cent and not more than 105 per cent of the labeled amount of 111 as iodide, expressed in micrograms or milliliters, at the time indicated in the labeling. Solution activity as iodide does not exceed 5 per cent of the labeled activity. Other chemical forms of radioactivity are absent.

Dosage calculations must take into account radioactive decay.

The half-life of Iodine-131 is 8.0 days. To prevent the 131 from being administered, all containers used to handle Sodium Radio-Iodide (111) Solution should be previously rinsed with a solution containing approximately 0.50 per cent of sodium hydroxide, 0.04 per cent of sodium bisulfite, and 0.25 per cent of sodium acetate followed by rinsing with purified water until the last rinsing is neutral to litmus.

To determine the activity of solutions containing less than 10 mg of radioactivity, a sample (50 mg) of the solution brought to a convenient concentration, is added to 0.5 ml of a solution containing potassium iodide (0.1M) and 1 ml of an buffered solution such that 5 ml of resulting solution have a specific activity of 12.5 mc/minute/gram. A 5 ml sample obtained from the 0.25 ml of radioactive solution is transferred to a measured 50 ml conical flask, 10 ml of buffer solution is added, and the flask is made up to the mark with water.

Sodium Radio-Iodide (111) Solution is the clear solution, colorless or having a color due to the bacteriostatic agent. Upon standing, the solution becomes cloudy due to the formation of aluminum complexes. The beta radiation from Sodium Radio-Iodide (111) Solution shows a yellowish color, and the sample contains approximately 0.50 per cent of sodium hydroxide, 0.04 per cent of sodium bisulfite, and 0.25 per cent of sodium acetate.

The pH of Sodium Radio-Iodide (111) Solution is 7.0 to 8.5. Other requirements—Sodium Radio-Iodide (111) Solution for intravenous use meets the requirements set forth in the monograph, page 804, except that the solution may be distributed or dispensed prior to completion of the test for sterility.

Limit of total radioactivity—Dilute 0.1 ml of Sodium Radio-Iodide (111) Solution with 6 ml of water, and add a few drops of ferric chloride T.S. and 1 ml of chloroform, and shake vigorously. The chloroform remains clear and colorless.

Radio-chemical purity—Place 1 drop of a solution containing 0.1 ml of potassium iodide, 0.25 ml of sodium bromide, 0.001 M ammonium hydroxide, 0.25 ml of water, 1 ml of sodium chloride, and 1 ml of sodium hydroxide on a clean, dry, white filter paper, and allow to dry. The sample is considered acceptable if the color of the spot does not differ from that of the control, which is obtained by treating 0.5 ml of a solution of the same composition with 0.5 ml of water, and adding 1 ml of 0.1 M sodium hydroxide, and 1 ml of 0.1 M sodium chloride, and allowing the mixture to stand for 24 hours. The total activity of the iodide ion does not exceed 5 per cent of the labeled activity.

The activity of the solution is determined by the addition of a sufficient amount of sodium chloride to the solution to give a specific activity of 12.5 mc/minute/gram. The specific activity is determined by the addition of a sufficient amount of sodium chloride to the solution to give a specific activity of 12.5 mc/minute/gram. A 5 ml sample obtained from the radioactive solution is transferred to a measured 50 ml conical flask, 10 ml of buffer solution is added, and the flask is made up to the mark with water.
Important precedents were set in this first monograph

- Allowed distribution of the product before completion of the test for sterility
- Used a non-radioactive standard for purposes of ID
Radioactivity

Determinations of radioactivity are exacting and may involve a degree of personal hazard so that they should be conducted by personnel having expert training in handling radioactive materials. Suitable shielding for both operators and apparatus is necessary when the level of radioactivity exceeds maximums accepted as safe, and checks on the level of exposure to radiation should be made periodically. An appropriate system of disposal of radioactive wastes must be instituted.

Isotopes are species of the same element, the nucleus of the atoms having the same number of protons but differing in the number of neutrons. There are two classes of isotopes, stable and unstable, depending on the stability of the nucleus. Unstable isotopes are called radioactive isotopes since, when decay occurs, ionizing radiation in the form of alpha (α), beta (β), or gamma (γ) radiation, singly or in combination, is emitted from the nucleus. Individual radioactive isotopes differ from one another in the type of ionizing radiation emitted (α, β, or γ); the energy with which the ionizing radiation is ejected, usually expressed in millions of electron volts (mev.); the rate of radioactive decay, usually expressed in terms of the half-life; and the method of decay process, spoken of as the “decay scheme.”

The extent of radioactivity is expressed in absolute units (total number of atoms disintegrating per unit time) or comparative units (counts or divisions of the scale of
General chapter on radioactivity also became official in 15th revision...
15th Revision of the USP (1955)

• Who made it happen?
• There were no Committees, Panels, Subcommittees, Advisory Boards, etc. responsible for radioactive drugs at the time*
• John Christian, Ph.D., (Purdue) served on General Committee of Revision

*There was an advisory panel on radiology and other medical specialties
Milestones for Radioactive Iodine

- **1936**: Initial studies to explore use of radioactive iodine in therapy at MGH/MIT ($^{128}$I)
- **1941**: First use of radioactive iodine in therapy ($^{130}$I)
- **1946**: Therapy became more widespread in the wake of WW II and Manhattan Project ($^{131}$I)
- **1950**: United States Pharmacopeial Convention meets in preparation for 15th revision
- **1955**: Monograph for sodium iodide-131 official

Becker DV, Sawin CT, Semin Nucl Med, 1996, 26(3):155-64; USP
Some Historical Context...

- **1938**: FDC Act passed by Congress, but AEC (now NRC) had regulatory authority for radioactive drugs
- **1940s, 50s**: Companies (e.g., Abbott and Squibb) began commercial supply of radioactive drugs
- **1940s, 50s, 60s, 70s**: Regulatory responsibility for radioactive drugs fell somewhere between the AEC and the FDA
  - Lines of authority must have been confusing at times
  - Authority finally settled with the FDA, which required that manufactured radioactive drugs be regulated as new drugs (i.e., preapproval)
My Conclusions

The early days of radioactive drugs were a very dynamic time...

• New class of products with a relatively small cadre of practitioners with required expertise

• Unclear and occasionally conflicting regulatory authorities and requirements

• In the middle of all this, the USP had the foresight to support the development of public standards for this new class of products
16th Revision of the USP (1960)
16th Revision of USP (1960)

- Six additional monographs for radioactive drugs appeared in this revision.
16th Revision of USP (1960)

- Iodine-131
  - Sodium iodide-131 solution
  - Sodium iodide-131 capsules
  - Iodine-131 serum albumin
- Sodium phosphate-32 solution
- Cyanocobalamin cobalt-60 solution
- Gold-198 colloid solution
- Sodium chromate-51 solution
General chapter on USP Reference Standards acknowledged absence of reference standards for radioactive drugs.

Because of the special circumstances surrounding the preparation, storage and distribution of standardized forms of radioactive substances suitable for use in drug analyses, some of which are called for in pharmacopeial assays and tests, no U. S. P. Reference Standards of radioactivity are provided. Reliable standards of some radioactive substances, including chromium-51, cobalt-60, gold-198, iodine-131, and phosphorus-32, are available upon order from commercial sources.*

*A firm distributing some radioactive standards is the Nuclear-Chicago Corp., 223 West Erie St., Chicago 10, Ill.
Radioactivity determinations are exacting and should be conducted by personnel having had expert training in handling radioactive materials. Isotopes are species of the same element, the nucleus of the atoms having the same number of protons but differing in the number of neutrons. There are two classes of isotopes, stable and unstable, depending on the stability of the nucleus. Unstable isotopes are called radioactive isotopes since, when decay occurs, ionizing radiation in the form of alpha (α), beta (β), or gamma (γ) radiation, singly or in combination, is emitted from the nucleus. Individual radioactive isotopes differ from one another in the type of ionizing radiation emitted (α, β, or γ); the energy with which the ionizing radiation is ejected, usually expressed in millions of electron volts (Mev.); the rate of radioactive decay, usually expressed in terms of the half-life (T₁/₂); and the method of decay process, spoken of as the “decay scheme”.

All sample radioactivity measurements must be corrected by subtracting background activity. In the Geiger-Müller counting of samples, correction must be made also for coincidence when counting samples at higher activity levels. Coincidence correction may be made as follows: Prepare two radioactive sources on identical mounts each having approximately the same activity in the range of 10,000 counts per minute. Carefully determine the activity of the sources individually and combined, being sure to retain identical geometry and backscattering effects and to make not less than 10⁶ total counts for each of the three separate sources. The resolving time, T (the period during which all incident ionizing radiation is recorded as a single count), is given by the equation

\[
T = \frac{n_1 + n_2 - n_3}{2n_1n_2}
\]
16th Revision of the USP (1960)

• Who made it happen?
• Still no Committees, Panels, Subcommittees, Advisory Boards, etc. responsible for radioactive drugs*
• John Christian at Purdue still making it happen on the General Committee of Revision

*There was an advisory panel on radiology and other medical specialties
17th Revision of the USP (1965)
17th Revision of USP (1965)

- Additional monographs (total > 10)
- Rose Bengal Sodium Iodine 131 Injection
- Sodium Iodohippurate Iodine 131 Injection
- Cyanocobalamin Cobalt 60 capsules
- Cyanocobalamin Cobalt 57 solution/capsules
- Removed Radiogold solution
Beginning with 17th revision...

- First appearance of a panel with expertise in radiopharmaceuticals
Members of USP Panel on Radioactive Pharmaceuticals (17th Revision)

- William Brownell (Abbott)
- John Christian (Purdue)
- Geoffrey Gleason (Oak Ridge)
- Edwin Laug (FDA)
- Paul Numerof (Squibb)
- C.T. Peng (UCSF)
Interesting Note in 17th Revision

Despite efforts to gain consistency in nomenclature throughout the volume, some inconsistency will be evident in such groups as the insulins, two of which are named according to the promptness of onset and the duration of action, respectively.

In the interest of typographic simplicity, the titles for the U. S. P. radioactive preparations are of the form “I 131,” e.g., Sodium Iodide I 131 Solution. These titles reflect the arbitrary adoption by the Revision Committee of a convention in keeping with a practice thoroughly established in the American pharmaceutical literature but contrary to international usage. The latter was recognized formally by action of the International Union of Pure and Applied Chemistry when it gave sanction to the form $^{131}$I in expressing the mass numbers and symbols of the radioactive nuclides.
Other Notes in 17th Revision

• Consistent names for radiopharmaceuticals
  – e.g., Sodium Radiochromate Injection becomes
    Sodium Chromate Cr 57 Injection, etc.

• General chapter on radioactivity expanded
18th Revision of USP (1970)

- Added several monographs
  - Iodinated I 125 serum albumin
  - Chlormerodrin Hg 197 Injection
  - Chlormerodrin Hg 203 Injection
  - Gold Au 198 Injection
  - Sodium Iodide I 125 solution
- Removed some monographs
  - Cyanocobalamin Cobalt 60 capsules and solution
- About 15 monographs in total
- General chapter on radioactivity further expanded
18th revision maintained Panel on Radioactive Pharmaceuticals...

- William Briner (NIH)
- William Brownell (Abbott)
- John Christian (Purdue)
- Floyd Hallett (Mallinckrodt)
- Geoffrey Gleason (Oak Ridge)
- Edwin Laug (FDA)
- Paul Numerof (Squibb)
- C.T. Peng (UCSF)
19th Revision of USP (1975)

- First appearance of a monograph for $^{99m}$Tc
  - Sodium Tc 99m Pertechnetate
  - Technetium Tc 99m Aggregated Albumin
  - Technetium Tc 99m Sulfur Colloid Injection
- Strontium Sr 85 Injection
- Fourth Supplement to the 19th revision (May 1, 1978)
  - Contained the first monograph for a PET radiopharmaceutical
  - Sodium Fluoride F 18 Injection
- Greatly expanded general chapter on radioactivity (this revision was not changed until recently)
Smaller USP Subcommittee for Radiopharmaceuticals in 19th Revision

- Jonathan Miller, Chair (Abbott)
- William Brownell (Abbott)
- James Potchen (Michigan St.)
- Samuel Tuthill (Mallinckrodt)
20th Revision of USP (1980)

• First revision with numbered general chapters
• First appearance of <85> Bacterial Endotoxins
• Radiopharmaceutical monographs revised to replace the pyrogen test with BET
• Removed monograph for Sodium Fluoride F 18
  – Monograph only appeared in supplements; never appeared in full printed version of compendium
Larger USP Subcommittee for Radiopharmaceuticals in 20th Revision

- Jonathan Miller, Chair (Abbott)
- William Briner (NIH/Duke)
- William Brownell (Abbott)
- Klaus Florey (Squibb)
- James Potchen (Michigan St.)
- Samuel Tuthill (Mallinckrodt)
21st Revision of USP (1985)

- Numerous monographs added (\(^{111}\text{In}, \(^{201}\text{Tl}, \(^{169}\text{Yb}, \(^{99m}\text{Tc}, \(^{133}\text{Xe}, \text{and more}), \text{possibly resulting from FDA approval requirements}

- Several monographs removed (\(^{198}\text{Au}, \(^{197}\text{Hg}, \(^{203}\text{Hg})\)
USP Subcommittee for Radiopharmaceuticals in 21st Revision

- William Briner, Chair (Duke)
- Rodney Ice (U of Oklahoma)
- Michael Loberg (Squibb)
- Roscoe Miller (Indiana)
- Robert Wolfangel (Mallinckrodt)
USP Subcommittee for Radiopharmaceuticals in 21st Revision

• Subcommittee appointed two advisory panels for radiopharmaceuticals
  – One for the development of a monograph for FDG
  – A second for the revision of the general chapter on radioactivity (but the revision was never completed)
22nd Revision of USP (1990)

• First appearance of a monograph for Fludeoxyglucose F 18 Injection
  – First PET drug monograph since the brief appearance of Sodium Fluoride F 18
  – First monograph to appear for a PET drug without an FDA-approved NDA

• First appearance of chapter <1015>, Automated Radiochemical Synthesis Apparatus

• A handful of non-PET monographs added
USP Subcommittee for Radiopharmaceuticals in 22\textsuperscript{nd} Revision

- Robert Wolfangel (Chair, Mallinckrodt)
- William Briner (Duke)
- Rodney Ice (U of Oklahoma)
- Edward Silberstein (U of Cinn)

Continued both advisory panels for radiopharmaceuticals
23rd Revision of USP (1995)

- Additional monographs for PET drugs
  - Ammonia N 13 Injection
  - Fluorodopa F 18 Injection
  - Sodium fluoride F 18 Injection
  - Carbon Monoxide C 11
  - Water O 15 Injection
  - Rubidium Chloride Rb 82 Injection
- A few additional monographs for non-PET drugs
- Numerous monographs removed
23rd Revision of USP (1995)

- Eighth supplement to the 23rd revision was published on May 15, 1998
- General chapter <823> Radiopharmaceuticals for Positron Emission Tomography – Compounding became official
USP Subcommittee for Radiopharmaceuticals in 23rd Revision

- William Briner, Chair (Duke)
- Carol Marcus (UCLA)
- Edward Silberstein (U of Cincinnati)
- Robert Wolfangel (Mallinckrodt)

Continued both advisory panels for radiopharmaceuticals
24th Revision of USP (2000)

• Additional monographs for both PET and non-PET radiopharmaceuticals
USP Subcommittee for Radiopharmaceuticals in 24th Revision

- William Briner, Chair (Duke)
- Dennis Swanson, Chair (UPMC)
- Jorge Barrio (UCLA)
- Ron Callahan (Harvard)
- Hank Chilton (Wake Forest)
- Ed Silberstein (U of Cincinnati)
- Robert Wolfangel (Mallinckrodt)

Continued both advisory panels for radiopharmaceuticals
Historical Context...

- **1980s**: FDA begins to explore the possibility of regulating PET drugs as new drugs (i.e., require FDA approval)
- **1990s**: FDA holds public meetings and prepares draft guidance documents on GMP regulations for PET manufacturing
- **1990s**: Lawsuits filed against FDA arguing that PET drugs are compounded under practice of pharmacy
- **1994**: FDA approves NDA #20-306 for FDG at Methodist Medical Center in Peoria
- **1997**: FDA Modernization Act defined PET drugs as compounded according to state law and USP standards until FDA develops approval procedures and GMPs for PET
My Conclusions

Like the early days of radioactive drugs, the early days of PET drugs were a very dynamic time...

• New class of products with a relatively small cadre of practitioners with required expertise

• Unclear and occasionally conflicting regulatory authorities and requirements

• In the middle of all this, the USP had the foresight to support the development of public standards for these new products

• My opinion: FDAMA would not have been possible without the USP and the work of the ECs in late 80s and early 90s
25th Revision of USP (2002)

- USP began yearly revisions of compendium
- “Subcommittee on Radiopharmaceuticals” became “Expert Committee (EC) on Radiopharmaceuticals and Imaging Agents”
- Committees remained on five-year cycle
25th Revision of USP (2002)

- In 2002, the EC drafted a compounding chapter entitled <1017> Radiopharmaceutical Quality Assurance and Compounding
  - Never published in Pharmacopeial Forum

General chapter <1017> was a tipping point for radiopharmaceuticals.

Had it become official, <1017> would have been a standard that was specific for the compounding of sterile radiopharmaceuticals (instead of <797>).
Members of RMI EC in 25th Revision

- Ron Callahan, Chair (Harvard)
- Ravi Kasliwal (FDA)
- Dennis Swanson (UPMC)
- Michael Tweedle (Ohio State)
- Ralph Weissleder (MGH)
- Robert Wolfangel (Mallinckrodt)

Also an EC for diagnostic information related to radiopharmaceuticals
28th Revision of USP (2005)

- None of the previous EC RMI members served in the 2005 - 2009 cycle
- USP scientific staff liaison assigned to the EC RMI also retired
- Consequently, completely new people involved
28th to 32nd Revision (2005 - 2009)

- Bonnie Dunn, Chair (NIH)
- Joseph Hung, Chair (Mayo)
- Thomas Boothe (Mt. Sinai)
- Patricia Cole
- Ravi Kasliwal (FDA)
- Hank Kung (U Penn)
- Jerome Lewis
- Sally Schwarz (Wash U)
- Steve Zigler (PETNET)

Also an EC for diagnostic information related to radiopharmaceuticals
The challenge—

- Develop a strategy for revisions to monographs and general chapters for PET drugs that were necessary based on the FDA’s pending implementation of FDAMA
28th to 32nd Revision (2005 - 2009)

• USP sponsored sessions at several SNMMI meetings to solicit stakeholder feedback
• First task was to revise <823>
• Established an Expert Panel for this purpose
• Recognized the need to revise other general chapters (but deprioritized until later)
• Wrote stimuli article in *PF* to describe the rationale behind the revision
Revision of USP General Chapter Radiopharmaceuticals for Positron Emission Tomography—Compounding (823)

Joseph C. Hung, PhD, a Sally W. Schwarz, RPh, MS, a,b Steve S. Zigler, PhD, a,b Ravi Ravichandran, PhD a

ABSTRACT This Stimuli article presents the reasons for the proposed revision of General Chapter Radiopharmaceuticals for Positron Emission Tomography—Compounding (823), as well as the basis for each of the major changes. The objectives of this Stimuli article are four-fold: (1) provide background about the need for the proposed revision, (2) offer rationale for each major change, (3) initiate discussion, and (4) solicit public comments that will be reviewed and considered by USP’s Expert Committee.

INTRODUCTION AND HISTORY

The first USP monograph for a positron emission tomography (PET) drug was published in 1989 (7). This monograph described acceptance criteria for identity, strength, quality, and purity characteristics associated with Fludeoxyglucose F 18 Injection. More monographs were published for various PET drugs throughout the 1990s so that the total number of USP monographs for PET drugs now stands at 12. In addition to individual monographs, USP has published two informational gen-

USP 32 will officially constitute the minimum CGMP requirements for investigational and research PET drugs used in human subjects under an Investigational New Drug application (IND) or under the approval of a Radioactive Drug Research Committee (RDRC) (8), and all other PET drugs will be subject to FDA’s new CGMP requirements. It should be noted that the revisions now being proposed to (823) will not be enforceable as part of the Final Rule unless the reference in the Final Rule to USP 32 is updated to reflect the official publication in which the revised (823) is published.

Pharmacopeial Forum 2011, 37(1)
33rd Revision (2010)

- USP eliminated a dedicated EC for Radiopharmaceuticals and Medical Imaging Agents
- Relied on Expert Panels for additional expertise as needed
  - Temporary assignments for targeted projects (e.g., revision of general chapters and evaluation of monographs)
33rd to 37th Revision (2010 - 2014)

- EC Members
  - EC for Physical Analysis (Sally Schwarz)
  - EC for Small Molecules (Steve Zigler)
33rd to 37th Revision (2010 - 2014)

- Revision of <823> became official
- Worked with USP staff and SNMMI Committee on Pharmacopeia* to develop strategy for USP monographs for non-approved PET drugs
  - Omitted these monographs from the USP to bring PET drug monographs in line with other monographs
- Organized an Expert Panel to begin revision of <821> and preparation of <1821> and <1823>

*now: Committee on Radiopharmaceuticals
The Future of USP Monographs for PET Drugs

Sally Schwarz1,2, Jeffrey Norenberg2,3, Marc Berridge2,4, Stephen Dragotakes2,5, Joseph Hung2,6, Jeanne Link2,7, N. Scott Mason2,8, Steve Mattmuller2, Richard A. Nickel2, Alan Packard2,9, Justin Paolino2,10, Neil Petry2,11, James Ponto2,12, Timothy M. Quinton2, Katherine L. Seifert2,13, Dennis Swanson2,14, Ronald E. Weiner2,15, and Steven Zigler2,16

1Washington University School of Medicine, St. Louis, Missouri; 2Committee on Pharmacopeia, Society of Nuclear Medicine and Molecular Imaging, Reston, Virginia; 3University of New Mexico Health Sciences Center, Albuquerque, New Mexico; 43D Imaging, LLC, University of Arkansas for Medical Sciences, Little Rock, Arkansas; 5Beth Israel Deaconess Medical Center, Boston, Massachusetts; 6Mayo Clinic, Rochester, Minnesota; 7University of Washington, Seattle, Washington; 8Department of Radiology, University of Pittsburgh, Pittsburgh, Pennsylvania; 9Boston Children’s Hospital and Harvard Medical School, Boston, Massachusetts; 10Brigham and Women’s Hospital, Boston, Massachusetts; 11Duke University Medical Center, Durham, North Carolina; 12University of Iowa, Iowa City, Iowa; 13Seifert and Associates, Los Angeles, California; 14University of Pittsburgh School of Pharmacy, Pittsburgh, Pennsylvania; 15Ron Weiner Services, Sherman Oaks, California; and 16Siemens PETNET Solutions, Knoxville, Tennessee

J Nucl Med 2013, 54, 472-475
38th Revision (2015)

- USP continued same approach for radiopharmaceutical ECs (i.e., responsibility for radiopharmaceuticals lies with EC for traditional drugs)
- EC for Chemical Medicines 4 (CHM4)
  - Jim Ponto and Steve Zigler
38th to 42nd Revision (2015 - 2019)

- Completed revision of <821> and preparation of <1821> and <1823>
- Organized an Expert Panel to evaluate, and revise as necessary, all monographs for radiopharmaceuticals (in progress)
- Redesigned <823> for consistency with other general chapters (in progress)
- Provided input to USP Sterile Compounding Committee related to compounding issues for sterile radiopharmaceuticals
Lessons from the Past

- USP recently decided to develop a separate general chapter to describe standards for the compounding of sterile radiopharmaceuticals
  - Based on inputs from CHM4 (Jim and Steve)
  - Based on White Paper written by SNMMI Committee on Radiopharmaceuticals, approved by SNMMI BOD, and sent to USP by SNMMI President Sally Schwarz
  - Based on comments received by the USP on the recently proposed revision of <797>
  - Based on Roundtable discussion hosted by USP (Feb 1)
USP Prospectus for <825>

“The objective of the new <825> Compounding—Radiopharmaceuticals is to provide clear and effective USP public standards that meet patient and practitioner needs for compounded sterile radiopharmaceuticals today and in the future. The proposed new general chapter will delineate compounding activities for radiopharmaceuticals and provide standards associated with these activities. When complete, <825> will contain standards for this class of products.”
USP Prospectus for <825>

Type of Posting: General Announcement
Posting Date: 01-Jan-2017
Expert Committee: Chemical Medicines Monographs 4

Expert Panel: Radiopharmaceutical Compounding Panel
Input Deadline: August 31, 2017

Suggested audience: Nuclear medicine professionals, nuclear pharmacists, nuclear pharmacies, radiopharmaceutical manufacturers, and regulatory professionals.

Estimated proposal PF: Pharmacopeial Forum 44(8) [Nov.-Dec., 2018]

Background and objective(s): Radiopharmaceuticals represent a unique class of drug products where compounding activities include the use of radionuclide generators, the preparation of commercially-manufactured radiopharmaceutical kits, the dilution of FDA-approved multi-dose vials, the labeling of human blood products with radionuclides, the preparation of patient-specific doses, etc. These activities occur in an environment where individualized patient needs and the safe handling of radioactive materials demand a high level of professional care and clearly-defined standards that support these activities.

Since 2004, General Chapter 〈797〉 Pharmaceutical Compounding—Sterile Preparations has described standards for the entire spectrum of compounded sterile preparations. Standards for radiopharmaceuticals have been addressed at various levels within 〈797〉, but it has been difficult to develop and maintain standards for radiopharmaceuticals in this manner due to the scope of 〈797〉 and the unique characteristics of radiopharmaceuticals.

On February 1, 2017, the USP hosted a roundtable discussion on compounding standards for radiopharmaceuticals. The roundtable was attended by stakeholders from the nuclear medicine community, regulatory agencies, and USP staff. During this day-long session, participants discussed potential approaches to address the challenges associated with this class of products. Based on this discussion, the stakeholders from the nuclear medicine community strongly favored the development of a new general chapter for radiopharmaceutical compounding. After considering these stakeholder inputs, the USP staff and Compounding Expert Committee agreed with the development of a separate chapter to effectively address these matters.

Related Resources:
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- Chromatographic Columns
- Sign Up for Newsletters & Updates

What's happening at USP? Read our blog to find out.

QM Quality Matters
USP Call for Candidates

Compounding- Radiopharmaceuticals

POSITION: Member
DEADLINE: Jul 9, 2017
REF#: 4636

Role(s):
The United States Pharmacopoeial Convention (USP) is seeking applications to a newly forming expert panel (EP) with a focus on compounding practices in Nuclear Pharmacy. Specifically, the EP will be asked to develop a new general chapter below 1000 that will reflect current practices which are consistent with the state and federal compounding guidelines as they apply to nuclear pharmacy practice. The proposed new general chapter will delineate compounding activities for radiopharmaceuticals and provide standards associated with these activities. Specifically, the panel will develop a chapter that allows flexibility, clarity, ease-of-use, risk/benefit, and evidence-based approaches to standard development.

Organization:
N/A

Expertise Required:
Specific expertise sought for this group includes a deep understanding of the background and concepts that were described in a white paper found at following link: http://snmni.files.cms-plus.com/SNMNI-USP-Recommendations-Final_2016.pdf. Experience with compounding radiopharmaceuticals at hospital and clinical settings during the past 10 years is essential.
The proposed new chapter will be presented in Pharmacopeial Forum in 2018 for public comments.

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Lessons from the Past

*Like the early days of radioactive drugs and more recently with PET drugs, the compounding of sterile radiopharmaceuticals is in the middle of a very dynamic time...*

• There are unclear and occasionally conflicting regulatory authorities/requirements related to compounding (e.g., different definitions of compounding exist)

• These practices are performed by a relatively small cadre of practitioners with the required expertise

• With the support of the nuclear medicine community, the USP will play a key role by bringing clarity to this dynamic situation
Going forward

• I encourage the nuclear medicine community to take an invigorated active role with the USP
• The USP can only serve us to extent that we are engaged participants in the USP process
• We have to be in the USP game, we can’t watch it from the bleachers
• The development of public standards is not quick or easy, but it is a lot better than living by standards developed elsewhere
In order to be, I must participate.

- Antoine de Saint-Exupery