January 30, 2026

USP Executive Secretariat
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA

Re: Proposed revisions to USP <825> "*Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging.*"

USP Small Molecules Therapeutic Area 4 Expert Panel:

On behalf of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), we commend the Expert Panel for their work in developing these proposed changes. We appreciate the opportunity to submit comments in response to the U.S. Pharmacopeia proposed revisions to USP <825> "*Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging.*"

About SNMMI
SNMMI is a global nonprofit organization dedicated to advancing nuclear medicine, molecular imaging, and theranostics through its education and research programs. Founded in 1954, SNMMI brings together more than 15,000 members who are professionals from all parts of the field to drive innovation, establish practice standards, and enhance education in precision medicine, improving patient care through advanced imaging and therapies that transform diagnosis and treatment. SNMMI's members set the standard for molecular imaging and nuclear medicine practice by creating guidelines, sharing information through journals and meetings, and leading advocacy on key issues that affect molecular imaging and therapy, research, and practice.

SNMMI is grateful for the chance to provide the comments below and thanks the USP for considering them.

General Comments:

Lack of Focus:
While the intent of <825> is to provide uniform minimum standards for the preparation, compounding, dispensing, and repackaging of sterile and nonsterile radiopharmaceuticals, the application of a single uniform standard as proposed by this draft across a wide range of practice settings presents significant challenges, given the highly diverse workflows and settings the chapter encompasses. As written, we find that portions of the chapter are overly prescriptive, confusing, or too vague; are inconsistent with other USP chapters; or are insufficiently supported by scientific evidence. Other sections lack clarity regarding applicability outside of nuclear pharmacy operations e.g., hospital and clinical practice settings. We believe that further revision of the chapter to address different activities in different practice settings is warranted, along with the input of additional expertise on the Expert Panel from practitioners with experience in receiving, manipulating, and preparing unit dose radiopharmaceuticals prior to patient administration in nuclear medicine department settings.

Lack of Harmonization with existing USP chapters:
There is a lack of harmonization in the proposed revisions, specifically with radiopharmaceutical beyond-use dates (BUDs) listed in Table 7 and BUDs listed in other chapters (USP <797>). In this light, we recommend further revision of <825> to remove the specific BUD times identified in the chapter and recommend that the USP implement guidelines for a risk-based approach when developing practical use times for the preparation, compounding, and dispensing of radiopharmaceuticals. Using a risk-based approach with USP guidance would enable the clinical setting to apply

appropriate radiopharmaceutical use times specific to its practice. Furthermore, the risk-based approach to developing practical use times aligns with the EANM guideline on quality risk management for radiopharmaceuticals.

Basis of Risk:
When <825> was proposed, it was encouraged and welcomed by the greater nuclear medicine community as a necessary delineation of radiopharmaceutical aseptic practices, which were poorly served by USP<797>.

However, it quickly became evident that the basis of risk applied in the development of <825> was strongly influenced by incidents unrepresentative of standard radiopharmaceutical aseptic practices and resulted in a chapter that was far more restrictive than what was appropriate for the risk levels involved; to whit the preparation of FDA-approved radioactive drugs in the clinical setting. Of note, the basis of risk assessment involving sterile radiopharmaceuticals in the two references provided by USP in their FAQ section (Patel PR et al and Moore ZS et al) show examples of patient harm from mishandled radiopharmaceuticals, but there was no breach in the sterile technique that was responsible for patient harm. Rather, it was in fact individuals who willfully ignored existing policies and procedures. This is demonstrably operational risk from poor supervision and training, and, as such, the articles cited do not provide scientific or validated support for many of the burdensome and overly prescriptive requirements laid out in this chapter (e.g., SRPA, immediate use timing, generator storage conditions).

Definitions:
In several locations in the chapter (2.2 Distance, 2.3 Shielding, etc.), the term “handlers” is used (“handlers of radiopharmaceuticals”). This is not a defined term in the glossary, nor is it a commonly used term across various regulatory entities. Since radioactive materials should not be handled by those who are not employed at a given facility licensed to handle radioactive materials, the terms personnel or employees should be used.

Specific Comments:

1. Introduction *“Furthermore, these standards apply to sterile intravascular radioactive devices (e.g., radioactive microspheres for intravascular brachytherapy).”*

Premise:
Brachytherapy sources, including sterile radioactive spheres for intravascular brachytherapy, are regulated as medical devices rather than as drugs and therefore should not be classified under radiopharmaceutical drugs.

Suggested change:
Given the title of the chapter specifies radiopharmaceuticals and not medical devices, to avoid confusion between the classes (devices versus drugs), a separate sub-chapter for brachytherapy devices with appropriate statements on applicability and limitations as well as specific definitions related to sterile brachytherapy devices should be added.

1.2 Sterile Radiopharmaceuticals
“The most important factor for maintaining sterility is the avoidance of touch contamination. Wipe….”

Premise:
This paragraph provides an extremely detailed discussion of how to handle wiping a vial septum; however, this is not the only place where touch contamination could occur (for example, removing a needle from a unit dose syringe prior to injection). Other areas in the chapter do not provide this level of detail on how to accomplish specific tasks.

Suggested change:
Maintain chapter continuity by removing detailed examples such as this. Creation of an additional informational chapter (USP <1825>) would be useful to provide additional detail to specific chapter requirements.

3. Immediate Use of Sterile Radiopharmaceuticals
"Intrathecally administered radiopharmaceuticals must not be dispensed according to immediate use standards."

Premise:
It is implied that this radiopharmaceutical must be dispensed in an appropriate ISO 5 workstation, due to the higher risk associated with intrathecal administration; however, there are other products referenced in this chapter which are administered via other higher risk routes (brachytherapy spheres administered via arterial administration, radiopharmaceuticals administered into ventricular shunts to evaluate shunt patency) that do not carry this same immediate use restriction. It is unclear why some actions are considered to be higher risk than others, and there has been no scientific support for statements such as these. Forcing the dispensing of these products to occur in an ISO 5 environment will be detrimental to patient access as most facilities do not have the space/equipment to carry out this requirement.

Suggested change:
Higher risk administration items along with their handling and use should be discussed in a separate sub-chapter or in an informational chapter.

3. Immediate Use of Sterile Radiopharmaceuticals

"All components involved must be discarded within 1 hour of being punctured or after administration to a single patient, whichever is first."

Premise:
There is no scientific validation of the 1-hour expiration time for immediate use radiopharmaceuticals, and this is inconsistent with the same section of USP <797> addressing immediate use requirements which allows a 4-hour immediate use time frame.

Per USP <797> FAQs:

18. Does a conventionally manufactured sterile products for administration to a single patient in accordance with manufacturer's approved labeling outside of ISO class 5 conditions have to be administered within 4 hours of reconstitution or mixing if it meets all the conditions in *Preparation Per Approved Labeling*?
ANSWER:
No. When all of the conditions in 1.4 Preparation Per Approved Labeling are met, the storage information in the manufacturer's approved labeling may be followed.

25. Why does the immediate use CSP provision allow for administration to begin within 4 hours following the start of the preparation?
ANSWER:
The immediate-use CSP provision was revised to allow up to 4 hours for beginning administration to balance the need for ensuring CSP quality with timely access to medication in a variety of healthcare settings. The allowance of up to 4 hours was based on the 4-to-6-hour lag phase of microbial growth, during which potential bacterial cells are adjusting to their environment and change very little, and they do not immediately start reproducing.[1] In the event bacterial cells were inadvertently introduced into a CSP during compounding, replication is unlikely and therefore there is a window of time in which a CSP can be held prior to administration.

[1]References:
• Daquigan N et al. Early recovery of Salmonella from food using a 6-hour non-selective pre-enrichment and reformulation of tetrathionate broth. Front Microbiol. 2016;7:2103.
• Jarvis, Basil. Statistical Aspects of the Microbiological Examination of Foods, Third Edition. Academic Press, 2016.
• Ryan, Kenneth et al. Sherris Medical Microbiology, Sixth Edition. McGraw-Hill Education, 2014.
• Wang J et al. A novel approach to predict the growth of Staphylococcus aureus on rice cake. Front Microbiol. 2017;8:1140.

It is difficult to understand why the radiopharmaceutical BUD is limited to 1 hour with no apparent scientific support, while the USP <797> extension to 4 hours is supported by data that indicates the 4-6-hour lag phase of microbial growth. This *scientifically supported* data should provide sufficient rationale for extending the immediate use window to 4 hours.

Suggested change:
Harmonize the BUD to USP<797> criteria for immediate use and include provision of following manufacturer approved labeling for storage and BUD when conditions of manufacture FDA-approved labeling are met. This change would need to be reflected throughout the document.

4. Personnel Qualification, Training and Hygiene
"Personnel must be trained to work with radiopharmaceuticals per the policies and SOPs authorized by an ANP or AU physician. These individuals (e.g., Nuclear medicine technologists or nuclear pharmacy technicians) must follow…."

Premise:
This introduction is confusing. As it reads, these training requirements appear to focus only on NM technologists or NP technicians. All individuals, including pharmacists and physicians, must follow the policies and SOPs.

Suggested change:
Personnel must be trained to work with radiopharmaceuticals per the policies and standard operating procedures (SOPs) of the facility where radiopharmaceuticals and associated components are handled. All individuals must follow the facility's policies and SOPs. As appropriate, this should include training on blood-borne pathogens.

4.2 Reevaluation, Retraining and Requalification: TIMING OF REEVALUATION AND REQUALIFICATION
"After a pause in sterile radiopharmaceutical processing: Individuals that have not performed preparation compounding, dispensing, or repackaging for more than 6 months must repeat ….."

Premise:
If training in this space occurs annually while working, it is not clear why 6 months absence is a specific time where retraining must occur. This raises the question of what, if any, data supports this specific time.

Suggested change:
USP <825> defines a "designated person" as an individual who is "responsible and accountable for the performance and operation of the radiopharmaceutical processing facility and for personnel who prepare, compound, dispense and repackage radiopharmaceuticals." It should be left to the discretion of the designated person to evaluate the competency of any employee who has had a pause in sterile radiopharmaceutical processing of any duration. If the designated person deems that the individual has a reduction or loss in competency in this area, requalification should be carried out.

4.3. Ancillary Individuals
"However, all personnel entering ISO-classified areas, whether employees or contractors, must meet the requirements for the specific classified area they need to access."

Premise:
Personnel entering these areas to perform any level of work which requires touching or interacting with equipment and materials within the ISO classified areas should be required to meet requirements, but there are many times where individuals who are brought in to observe in the area (outside students, shadowing opportunities, inspectors who are evaluating processes) who are in the ISO classified area for short periods of time and who do not interact with people or objects within the area. Gowning and garbing requirements should be standard, but some requirements are excessive for these individuals (e.g., not having painted nails, wearing jewelry). Individuals who have no direct contact with workspaces and are in the facility for short, observational time points should not need to follow all requirements for a specific workspace.

Suggested change:
This could be handled by a facility SOP, developed and enforced by the facility's designated person. This sentence could be changed to read "However, all personnel entering ISO-classified areas, whether employees of contractors, must meet the facility SOP requirements for the specific classified area they need to access. Another option would be a sentence as given in 4.5 Hand Hygiene and Garbing". "The designated person(s) may permit documented accommodations to personnel preparation as long as the quality of the radiopharmaceutical and the environment will not be adversely affected."

4.3. Ancillary Individuals
"For example, certification contractors…"

Premise:
As stated previously, some sections of this document give specific examples, while others do not.

Suggested change:
For continuity across the entire chapter, the remainder of this paragraph should be removed and referenced to an informational chapter that should be developed.

4.4. Hand Hygiene and Garbine for Immediate Use Preparations and Nonsterile Processing.
"RPs may be prepared and dispensed as immediate use and the precautions related to personal hygiene to be followed must include the following…."
Personnel are instructed to either don sterile gloves, or don nonsterile disposable gloves and then wipe gloves with sterile 70% IPA.

Premise:
It is difficult to understand the need to even mention sterile gloves when manipulations are being made in a completely non-sterile environment, which should be accounted for by the limited BUD that is assigned to immediate-use manipulations. The use of 70% IPA paired with standard nonsterile disposable gloves should be sufficient for any immediate use manipulations. In addition, as previously cited regarding the viability and growth patterns of bacteria and delayed reproduction of bacteria as pertaining to USP <797>, the use of sterile gloves in this environment should not be supported. This line item should be removed from this specific section.

Suggested change:
Don, Clean, Non-Permeable disposable gloves that may be sanitized according to process risk.

5.1 Facility Design and Environmental Controls
"The anteroom must have a permanent line of demarcation (e.g., epoxy paint, integrated flooring) to separate the clean side from the less clean side. The use of tape or tacky mats is not an acceptable means to construct a line of demarcation."

Premise:
This raises the questions of why is tape not an acceptable means and whether this has been changed in other regulatory guidance. If so, that should be highlighted. Specialized cleanroom tape is commercially available tape that has been created specifically for cleanroom operations (cleanroomtape.com).

Suggested change:
If there has been no regulatory standard passed down, this must be changed. The following statement should be included in the document: "If tape is used to identify the line of demarcation, tape designated as specifically for cleanroom operations should be used."

7. Cleaning and Disinfecting:
Entire section

Premise:
This section focuses specifically on cleaning classified areas, SRPAs and PEC with one section (7.6 Cleaning and disinfecting items from patient care area) which impacts nuclear medicine departments that operate under immediate use conditions. A significant challenge in interpreting <825> in the nuclear medicine environment is that guidelines are not given for cleaning requirements in this space.

Suggested change:
At minimum, guidelines for cleaning and disinfecting in the non-ISO immediate use environment should be developed, even if this area references internal policies and procedures per institutional environmental control departments, as a separate section in this area specific to immediate use operations. In other sections of this document, specifications are given to clean between use (food prep, dose calibrators after assaying blood products, etc.), which should be highlighted in this section as well.

7.6 Cleaning and Disinfecting Items from Patient Care Area
"Radiation shielding and equipment (e.g. syringe carrying containers, i.e. pigs) used in the classified area / SRPA or PEC that is exposed to patient care areas during the process of administration must be cleaned and disinfected before returning to any classified area (e.g., buffer or ante room)…"

Premise:
It is not clear whether the chapter's reference to "classified area" applies to environments where immediate-use activities are carried out, but, by definition in the glossary, a classified area is one that maintains an air quality classification in accordance with ISO guidelines. If a facility is operating under immediate use provisions, they will not have a defined classified area/SRPA or PEC. It should be specified that these materials should be cleaned when entering non-classified areas where RPs are handled or manipulated under immediate use provisions as well. Ideally, as mentioned previously, a specific section on cleaning and disinfecting in a non-classified area should be developed. This should also be outlined in table form (Table 5) or in a separate table for cleaning.

8. Assigning BUD
"The BUDs stated in Table 7 are maximum values in the absences of sterility testing and the assigned BUD may be shorter for a variety of reasons discussed below."

Premise:
This section has never provided scientific references to the chosen BUDs that are provided in table 7.

Suggested change:
At minimum, discuss the origins of these specified time points, especially those that deviate from recommended package insert time points. Harmonize with <797>.

8. Assigning BUD
Table 7 – BUD dates

"The BUDs stated in Table 7 are maximum values in the absences of sterility testing and the assigned BUD may be shorter for a variety of reasons discussed below."

Premise:
This should be expanded to include the fact that BUDs can also be extended by performing site-specific sterility testing. Placing this statement here rather than adding it at the end of the paragraph makes more sense.

8. Assigning BUD
Immediate use = 1 hour BUD

Premise:
Per earlier discussion, extending the BUD to 4 hours for immediate use should be addressed here.

8. Assigning BUD
Radiolabeled blood components for immediate use

Premise:
Considering FDA-approved labeling instructions on how to prepare Tc-99m red blood cells call for a 30-minute expiration, a 1-hour BUD from time of preparation is reasonable.

Suggested change:
No change needed – this should not follow the same BUD change for immediate use as other preparation and dispensing activities.

12.3 Direct Multidose Radiopharmaceutical Infusion Systems
"Setup attachment or needle puncture should be performed in a defined environment"

Premise:
The definition of "defined environment" is unclear. This term is not listed in the glossary. It is not clear if this is, for example, an ISO 5 PEC or a hot lab that has recently been cleaned.

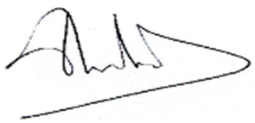
Suggested change:
Define "defined environment" or give additional information as to what is acceptable for this action. Further, in this section, it is specified that the generator tubing assembly and connections should take place aseptically in an ISO class 5 PEC. If this is the definition of a defined environment, then there is no need to use the term defined environment; replace it with ISO class 5 PEC. This is challenging in a typical nuclear medicine department.

Conclusion:

SNMMI provides these comments in good faith based on current scientific evidence, established regulatory frameworks, and validated PET manufacturing practices, with the intent of reducing unnecessary minimum burdens while preserving patient safety; these suggestions are not intended to limit or discourage any facility from adopting more rigorous controls or quality assurance measures as determined appropriate within their own risk-based quality programs via scientifically validated process.

Thank you for your consideration. Please contact SNMMI's Director of Health Policy and Regulatory Affairs, Julia Bellinger, MPP (jbellinger@snmmi.org), if you have any additional questions or need further information.

Sincerely,



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