USP CHAPTER <825>

Paul B Mahan, RPh., BCNP
Disclosures

- Regulatory Affairs department of PETNET Solutions/Siemens Corporation
- Member of the USP <825> Expert Panel, but not representing the USP organization in this presentation
USAF SERIES AIRCRAFT

T-43A

FLIGHT MANUAL

BASIC AND ALL CHANGES HAVE BEEN MERGED TO MAKE THIS A COMPLETE PUBLICATION
USP Significance in the Regulatory World

- Was recognized in the Federal Food and Drugs Act of 1906 and again in the Federal Food, Drug, and Cosmetic Act of 1938 (esp. related to adulteration, misbranding)
General Chapters numbered less than <1000> are enforceable

General Chapters may contain the following:

- Descriptions and specifications of conditions and practices for pharmaceutical compounding
USP standards are also enforced at the non-federal level (e.g. BOP Statutes and Regulations)

### How They Are Incorporated/Applied:

- By Direct Reference
- Using USP Standards as Framework for Laws
- Hybrid (State Law + USP Standard)
USP Significance OUTSIDE the Regulatory World

USP Standards also serve as a gauge for quality in the private sector. In as much, USP standards are an expectation for doing business or for the continuation of business

- Internal Hospital Quality/Pharmacy Departments
- Third-Party Accreditation (e.g. Joint Commission)
- Third-Party Inspections (e.g. NABP VPP)
FDA study Jun-Dec 2001 found 34% of compounded sterile preparations failed one or more standard quality tests

Because voluntary compliance was deemed inadequate to protect the public, USP set forward in the development of standards that could be enforced by state boards of pharmacy, accreditation organizations, etc.

2004: <797> Pharmaceutical Compounding - Sterile Preparations

Radiopharmaceuticals were not specifically mentioned
USP General Chapter <797> (cont’d)

- **PF 32(3) May-June 2008** revision proposal of <797>
  - Added a short section on “Radiopharmaceuticals as CSPs”
  - e.g., Tc 99m generators can be eluted in ISO Class 8 room
- **PF 41(6) Nov-Dec 2015** revision proposal of <797>
  - “Radiopharmaceuticals as CSPs” section slightly expanded, but lacks sufficient details to fully differentiate the aspects specific to radiopharmaceuticals
  - >8000 comments received from >2500 stakeholders About 100 of these comments addressed Section 17 Radiopharmaceuticals as CSPs -- all indicated inadequacy of this section
  - A modified proposed revision will be published in **PF 44(5)** Sept-Oct 2018 for an additional round of public comment, with proposed implementation date of Dec 1, 2019
FDA Listening Session

- September 2014: FDA held a listening session to begin gathering stakeholder input regarding radiopharmaceutical compounding
- Of special interest was differentiating preparation vs. compounding, and preparation with minor deviations
CORAR Response

- November 2014: The Council on Radionuclides and Radiopharmaceuticals (CORAR), with support from groups listed below, responded to FDA with proposed definitions and descriptions of preparation, minor deviations, and compounding:
  - American Pharmacists Association (APhA)
  - National Association of Nuclear Pharmacies (NANP)
  - Society of Nuclear Medicine and Molecular Imaging (SNMMI)
  - United Pharmacy Partners (UPPI)
2nd FDA Listening Session

- April 2016: more discussion of preparation vs. compounding and examples of activities that would be considered minor deviations
June 2017: more discussion of various items described in the Draft Guidance for Compounding and Repackaging of Radiopharmaceuticals

- FDA draft guidance document for radiopharmaceutical compounding (12/29/2016) is still undergoing public comment
- currently, different interpretations by different inspectors
New USP Chapter on Radiopharmaceutical Compounding

- April 2016: Jim Ponto and Steve Zigler (members of USP Chemical Medicine Monographs 4 Expert Committee) met with USP staff and discussed the need for a new separate chapter for compounding radiopharmaceuticals

  • precedent for a separate chapter: <800> Hazardous Drugs – Handling in Healthcare Settings
  
  • precedent for radiopharmaceutical chapter: <823> Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses
  
  • other general chapters dedicated to radioactivity/radiopharmaceuticals:
    o  <821> Radioactivity
    o  <1821> Radioactivity – Theory and Practice
    o  <1823> Positron Emission Tomography Drugs - Information
SNMMI White Paper

USP Public Standards for Compounded Sterile Radiopharmaceuticals: Recommendations from the SNMMI

Written and approved by the SNMMI Committee on Radiopharmaceuticals (COR)

Robert W. Atcher\textsuperscript{1,2}, Marc S. Berridge\textsuperscript{1,3}, Eszter Boros\textsuperscript{1,4}, Roy W. Brown\textsuperscript{1,5}, Cathy S. Cutler\textsuperscript{1,6}, Stephen C. Dragotakes\textsuperscript{1,7}, D. Scott Holbrook\textsuperscript{1,8}, Alan R. Ketrin\textsuperscript{1,9}, Suzanne Lapi\textsuperscript{1,10}, Jeanne M. Link\textsuperscript{1,11}, Steve Mattmuller\textsuperscript{1,12}, Renata Mikołajczak\textsuperscript{1,13}, Ashley E. Mishoe\textsuperscript{1,14}, Alan B. Packard\textsuperscript{1,15}, Michele A. Panichi-Egberts\textsuperscript{1,16}, Neil A. Petry\textsuperscript{1,17}, James A. Ponto\textsuperscript{1,18}, Wolfgang Runde\textsuperscript{1,19}, David M. Schuster\textsuperscript{1,20}, Sally W. Schwarz\textsuperscript{1,21}, Katherine L. Seifert\textsuperscript{1,22}, George Sgouros\textsuperscript{1,23}, Michael G. Stabin\textsuperscript{1,24}, Dennis P. Swanson\textsuperscript{1,25}, Kara D. Weatherman\textsuperscript{1,26}, Steven S. Zigler\textsuperscript{1,27}

\textsuperscript{1}Committee on Radiopharmaceuticals, Society of Nuclear Medicine and Molecular Imaging, Reston, Virginia; 2University of New Mexico Health Sciences Center, Albuquerque, New Mexico; 33D Imaging, University of Arkansas for Medical Sciences, Little Rock, Arkansas; 4Harvard Medical School, Charlestown, Massachusetts; 5Mallinckrodt Pharmaceuticals, St. Louis, Missouri; 6Brookhaven National Laboratory, Upton, New York; 7Beth Israel Deaconess Medical Center, Boston, Massachusetts; 8Clinical Pharmacy Service, Gray, Tennessee; 9University of Missouri School of Medicine, Columbia, Missouri; 10University of Alabama at Birmingham, Birmingham, Alabama; 11University of Washington, Seattle, Washington; 12Kettering Medical Center, Kettering, Ohio; 13National Centre for Nuclear Research, Otwock, Poland; 14University of California San Francisco School of Medicine, San Francisco, California; 15Harvard Medical School, Cambridge, Massachusetts; 16Nuclear Diagnostic Products, Cherry Hill, New Jersey; 17Duke University Medical Center, Durham, North Carolina; 18University of Iowa Hospitals and Clinics, Iowa City, Iowa; 19Los Alamos National Laboratory, Los Alamos, New Mexico; 20Emory University School of Medicine, Atlanta, Georgia; 21Washington University School of Medicine, St. Louis, Missouri; 22Seifert and Associates, Los Angeles, California; 23Johns Hopkins University School of Medicine, Baltimore, Maryland; 24Vanderbilt University School of Medicine, Nashville, Tennessee; 25University of Pittsburgh School of Pharmacy, Pittsburgh, Pennsylvania; 26Purdue University College of Pharmacy, West Lafayette, Indiana; 27Siemens PETNET Solutions, Knoxville, Tennessee
SNMMI White Paper

- Fall 2016 – SNMMI COR developed a white paper entitled *USP Public Standards for Compounded Sterile Radiopharmaceuticals: Recommendations from SNMMI*

- Three recommendations from the white paper:

  1. **Delineate** common practices that are defined as sterile compounding within the practice of nuclear pharmacy

  2. Create a public standard for the **preparation, compounding, and dispensing** of sterile radiopharmaceuticals with the practice of nuclear pharmacy [i.e., create a new general chapter]

  3. **Reinstate** an expert committee dedicated to all standards for radiopharmaceuticals [i.e., chapters and monographs]
White Paper published in INM and sent to USP

Dear Dr. Venema,

On behalf of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), I would like to share with you a white paper pertaining to USP public standards for radiopharmaceuticals. The goal of the white paper, which was recently approved by the SNMMI Board of Directors and will soon appear in the Journal of Nuclear Medicine, is to review a complex set of issues that have confronted nuclear pharmacists, boards of pharmacy, federal regulators, and other specialists in the field of radiopharmaceuticals. I am writing to you today because the USP can play a critical role in resolving these issues through the innovative leadership that has been a hallmark of USP involvement in radiopharmaceuticals for more than 50 years. Before getting to the details, let me first provide some background on this topic.

The SNMMI is the world's leading professional organization dedicated to nuclear medicine and molecular imaging. In support of more than 18,000 members worldwide, the SNMMI disseminates educational information, provides a forum for the exchange of basic scientific information, and leads advocacy efforts related to nuclear medicine. Within the society, the Committee on Radiopharmaceuticals (COR) provides leadership to SNMMI members on the preparation, handling, and compounding of radiopharmaceuticals. As such, COR represents the discipline within the SNMMI that is most pertinent to the USP. The membership of the COR currently consists of 20 leading scientists in the field of nuclear medicine from academic institutions and commercial manufacturers. Several COR members have served or currently serve in volunteer capacities for the USP, including membership on expert committees and delegations to the USP convention. I estimate that the collective professional experience of the COR is almost 500 years! This argues that the COR is the world's leading authority on the preparation and handling of radiopharmaceuticals and medicinal uses.

Over the years through its involvement with the USP, as well as related activities with the FDA, state boards of pharmacy, trade associations, etc., the COR has concluded that certain common practices in the field of nuclear pharmacy are not adequately defined by generally accepted practice standards. Even worse, the COR has found that the few standards that do exist differ depending on which organization set the standards. I think you will agree that the shortcomings are not insignificantly different in many cases, and even threaten the safe use of radiopharmaceuticals in the U.S. In response to these challenges, the COR has 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 there still remains a need for suitable standards that are generally accepted for common practices in nuclear pharmacy. In order to resolve the remaining challenges, the COR has prepared the following recommendations.

Sally Schwartz
President, SNMMI
USP Stakeholders Workshop on Radiopharmaceutical Compounding

- Held at USP HQ on Feb 1, 2017
- Invited participants included representatives from:
  - Chemical Medicines Monographs 4 Expert Committee
  - Compounding Expert Committee
  - Nuclear pharmacists in hospital, commercial, and academic settings
  - FDA
  - SNMMI COR
  - USP staff

- Practitioner stakeholders were strongly in favor of developing a separate chapter for radiopharmaceutical compounding
Draft <795>

- <795> Pharmaceutical Compounding – Nonsterile Preparations
  - Potential Implementation date of December 1, 2019

“Specialty areas such as radiopharmaceuticals require special training and are beyond the scope of this chapter.”
USP Chapter <825>

- Encompasses both sterile and non-sterile radiopharmaceutical processing
USP Chapter <825>

- Scope and Rationale (posted June 1, 2017):
  “The objective of the new General Chapter <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.”
Proposed New General Chapter <825>

- Now Titled: Radiopharmaceuticals – Preparation, Compounding, Dispensing and Repackaging
Formation of Expert Panel

• Call for Candidates sent June 2017
• More than 60 applicants for the Expert Panel (!!)
Formation of Expert Panel

- Preferred candidate characteristics:
  - nuclear pharmacy experience in a commercial setting
  - nuclear pharmacy experience in a hospital setting
  - experience teaching nuclear pharmacy (academic setting)
  - experience interacting with State Boards of Pharmacy
  - hold board certification in nuclear pharmacy
  - participant at USP Stakeholders Roundtable meeting
  - participant at FDA listening sessions
  - members of CHM4 EC and Compounding EC
  - work for regulatory agency
## Selected <825> Panel

<table>
<thead>
<tr>
<th>David Barnes</th>
<th>Brenda Jensen*</th>
<th>James Ponto †</th>
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<tr>
<td>Allegra DePietro</td>
<td>Ravi Kasliwal #</td>
<td>Sara Rothman #</td>
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<td>Wendy Galbraith</td>
<td>Patricia Kienle*</td>
<td>Vivian Loveless</td>
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<td>Fred Gattas</td>
<td>Paul Mahan</td>
<td>Steve Zigler †</td>
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<td>Richard Green</td>
<td>Rezaul Mannon</td>
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**USP staff:** Domenick Vicchio, Ravi Ravichandran, Gerald Hsu, James Austgen

† member, Chemical Medicines Monographs 4 Expert Committee  
* member, Compounding Expert Committee  
# FDA representative
**Representation within 〈825〉**

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<tr>
<th>Institution</th>
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<th>Regulatory</th>
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<th>Hospital Pharmacy Chain</th>
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1. Introduction
2. Radiation Safety Considerations
3. Personnel Qualifications, Training, and Hygiene
4. Facilities and Engineering Controls
5. Microbiological Air and Surface Monitoring
6. Cleaning and Disinfecting
7. Assigning BUD
8. Documentation
9. Preparation
10. Compounding
11. Dispensing
12. Repackaging
13. Quality Assurance (QA) and Quality Control (QC)
14. Glossary
Important Dates for <825>!

- JULY 27, 2018: Proposed Chapter <825> to be Posted on the USP Website (Public Comment Period Opens)

http://www.usp.org/chemical-medicines/radioactive-articles
Important Dates for <825>!

- September 4, 2018: Official Publication in Pharmacopeial Forum
- October 10, 2018: Tentative Date for Open Microphone Session (USP/Expert Panel will highlight changes in the proposed <825> and answer stakeholder questions). This Will be Recorded!
Important Dates for <825>!

- November 30, 2018: Public Comment Period Ends
- November 30, 2018 Through Early 2019: EP Will Review ALL Public Comments and Revise <825> as Appropriate
- June 1, 2019: Anticipated Publication Date of Final <825>
- December 1, 2019: Anticipated Date <825> Becomes Official
What We Need!

- Please review and submit comments during the comment period (July 27, 2018 through November 30, 2018)
- Comments of agreement and support are as important (possibly more important) as comments asking for changes
A significant thanks to James A. Ponto MS, RPh, BCNP and James R Austgen PhD for their extensive content contributions for Chapter <825> this presentation
THANK YOU!!!