Open Microphone Session on USP General Chapter <825>
Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging

October 10, 2018
11:00 am – 1:00 pm ET
NOTICE TO PARTICIPANTS:

- To minimize background noise, all lines will be muted upon joining the session.

- During the meeting, you may ask questions or make comments at any time by using the Chat function
  - Select the Chat icon from the task menu on the bottom of your WebEx view page
  - Use the text box to enter your question
  - In the “Send” dropdown, select “Host”

- Questions will be collated for the Q&A portion of the WebEx.

Your meeting controls will appear on the bottom of the screen. Select the chat feature.
NOTICE TO PARTICIPANTS:

- Please note this session is currently being recorded and will be made available on USP’s website at http://www.usp.org/chemical-medicines/general-chapter-825

**USP General Chapter <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging**

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

**Important Updates**

- July 27, 2018 - The proposed <825> is now posted for public comment*

[Download the Proposed GC <825>]
[Submit Comments to the Proposed GC <825>]

*Public comment period closes August 24, 2018.
# Agenda

<table>
<thead>
<tr>
<th>Session Overview</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP Overview</td>
<td>James Austgen, Expert Committee Manager</td>
</tr>
<tr>
<td>Overview of General Chapter &lt;825&gt;</td>
<td>James Ponto, Chair, &lt;825&gt; Expert Panel</td>
</tr>
<tr>
<td>*Radiopharmaceuticals—Preparation, Compounding,</td>
<td></td>
</tr>
<tr>
<td>Dispensing, and Repackaging*</td>
<td></td>
</tr>
<tr>
<td>Submitting Comments</td>
<td>James Austgen</td>
</tr>
<tr>
<td>Timeline and Next Steps</td>
<td>James Austgen</td>
</tr>
<tr>
<td>Question &amp; Answer Session</td>
<td><strong>Moderator:</strong> Ravi Ravichandran, Principal Scientific Liaison, Chemical</td>
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<tr>
<td></td>
<td>Medicines</td>
</tr>
<tr>
<td></td>
<td><strong>Panelists:</strong> (&lt;825&gt; Expert Panel Members)</td>
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<td></td>
<td>• James Ponto</td>
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<td>• Brenda Jensen</td>
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<td>• Paul Mahan</td>
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<td></td>
<td>• Allegra DePietro</td>
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</tbody>
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USP Overview

James R. Austgen, PhD
Expert Committee Manager, Chemical Medicines
Building foundations for a healthier world
Empowering a healthy tomorrow

A healthier world needs a strong foundation—one that establishes quality, sets the bar for scientific rigor and technological progress, and epitomizes collaboration between industry, nonprofits, government and academia.

From the standards we create to the partnerships and conversations we foster, our scientists, advocates and network of experts are critical to constructing and reinforcing this foundation to ensure people stay healthy.
200 years building quality foundations for a healthier world
Mission

To improve global health through public standards and related programs that help ensure the quality, safety and benefit of medicines and foods
Advocating for quality

USP is an organization of organizations, with 450+ members representing academia, health practitioners, manufacturers, governmental bodies and consumer organizations.
800+

external experts
from industry, governments, nonprofits and academia
The experts behind our standards

2015–2020 Council of Experts

Healthcare Quality Standards Collaborative Group
- Nomenclature & Labeling
- Compounding
- Healthcare Quality

Chemical Medicines Monographs Collaborative Group
- Chemical Medicines Monographs 1
- Chemical Medicines Monographs 2
- Chemical Medicines Monographs 3
- Chemical Medicines Monographs 4
- Chemical Medicines Monographs 5

Biologics Collaborative Group
- B101 Peptides
- B102 Proteins
- B103 Complex Biologicals
- BIO4 Antibiotics
- GC Biological Analysis

Excipient Monographs Collaborative Group
- Excipient Monographs 1
- Excipient Monographs 2

Dietary Supplements/Herbal Medicines/Foods Collaborative Group
- Botanical Dietary Supplements & Herbal Medicines
- Food Ingredients

General Chapters Collaborative Group
- Non-Botanical Dietary Supplements
- Chemical Analysis
- Physical Analysis
- Statistics
- Microbiology
- Dosage Forms
- Packaging & Distribution

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## <825> Expert Panel

**Chair:** James Ponto, MS, University of Iowa; Chemical Medicines 4

<table>
<thead>
<tr>
<th>Member</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steve Zigler, PhD [CHM4 EC]</td>
<td>PETNET Solutions</td>
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<tr>
<td>Brenda Jensen, MA [Compounding EC]</td>
<td>Compounding Consultants, LLC</td>
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<td>Patricia Kienle, MPA [Compounding EC]</td>
<td>Cardinal Health</td>
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<td>David Barnes, BS Pharm</td>
<td>GE Healthcare</td>
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<td>Allegra DePietro, MS</td>
<td>Massachusetts General Hospital</td>
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<td>Wendy Galbraith, PharmD</td>
<td>University of Oklahoma</td>
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<td>Fred Gattas, PhamD</td>
<td>Curium</td>
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<td>Richard Green, BS Pharm</td>
<td>Cardinal Health</td>
</tr>
<tr>
<td>Vivian Loveless, PharmD</td>
<td>University of Tennessee</td>
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<tr>
<td>Paul Mahan BS Pharm</td>
<td>PETNET Solutions</td>
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<td>Rezaul Mannan, PhD</td>
<td>Health Canada</td>
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<td>Ravindra Kasliwal, PhD</td>
<td>FDA</td>
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<tr>
<td>Sara Rothman, JD</td>
<td>FDA</td>
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</tbody>
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How we work

**Stakeholders**
- USP actively seeks engagement with stakeholders throughout the standard-setting process through stakeholder meetings, advisory roundtables, and open-microphone webinars.
- Healthcare Practitioners
- Patients
- Academicians
- Healthcare Industry
- Regulatory Authorities
- Manufacturers

**USP Process**
1. **Public Health Need**
   - Need identified by any stakeholder or USP
   - Need evaluated for possible standard development

2. **Draft Standard**
   - Best practices and scientific information collected

3. **Public Comment Period**
   - Draft standard published for stakeholder input

4. **Review & Approval**
   - Comments evaluated and addressed
   - Comments evaluated and further revision and comment needed

5. **Publication**
   - Final standard published with official date at least 6 months after publication

**USP Expert Committee**
- USP convenes a committee of independent experts that are knowledgeable on the public health issue to develop the standard.
- Healthcare Practitioners
- Academicians
- Healthcare Industry
- Regulatory Authorities (Non-voting Liaisons)
- Manufacturers

**Stakeholder Implementation**
Early days of sterile compounding....
With growth and complexity, need for “instruction manual”
Sterile compounding now....
Radiopharmaceuticals are similar yet different…. Need for a separate “instruction manual”
Radiopharmaceuticals in <797>

- 2004: <797> Pharmaceutical Compounding - Sterile Preparations
  - Radiopharmaceuticals were not explicitly mentioned

- 2008: First revision <797>
  - Added a short section on “Radiopharmaceuticals as CSPs”
  - e.g., Tc 99m generators can be eluted in ISO Class 8 room

- 2015: Proposed second revision <797> published in Pharmacopeial Forum (PF) for public comment
  - “Radiopharmaceuticals as CSPs” section slightly expanded
  - about 100 comments addressed Radiopharmaceuticals as CSPs—all indicated inadequacy of this section
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:

- Delineate common practices that are defined as sterile compounding within the practice of nuclear pharmacy
- 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]
- Reinstate an expert committee dedicated to all standards for radiopharmaceuticals [i.e., chapters and monographs]

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
After serious discussion and deliberation, in May 2017 the decision was made to create a new chapter

Scope and Rationale (posted June 1, 2017):

http://www.usp.org/usp-nf/notices/825-compounding-radiopharmaceuticals

“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.”
Expert Panel Membership, August 2017

David Barnes       Brenda Jensen*       James Ponto†
Allegra DePietro   Ravi Kasliwal #      Sara Rothman #
Wendy Galbraith    Patricia Kienle*     Vivian Loveless
Fred Gattas        Paul Mahan          Steve Zigler†
Richard Green      Rezaul Mannon

USP staff: Domenick Vicchio, Ravi Ravichandran, Gerald Hsu, James Austgen

† member, Chemical Medicines Monographs 4 Expert Committee
* member, Compounding Expert Committee
# FDA representative
<825> Timeline

- Sept 28, 2017: First face-to-face meeting of Expert Panel
- Sept-Nov 2018: Published in *Pharmacopeial Forum* 44(5)
- Oct 10, 2018: Open microphone session (webcast)
- Nov 30, 2018: Public comment period closes
- Jun 1, 2019: Anticipated revised, final <825> published in USP-NF
- Dec 1, 2019: Anticipated official date
<825> Major Objectives

- Describe all various non-manufacturing processing activities for radiopharmaceuticals, not just ‘compounding’
  
  Title changed to “Radiopharmaceuticals -- Preparation, Compounding, Dispensing, and Repackaging”

- Include both nonsterile and sterile radiopharmaceuticals

- Describe reasonable standards that balance radiation risks with aseptic handling practices

- Add sections important for radiopharmaceuticals, including:
  - preparation with minor deviations
  - extension of manufacturer-suggested use-by times for kit preparations
  - immediate-use RBC labeling
  - labeling of blood components
Development of Content

- Start with existing documents and modify as appropriate
  - USP standards (e.g., <797>)
  - Regulatory rules and guidances (e.g., NRC, FDA, CDC, state boards of pharmacy)
  - Other radiopharmaceutical handling guidelines (e.g., SNMMI, APhA)

- Although the Expert Panel members were chosen to represent the majority of users, the EP encourages and welcomes public comment for improvement
1. INTRODUCTION

Describes intent and applicability

Does not apply to:

- Manufacturing radiopharmaceuticals in drug establishments
- Compounding radiopharmaceuticals in 503B outsourcing facilities
- Preparing PET drugs under USP <823>
- Administration to patients
- Non-radioactive drugs (e.g., pharmacologic adjuncts)

1.1 Nonsterile Radiopharmaceuticals

1.2 Sterile Radiopharmaceuticals
2. RADIATION SAFETY CONSIDERATIONS

*Emphasize importance of radiation safety and the need to balance it with aseptic handling practices*

2.1 Time

2.2 Distance

2.3 Shielding

2.4 Radiation Contamination Control
3. PERSONNEL QUALIFICATIONS, TRAINING, AND HYGIENE

3.1 Aseptic Qualifications

3.2 Re-evaluation, Retraining, and Requalification

3.3 Ancillary Personnel

3.4 Hand Hygiene and Garbing for Immediate Use Preparations

3.5 Hand Hygiene and Garbing for Buffer Rooms and Segregated Radiopharmaceutical Processing Area
4. FACILITIES AND ENGINEERING CONTROLS

4.1 Facility Design and Environmental Controls
4.2 Creating Areas to Achieve Easily Cleanable Conditions
4.3 Water Sources
4.4 Placement and Movement of Materials
4.5 Classified Rooms
4.6 Remote Aseptic Processing Involving a Hot-Cell
4.7 Environmental Controls
5. MICROBIOLOGICAL AIR AND SURFACE MONITORING

5.1 General Monitoring Requirements

5.2 Monitoring Air Quality for Viable Airborne Particles

5.3 Monitoring Surfaces for Viable Particles
6. CLEANING AND DISINFECTING

6.1 Cleaning, Disinfecting, and Sporicidal Agents
6.2 Cleaning Supplies
6.3 Cleaning and Disinfecting the PEC
6.4 Disinfecting Supplies for Classified Rooms and SRPAs
6.5 Disinfecting Critical Sites within the PEC
6.6 Cleaning and Disinfecting Items from Patient Care Areas
7. ASSIGNING BUD

Table 7 summarizes maximum BUDs for various radiopharmaceutical processing activities and in various environmental air quality conditions.

Also includes a discussion of issues to be considered in assigning BUDs for radiopharmaceuticals, such as:

- Radiochemical purity
- Radionuclidic purity
- Age of generator eluate
- Number of particles
- Specific activity (molar mass)
- Container type
8. DOCUMENTATION

8.1 Master Formulation Record

8.2 Records for Preparation with Minor Deviation/Compounding
9. PREPARATION

9.1 Preparation Following Manufacturer Instructions

9.2 Preparation with Minor Deviations
   (e.g., activity, volume, dilution, heating, radiochemical purity testing methods, filtering)

9.3 Preparation of Radiolabeled Blood Components
   (e.g., autologous leukocytes)

9.4 Immediate Use of Red Blood Cell Labeling
10. COMPOUNDING

10.1 Compounding Nonsterile Radiopharmaceuticals
(e.g., oral capsules, radiolabeling food)

10.2 Compounding Using Conventionally Marketed Drug Products
(e.g., mixing two sterile injections, kit-splitting)

10.3 Sterile Compounding Using a Nonsterile Drug Substance or Components
11. DISPENSING

11.1 Dispensing and Radioassay

11.2 Labeling

11.3 Direct Infusion Systems

11.4 Transporting Generators Between Facilities
12. REPACKAGING

13. QUALITY ASSURANCE AND QUALITY CONTROL
   13.1 Notification About and Recall of Out-of-Specification Dispensed Radiopharmaceuticals
   13.2 Complaint Handling
   13.3 Adverse Event Reporting
GLOSSARY

APPENDICES

Appendix 1: Abbreviations [acronyms]

Appendix 2: Example Designs for Radiopharmaceutical Handling
Submitting Comments
USP General Chapter <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging

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Important Updates

- July 27, 2018 - The proposed <825> is now posted for public comment*

  - Download the Proposed GC <825>
  - Submit Comments to the Proposed GC <825>
  - Instructions on how to submit comments to the Proposed GC <825>
Welcome to the electronic form for submitting comments on USP's proposed revisions to General Chapter <825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging. USP General Chapter <825> provides standards for processing radiopharmaceuticals. Please use this electronic form to submit your comments to the proposed revisions to <825>.

Instructions
Submit your specific comments with the relevant line numbers provided in the proposed chapter (preferred). [NOTE – line numbers are located on the left side of the proposed chapter chapter revision]. If you have general comments not associated with a line number, enter them in the text box when prompted in the form. Email Raw Bunchard at if you have any questions or need additional information.

General Chapter Overview
Radiopharmaceuticals (radioactive drugs) represent a distinct class of drugs where processing activities include the use of radionuclide generators, preparation and dispensing from commercially-manufactured radiopharmaceutical kits, the dispensing and repackaging of commercially-manufactured radiopharmaceutical finished products into a patient-ready container, compounding sterile and nonsterile radiopharmaceuticals, and the labeling of blood components with radionuclides. These activities occur in an environment where individualized patient needs and the safe handling of radioactive materials demand a high level of professional expertise and clearly-defined standards that support these activities.

Many aspects of sterile radiopharmaceutical practices are similar to sterile compounding of conventional drugs (e.g., aseptic practices, environmental facilities). However, radiopharmaceutical processing also involves (as applicable) many unique aspects, including worker and public radiation protection measures (e.g., time, distance, shielding, negative pressure gradients), presence and use of special auxiliary supplies (e.g., radiation shields, absorbent pads for radioactive contamination control), and special equipment (e.g., radioactivity measuring devices, radiation monitors, remote manipulators). Radiation safety considerations often necessitate a deviation from the standard sterile practices described in Pharmaceutical Compounding—Sterile Preparations (795) and the nonsterile practices detailed in Pharmaceutical Compounding—Nonsterile Preparations (796). The intent of this chapter is to describe practices to provide a reasonable assurance of maintaining patient safety.
Public Comment Form

Please enter your contact information.

First Name
Last Name
Degree
Email
Phone Number
Title
Organization

NEXT
<825> Public Comment Form

Please select the type of comments you would like to submit on General Chapter <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging.

Select Specific Comments if you have specific line numbers corresponding to your comments.
Select General Comments if you have a general comment that does not have a corresponding line number.

If you have both general and specific comments, please select both options. You will be prompted to enter your general comments first, followed by your specific comments.

- Specific Comments - Preferred [Only 20 specific comments allowed per log-in]
- General Comments
<825> Public Comment Form

**General Comment Entry**
This entry format is for comments that do not have corresponding line numbers.

Please enter the comment or specific change requested.

Please enter the rationale for your comment or change requested.
Specific Comment Entry
Please submit one comment at a time.

Please enter the **line number(s)** corresponding to your comment.
(The line number can be found on the left margin of the proposed general chapter.)

Please enter the **specific change** requested.

Please enter the **rationale** for the specific change requested above.
<797> Public Comment Form

Thank you for submitting comments for <825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging. You will receive an email from USP within 5-7 business days confirming receipt of your comments. If you have any questions, please email rr@usp.org.

Sign-up to receive the latest news on USP activities by signing up for email updates or visit the USP Website for more information.
Timeline and Next Steps
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**Important Updates**

- July 27, 2018 - The proposed <825> is now posted for public comment*
  
  Download the Proposed GC <825>  
  Submit Comments to the Proposed GC <825>

  Instructions on how to submit comments to the Proposed GC <825>
USP Timeline for General Chapter Revisions

- November 30, 2018 - Public Comment Period for <825> will close
- June 1, 2019 - Intended Publication Date of <825> in USP–NF
- December 1, 2019 - Anticipated Official Date for <825>
Next Steps

- Stakeholders submit comments using the electronic form
  - <825> Expert Panel will review all comments
  - Comments will be addressed through commentary posted on the USP website
Question & Answer Session

Moderator: Ravi Ravichandran
Panelists (Expert Panel Members):
- James Ponto
- Brenda Jensen
- Paul Mahan
- Allegra DePietro
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To submit a question, send a message to James Austgen (the Host) in the chat feature.
Thank You

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Stay Connected

CompoundingSL@usp.org

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