



Commentary

USP 42–NF 37, Second Supplement

June 1, 2019

In accordance with USP's Rules and Procedures of the Council of Experts ("Rules"), and except as provided in Section 7.02 Accelerated Revision Processes, USP publishes proposed revisions to the *United States Pharmacopeia and the National Formulary (USP–NF)* for public review and comment in the *Pharmacopeial Forum (PF)*, USP's free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee deems appropriate, the proposal may advance to official status or be re-published in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status without re-publication in *PF*, a summary of comments received, and the appropriate Expert Committee's responses are published in the Revisions and Commentary section of USP.org at the time the official revision is published.

The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees' responses to public comments on proposed revisions. If there is a difference between the contents of the *Commentary* and the official text, the official text prevails. In case of a dispute or question of interpretation, the language of the official text, alone and independent of the *Commentary*, shall prevail.

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General Chapter/Section(s): <825> Radiopharmaceuticals- Preparation, Compounding, Dispensing, and Repackaging
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 125

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General Comments

There were commenters that provided positive feedback on the proposed chapter and applauded USP efforts. USP acknowledges this feedback. There were also comments regarding implementation of the proposed requirements that did not specify which changes should be made. USP also acknowledges these comments, but the comments cannot be incorporated without additional information.

Comment Summary #1: Commenters indicated that the requirements for preparation, compounding, dispensing, and repackaging of immediate use sterile radiopharmaceuticals are found throughout the chapter and recommended placing them all in one section to make it easier for users.

Response: Comment incorporated. A section with all the requirements for immediate use of radiopharmaceuticals, which had been distributed throughout the proposal, have been merged to create a new section, 3. "Immediate Use of Sterile Radiopharmaceuticals." The subsequent sections and subsections have been renumbered as a result.

Comment Summary #2: Commenters requested including specific details on how to perform bacterial endotoxin tests and sterility tests in the proposed chapter.

Response: Comment incorporated. References to General Chapter <85> *Bacterial Endotoxins Test* and General Chapter <71> *Sterility Tests* have been included, which harmonizes <825> with General Chapter <797> *Pharmaceutical Compounding-Sterile Preparations*.

Comment Summary #3: Commenters challenged the need for General Chapter <825> because compounding radiopharmaceuticals is addressed in General Chapter <795> *Pharmacopeial Compounding-Nonsterile Preparations* and General Chapter <797>.

Response: Comment not incorporated. The chapter is needed because all references to compounding radiopharmaceuticals and radiation safety have been removed from <795> and <797> and replaced with a reference to <825>.

Comment Summary #4: Commenters had concerns regarding the cost of updating facilities to meet the regulatory requirements outlined in the proposed chapter.

Response: Comment not incorporated. The chapter content is consistent with balancing radiation safety, patient safety, and patient access.

Comment Summary #5: Commenters requested changes to the proposed chapter so that radiopharmaceuticals would be classified by risk- and performance-based parameters.

Response: Comment not incorporated. Commenters did not provide sufficient data regarding the risk- and performance-based requirements and the lack of acceptance by regulatory agencies. The Expert Committee will consider a revision to incorporate risk- and performance-based requirements as data become available.

Comment Summary #6: Commenters requested including specific guidelines regarding radiation exposure.

Response: Comment not incorporated. This is outside the scope of the chapter.

Comment Summary #7: Commenters requested inclusion of all possible health care settings where General Chapter <825> is applicable in the *Introduction*.

Response: Comment not incorporated. Existing text sufficiently describes the applicability of the General Chapter to all the presently known healthcare settings and potential future healthcare settings.

Comment Summary #8: Commenters requested a distinction between the words space/room/area.

Response: Comment incorporated. Replaced "space" and "room" with "area" wherever appropriate.

Comment Summary #9: Commenters noted the need to include disinfecting after cleaning wherever cleaning of the classified areas, components, and equipment used in the preparation, compounding, dispensing, and other activities is called out.

Response: Comment incorporated. The need for a disinfecting procedure was added wherever a cleaning procedure is listed.

Comment Summary #10: Commenters requested units for parameters, such as temperature or certain abbreviations, to be noted or defined in the proposed text.

Response: Comment not incorporated. This information is listed in the specified *General Notices*.

Comment Summary #11: Commenters recommended changing or removing the proposed text to eliminate perceived redundant text in many sections of the proposed chapter.

Response: Comment not incorporated. The Expert Committee considers repeated text necessary for easy access within specific sections due to the length of the chapter. In addition the segments of the repeated text cannot be easily cross-referenced.

Comment Summary #12: Commenters suggested replacing the word “dirty” with “less clean” where two different ISO classified areas are present.

Response: Comment incorporated. "Dirty" was changed to "less clean" throughout the proposed text.

Comment Summary #13: Commenters requested harmonization with General Chapter <797> with respect to *Environmental and Engineering Controls*.

Response: Comment partially incorporated. The chapter has only been partially harmonized with <797> because of the need to balance patient safety and radiation safety.

Comment Summary #14: Commenters expressed concern about the need to establish identity, strength, purity, and quality of food preparations.

Response: Comment incorporated. A statement was added to the proposed text to exclude food preparations from this requirement.

INTRODUCTION

Comment Summary #1: Commenters were concerned that the chapter would limit access to radiopharmaceuticals used for specific types of treatments available from 503A or 503B facilities.

Response: Comment partially incorporated. Language in *Introduction and Dispensing* sections was modified to facilitate broader access to radiopharmaceuticals.

Comment Summary #2: Commenters requested additional language to clarify the applicability of General Chapter <825> to allow state boards of pharmacy to refer to <825>.

Response: Comment not incorporated. The Expert Committee considers the current language adequate to facilitate adoption by state boards of pharmacy.

Comment Summary #3: Commenters requested inclusion of types of nuclear cardiology clinics (mobile and stationary) to assure patient safety.

Response: Comment incorporated.

Comment Summary #4: Commenters requested inclusion of intra-organ instillation as a route of administration in the subsection, *Sterile Radiopharmaceuticals*.

Response: Comment incorporated.

Comment Summary #5: Commenters requested clarification of the necessary disinfection technique when multiple punctures are involved in the subsection, *Sterile Radiopharmaceuticals*.

Response: Comment incorporated.

Comment Summary #6: Commenters requested the removal of language regarding strict adherence to sterile techniques that are not always possible with radiopharmaceuticals because of the perceived lack of control.

Response: Comment not incorporated. This language is necessary to comply with regulatory requirements of different agencies and to maintain consistency with General Chapter <797>.

Comment Summary #7: Commenters requested additional language specifying exclusion of positron emission tomography (PET) drugs for research and investigational uses.

Response: Comment incorporated.

Comment Summary #8: Commenters requested examples and a definition of non-radioactive drugs.

Response: Comment not incorporated because of the existing large number of different classes of non-radioactive drugs.

Comment Summary #9: Commenters requested clarification about the flexibility of using the primary engineering control for both radioactive and non-radioactive drugs.

Response: Comment not incorporated. General Chapter <825> describes the requirements for radioactive materials. Compounding of non-radioactive drugs is sufficiently described in General Chapter <795> and General Chapter <797>.

Comment Summary #10: Commenters requested inclusion of language recognizing the fact that radiopharmaceuticals exist in a special environment where evolution and development of new methods and procedures based on scientifically valid and defensible practices must be acknowledged as integral to existing practice as well as to the continued progress and improvement in quality for existing and new radiopharmaceuticals and how they are prepared.

Response: Comment not incorporated. The Expert Committee determined that the chapter already includes text that allows the use of alternative technologies.

Comment Summary #11: Commenters requested additional examples of types of nonsterile radioactive preparations.

Response: Comment not incorporated. Listing all possible examples may preclude the use of future dosage forms.

Comment Summary #12: Commenters requested the expansion of nonsterile preparations to following <795> with as low as reasonably achievable (ALARA) principle considerations, radioactive materials (RAM) licenses, facility standard operating procedures (SOPs), and state/local regulations.

Response: Comment not incorporated. Language in <825> is sufficient and clear regarding nonsterile radioactive preparations.

Comment Summary #13: Commenters requested removal of all language regarding food preparation as there are no monographs for food (e.g., eggs, oatmeal).

Response: Comment not incorporated. Food preparations, in conjunction with radiopharmaceuticals, are within the scope of the chapter and covered by facility SOPs.

Comment Summary #14: Commenters requested inclusion of language that will allow a new type of generator in the subsection *Sterile Radiopharmaceuticals*.

Response: Comment not incorporated. The request is inconsistent with language regarding beyond use times.

Comment Summary #15: Commenters requested inclusion of examples of elutions of specific generators and sterilization procedures.

Response: Comment not incorporated. The Expert Committee determined that the chapter provides sufficient general descriptions.

Comment Summary #16: Commenters requested clarification on whether bacterial endotoxin testing is needed for all dosage form preparations.

Response: Comment partially incorporated. Language added to denote "injectable" as the dosage form that requires bacterial endotoxin testing.

RADIATION AND SAFETY CONSIDERATIONS

Comment Summary #1: Commenters requested clarifications to: 1) radiation exposure; 2) RAM license requirements; 3) personnel handling radiopharmaceuticals; 4) needleless systems; and 5) placement of shielding in International Organization for Standardization (ISO) classified primary engineering controls (PECs) to clarify or improve the readability of the text.

Response: Comment incorporated.

Comment Summary #2: Commenters requested clarifications to the use of PECs in relation to radiation safety considerations to assist auditors/inspectors with interpretation and assist the implementation and adoption of <825>.

Response: Comment not incorporated. The Expert Committee will consider this comment when additional data become available.

Comment Summary #3: Commenters requested inclusion of language clarifying sterility requirements.

Response: Comment not incorporated as the section exclusively deals with radiation safety.

Comment Summary #4: Commenters requested that text be added noting that all pads used in the PEC are not required to be sterile.

Response: Comment not incorporated. This is out of scope for the chapter and the proposed text is restrictive.

Comment Summary #5: Commenters challenged using airflow as a measure of radiation contamination control.

Response: Comment partially incorporated. Language updated to better describe the action of the vertical airflow system with radiation contamination control.

Comment Summary #6: Commenters requested changes to the equipment allowed in a classified area.

Response: Comment not incorporated. The examples given in the proposed chapter are used in commercial settings and are present during recertification of the PEC. The Expert Committee determined it is not necessary to have specific qualified equipment assigned to a specific hood.

Comment Summary #7: Commenters requested language detailing the cleaning procedure and agents associated with dosimeter cleaning.

Response: Comment not incorporated. Dosimeter rings are cleaned during normal hand hygiene procedures. Dosimeter body badges are worn underneath personal protective equipment and are not a source of contaminants.

Comment Summary #8: Commenters requested the removal of the provision of body dosimeters being worn under the gown because wearing under the gown may not provide accurate measure of radiation exposure.

Response: Comment not incorporated. The gowns are transparent to radiation emitted by radiopharmaceuticals and thus the concern of inaccurate radiation exposure does not exist.

Comment Summary #9: Commenters requested additional language defining "supervision."

Response: Comment not incorporated. The individual facility SOPs will serve as the source for this definition.

Comment Summary #10: Commenters requested the removal of examination for radioactive contamination and disposal of absorbent pads at the end of each shift.

Response: Comment not incorporated. The requested change would make the chapter more restrictive.

Comment Summary #11: Commenters requested emphasis on wearing a finger dosimeter over other styles.

Response: Comment not incorporated. Emphasis could prevent use of other styles of dosimeters.

PERSONAL QUALIFICATIONS, TRAINING, AND HYGIENE

Comment Summary #1: Commenters requested clarifications with respect to: 1) cleaning of classified areas; 2) garbing requirements; 3) media-fill testing; and 4) hand hygiene to improve the readability of the text.

Response: Comment incorporated.

Comment Summary #2: Commenters requested the inclusion of additional requirements regarding: 1) supervision by authorized nuclear pharmacists/authorized users (ANP/AU); 2) hand hygiene; 3) garbing; 4) incubation times; 5) media-fill testing; and 6) placement of sink in the controlled areas in such way the chapter will be completely be harmonized with General Chapter <797>.

Response: Comments partially incorporated. It is not possible to completely harmonize the text with General Chapter <797> as there is a need to balance between radiation safety and patient safety. Harmonization with General Chapter <795> and General Chapter <797> was achieved where possible.

Comment Summary #3: Commenters requested a summary table for requalification times, similar to General Chapter <797> text.

Response: Comment not incorporated. This table has been removed from the proposed revision of General Chapter <797>.

Comment Summary #4: Commenters requested language be changed from “authorized user physician” or “authorized nuclear pharmacists” to “authorized personnel,” to accommodate manufacturing environments.

Response: Comment not incorporated. This request is out of scope of the chapter.

Comment Summary #5: Commenters requested language to be altered to accommodate the absence of a designated person.

Response: Comment not incorporated. The definition of *designated person* is broad enough to accommodate the needs.

Comment Summary #6: Commenters requested increasing the retraining times for core competencies testing from 6 months to 12 months.

Response: Comment incorporated.

Comment Summary #7: Commenters requested the inclusion of thumb sampling whenever fingertip sampling was required.

Response: Comment incorporated.

Comment Summary #8: Commenters requested exclusion of glove fingertip and thumb sampling qualification while working in hot-cells.

Response: Comment not incorporated as the proposed chapter includes such an exclusion.

Comment Summary #9: Commenters requested the removal of the retesting requirements for those individuals who perform sterile compounding with non-sterile ingredients.

Response: Comment not incorporated. This text is needed to ensure patient safety. However, the text has been moved and updated in the subsection, *Reevaluation, Retraining, and Requalification After Requalification Failure*.

Comment Summary #10: Commenters requested the removal of the provision that required the use of sterile gloves.

Response: Comment not incorporated. Sterile gloves are necessary to ensure patient safety.

Comment Summary #11: Commenters requested a definition for "container–closure" as it has not been defined anywhere in the proposal.

Response: Comment incorporated. The definition is included in the *Glossary*.

Comment Summary #12: Commenters requested clarification of the meaning of "investigation of failures."

Response: Comment incorporated by deleting the text because "investigation of failure" is a vast area and any clarification will not be all inclusive.

Comment Summary #13: Commenters requested additional text disqualifying personnel that fail competency requalification from compounding sterile preparations.

Response: Comment not incorporated. Language in the subsection, *Reevaluation, Retraining, and Requalification* in the proposed text is sufficient.

Comment Summary #14: Commenters requested clarification of the personal hygiene requirements described in the subsection *Ancillary Personnel*.

Response: Comment not incorporated. Text in this section is sufficiently clear.

Comment Summary #15: Commenters requested that text regarding personal hygiene in classified areas be harmonized with General Chapter<797>.

Response: Comment incorporated.

Comment Summary #16: Commenters requested removal of the requirement that personnel wash their arms to the elbows.

Response: Comment incorporated.

Comment Summary #17: Commenters requested clarification of the word "different". NOTE—A different lab coat must be worn to care for a patient than the coat/gown used for radiopharmaceutical preparation.

Response: Comment not incorporated. The language in the subsection, *Hand Hygiene and Garbing for Immediate Use Preparations* in the proposed text is sufficient.

Comment Summary #18: Commenters requested that dosimeters be disinfected prior to entering classified area.

Response: Comment not incorporated. Alteration of this language would suggest that all dosimeters would require disinfection, which would be more restrictive.

Comment Summary #19: Commenters requested the deletion of the phrase "and then apply a suitable alcohol-base hand rub with persistent antimicrobial activity" or further clarification of "persistent" in the subsection, *Hand Hygiene and Garbing for Buffer Rooms and SRPA* under the section, *Personnel Qualifications, Training, and Hygiene*.

Response: Comment incorporated. The phrase "...persistent antimicrobial activity" was deleted from the proposed text.

Comment Summary #20: Commenters proposed additional language to specifically detail remediation of touch contamination.

Response: Comment not incorporated. The current proposed text is consistent with ALARA principles.

Comment Summary #21: Commenters requested clarification on the reuse of gowns within a shift.

Response: Comment incorporated. New language was added to allow gown reuse under specified conditions.

Comment Summary #22: Commenters requested additional language to allow for personnel to work at multiple sites under the same quality program within the same organization without undergoing additional training.

Response: Comment incorporated.

Comment Summary #23: Commenters requested clarification of the training needs of personnel who handle blood components.

Response: Comment incorporated.

Comment Summary #24: Commenters requested clarification on the aseptic qualification requirements for technologists who administer a radiopharmaceutical to patients.

Response: Comment not incorporated. Administration to patients is out of scope of the chapter.

Comment Summary #25: Commenters requested clarification on what constitutes a "trained individual."

Response: Comment incorporated. "Trained individual" will be replaced with "designated person."

Comment Summary #26: Commenters requested a provision to use alternative methods in incubation protocols.

Response: Comment not incorporated. Proposed text in the INTRODUCTION allows the use of alternative methods if they are validated.

Comment Summary #27: Commenters requested the inclusion of specific information on restrictive access barrier systems (RABS) and isolators.

Response: Comment not incorporated. The Expert Committee determined that the proposed text in FACILITIES AND ENGINEERING CONTROL does not exclude RABS and isolators, though these devices are not specifically mentioned.

Comment Summary #28: Commenters requested clarification on the competency requirement of ancillary personnel and visitors.

Response: Comment partially incorporated. "Student observers" was added as an additional example.

Comment Summary #29: Commenters requested clarification of aseptic qualification requirements in the situations in which the provisions of immediate use can be utilized.

Response: Comment incorporated in the new section, *Immediate Use Sterile Radiopharmaceuticals*.

Comment Summary #30: Comment requested changing the proposed text to allow for the use of sterile isopropyl alcohol wipes.

Response: Comment not incorporated. Current proposed language does not preclude the use of these types of wipes.

Comment Summary #31: Commenters noted it is excessive to require technologists to use a separate gown each time they enter into the hot-cell area.

Response: Comment not incorporated. Current proposed text requires a separate clean gown to be used within the hot-cell area and a different gown within a patient care area.

Comment Summary #32: Commenters requested inclusion of additional language to reinforce lab coat hygiene in radiopharmaceutical preparation areas.

Response: Comment not incorporated. The Expert Committee concluded that this provision should be a part of the facility SOPs.

Comment Summary #33: Commenters expressed concern that the phrase "ear buds and headphones or other similar devices" could result in exclusion of hearing aids in the subsection, *Hand Hygiene and Garbing for Buffer Areas and Segregated Radiopharmaceuticals Processing Area* under the section, *Personnel Qualifications, Training, and Hygiene*.

Response: Comment incorporated. Proposed language narrowed to disallow only earbuds and headphones by removing the phrase "other similar devices."

Comment Summary #34: Commenters requested clarification on whether personal protective equipment (PPE) requirements apply to nuclear medical technologists.

Response: Comment not incorporated. The PPE requirements within the proposed text apply to any individual within the radiopharmaceutical processing area.

FACILITY AND ENGINEERING CONTROLS

Comment Summary #1: Commenters requested clarifications with respect to 1) RAM license requirements; 2) immediate use; 3) blood handling/processing area requirements; 4) garbing; 5) media-fill testing; 6) hand hygiene; and 7) hot-cell monitoring requirements to improve the readability of the text.

Response: Comment incorporated.

Comment Summary #2: Commenters requested inclusion of: 1) requirements allowing nonsterile gloves; 2) the need for smoke visualization studies in PECs; and 3) requirements for garbing in general in unclassified areas where a hot-cell may be located.

Response: Comment not incorporated. The requested changes would make the chapter more restrictive.

Comment Summary #3: Commenters requested: 1) removing verification frequency or increasing the verification frequency from 1 year to 5 years; 2) removing minimum needed airflow velocity; 3) changing the design of ISO classified areas; 4) lowering the beyond use date (BUD) for sterile preparations from the segregated radiopharmaceutical processing area (SRPA) from 12 hours to 6 hours; and 6) allowing the use of free-standing humidifiers in ISO classified areas.

Response: Comments not incorporated because of the need to harmonize with General Chapter <795> and General Chapter <797>.

Comment Summary #4: Commenters requested deletion of statements regarding touch contamination in a facility where BUD does not exceed 8 hours.

Response: Comment not incorporated. BUD assignment is based on several factors in addition to facility design and engineering controls. Microbial burden due to touch contamination must be controlled to ensure patient safety.

Comment Summary #5: Commenters requested proposed language be updated to be consistent with <797> or General Chapter <800> *Hazardous Drugs-Handling in Healthcare Settings*.

Response: Comment not incorporated. Current radiopharmaceutical practices preclude total harmonization with General Chapter <797>. The Expert Committee determined that harmonization with General Chapter <800> is not appropriate for radiopharmaceuticals which are not classified as hazardous substances.

Comment Summary #6: Commenters requested clarification on the responsibilities of the designated person.

Response: Comment not incorporated. The Expert Committee determined that proposed text adequately describes the responsibilities of the designated person.

Comment Summary #7: Commenters requested mandating the use of equipment such as refrigerators which are specially designed for clean rooms.

Response: Comment not incorporated. The requested change to proposed text would make the chapter more restrictive.

Comment Summary #8: Commenters requested additional language to allow the storage and elution of radionuclide generators in the SRPA.

Response: Comment incorporated.

Comment Summary #9: Commenters requested clarification regarding the nature of unidirectional airflow in the PEC to account for radiation shielding.

Response: Comment incorporated.

Comment Summary #10: Commenters requested the inclusion of specific information on the use of 1) compounding aseptic isolators (CAIs); 2) containment isolators (CACIs); 3) RABs; and 4) isolators.

Response: Comment not incorporated. The Expert Committee determined that the proposed text in FACILITIES AND ENGINEERING CONTROLS does not require the inclusion of all examples of PECs.

Comment Summary #11: Commenters requested the exclusion of a laminar airflow workbench (LAFW) as an example of an acceptable PEC within the proposed text.

Response: Comment not incorporated. The use of a LAFW is an acceptable practice with radiopharmaceuticals and the exclusion of LAFW would reduce patient access.

Comment Summary #12: Commenters requested the inclusion of a hot-cell in Table 1.

Response: Comment not incorporated. A hot-cell is not a static environment and testing procedures are out of scope of the chapter.

Comment Summary #13: Commenters requested a clarification of language regarding the sterilization of items brought into the SRPA to ensure patient safety.

Response: Comment partially incorporated. Proposed language updated to take radiation safety into consideration.

Comment Summary #14: Commenters requested definition of "clearly separated" in the subsection, *Classified Areas* under the section, FACILITIES AND ENGINEERING CONTROLS.

Response: Comment not incorporated. The Expert Committee determined that the language is clear and no additional clarification is needed.

Comment Summary #15: Commenters requested examples of PEC devices within a hot-cell.

Response: Comment not incorporated. Providing these specific examples is outside the scope of the chapter.

Comment Summary #16: Commenters requested clarification of the types of lead shielding in the subsection, *Environmental Control* under the FACILITIES AND ENGINEERING CONTROLS section.

Response: Comment not incorporated. The proposed language is an example and does not preclude the use of other types of shielding materials.

Comment Summary #17: Commenters requested removing the requirement for a double pass-through window in the subsection, *Secondary Engineering Controls* under the section, *Facilities and Engineering Controls*.

Response: Comment partially incorporated. Proposed language was updated so that the window system is mechanical or uses an established SOP to function.

Comment Summary #18: Commenters requested the removal of the adjective "volatile" for radiopharmaceuticals because radiopharmaceuticals are not volatile.

Response: Comment not incorporated. Iodine is known to sublime.

Comment Summary #19: Commenters requested clarification of the proposed text regarding the location of the SRPA in conjunction with environmental control challenges in the opening paragraph of the subsection, *Types of Secondary Engineering Controls* under the *Facilities and Engineering Controls* section.

Response: Comment incorporated.

Comment Summary #20: Commenters requested the inclusion a definition of *Direct Processing Area* in the *Glossary*.

Response: Comment incorporated.

Comment Summary #21: Commenters requested that proposed text regarding the biological safety cabinet (BSC) be harmonized with text in the definitions.

Response: Comment not incorporated. The text in the definitions was shortened. The text in *Facilities and Engineering Controls* was updated separately.

Comment Summary #22: Commenters requested that the proposed text regarding the BSC be updated to explicitly call out the use of this PEC type during blood labeling.

Response: Comment not incorporated. This information is called out in detail in the section on blood labeling.

Comment Summary #23: Commenters requested the inclusion of a provision to allow storage and elution of generators in the *Placement of the PEC*.

Response: Comment incorporated. Text has been added to the section on *Secondary Engineering Controls*.

Comment Summary #24: Commenters requested the inclusion of compounding from non-sterile ingredients in the proposed text in the subsection, *Placement of the PEC* under the section, *Facilities and Engineering Controls*.

Response: Comment not incorporated. The requested inclusion may have an impact on the sterile preparations and thus patient safety. The Expert Committee will consider inclusion of this when supporting data are made available.

Comment Summary #25: Commenters requested inclusion of the cleaning requirements for remote manipulator systems.

Response: Comment not incorporated. The Expert Committee determined that cleaning requirements for the remote manipulator systems is out of scope for the section on *Creating Areas to Achieve Easily Cleanable Conditions*.

Comment Summary #26: Commenters requested clarification of the location of the sink within the SRPA.

Response: Comment not incorporated. The Expert Committee determined that the current proposed language is sufficiently clear.

Comment Summary #27: Commenters requested that particle-shedding items should be excluded from the SRPA to eliminate another source of particulate burden.

Response: Comment incorporated.

Comment Summary #28: Commenters requested inclusion of a cleaning and disinfection provision in the subsection on *Placement and Movement of Materials*.

Response: Comment incorporated.

Comment Summary #29: Commenters requested clarification of the phrase “patient’s blood derived” in the subsection, *Classified Rooms*.

Response: Comment partially incorporated. The word “patient’s” has been removed. The Expert Committee determined that “blood-derived” includes all blood components and does not require additional clarification.

Comment Summary #30: Commenters requested clarification on the garbing requirements in the subsection, *Remote Aseptic Processing Involving a Hot-Cell* under the FACILITIES AND ENGINEERING CONTROLS section.

Response: Comment not incorporated. The garbing requirements are dependent on the location of the hot-cell and should be decided by facility SOPs.

Comment Summary #31: Commenters requested that all references to “RAM license” be removed from the *Environmental Controls* section.

Response: Comment not incorporated. This section details necessary engineering controls to minimize radioactive contamination consistent with RAM license requirements.

Comment Summary #32: Commenters requested radiopharmaceuticals be listed as “hazardous” to align with General Chapter <800>.

Response: Comment not incorporated. Radiopharmaceuticals are not classified as hazardous substances.

Comment Summary #33: Commenters requested changes to the proposed text so that the restricted area air pressure is positive to the unrestricted area in the subsection, *Environmental Controls*. Commenters also requested consideration for the presence of volatile radiopharmaceuticals.

Response: Comment partially incorporated. Text has been added to include the consideration of the presence of volatile radiopharmaceuticals, and also to the statement “the RAM license conditions may supersede the stated requirements” in the subsection on *Environmental Controls*.

Comment Summary #34: Commenters requested the deletion of the ISO Class 8 requirement for the storage and elution of radionuclide generators with short half-lives.

Response: Comment partially incorporated. Language changed so that only non-direct infusion generator storage and elution take place within ISO Class 8.

Comment Summary #35: Commenters indicated that there was no clear specification for total particle counts in SRPAs.

Response: Comment incorporated. Text clarified to include "total airborne particle count."

Comment Summary #36: Commenters requested inclusion of manufacturer verification instructions and professional expertise to certify PECs.

Response: Comment partially incorporated. Proposed text was updated to include facility SOPs with the PEC certification process.

Comment Summary #37: Commenters indicated that all sterile preparations of radiopharmaceuticals must be completed in an ISO classified area. Commenters also requested clarification of the use of nonsterile gloves and lab coat in a hot-cell.

Response: Comments not incorporated. Proposed text is a balance between radiation safety and patient safety.

MICROBIOLOGICAL AIR AND SURFACE MONITORING

Comment Summary #1: Commenters requested grouping the activities related to viable air sampling in the subsection on *Viable Air Sampling: Timing and Locations* using a bulleted list to make it easy to follow.

Response: Comment incorporated.

Comment Summary #2: Commenters suggested that the proposed action levels for viable air and surface sampling be made consistent with General Chapter <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments*.

Response: Comment not incorporated. The Expert Committee will consider this in a future revision if appropriate.

Comment Summary #3: Commenters requested: 1) reducing the air sampling frequency from every 6 months to every month; 2) increasing the surface sample requirement from every month to every 3 or 6 months; 3) specifying the frequency of incubator temperature monitoring requirements; and 4) harmonizing the text with General Chapter <795> and General Chapter <797> in the proposed chapter.

Response: Comment partially incorporated. Text revised to harmonize with General Chapter <795> and General Chapter <797> where feasible without compromising radiation safety and patient safety.

Comment Summary #4: Commenters requested the removal of sampling requirements for facilities that only process radiopharmaceuticals with BUDs under 12 hours.

Response: Comment not incorporated. Requirements within this section are based on ISO class and use, not BUDs, and are necessary to ensure patient safety.

Comment Summary #5: Commenters requested that sampling take place only in simulated conditions for microbiological air and surface monitoring.

Response: Comment not incorporated. Current text provides flexibility to choose between dynamic or simulated conditions.

Comment Summary #6: Commenters requested the removal of repetitive language found in multiple sections.

Response: Comment not incorporated. Repetitive language is considered necessary to ensure that requirements are understood by the end-users.

Comment Summary #7: Commenters requested specifying that with respect to microbiological testing, the incubators used for microbiological testing must be placed outside of any classified area or SRPA and away from areas where processing or compounding activities occur.

Response: Comment incorporated.

Comment Summary #8: Commenters requested inclusion of remediation steps in cases where colony-forming unit (cfu) exceeds the action level as the definition for “Remediation” in the *Glossary*.

Response: Comment not incorporated. Remediation protocols are best captured in the facility SOPs. The Expert Committee will consider including this in a future revision upon receipt of supporting information.

Comment Summary #9: Commenters requested clarification of incubation times and parameters to match those used in industry.

Response: Comment incorporated.

Comment Summary #10: Commenters challenged the advantage of reducing the BUD during corrective action following a particle count exceeding the action levels in Table 3.

Response: Comment not incorporated. The reduction of BUD enables the continued handling of radiopharmaceuticals with considerations to patient safety.

Comment Summary #11: Commenters requested that action levels in Table 3 be consistent with 2004 Food and Drug Administration (FDA) guidance.

Response: Comment not incorporated. Table 3 was harmonized with General Chapter <797>.

Comment Summary #12: Commenters requested deletion of text, “surface sampling must be performed at the end of the radiopharmaceutical aseptic activities or shift, but before the area has been cleaned and disinfected,” citing radiation exposure concerns.

Response: Comment not incorporated. This section has language that offers flexibility in sample procedures which are consistent with radiation safety/ALARA principles.

Comment Summary #13: Commenters requested the addition of an industrial hygienist whenever consultation of a microbiologist is called out.

Response: Comment incorporated. Replaced "Microbiologists" with "qualified individuals (Microbiologists or Industrial Hygienists)."

Comment Summary #14: Commenters recommended the addition of language detailing the identification of any microorganism, regardless of action level.

Response: Comment not incorporated. This text has been harmonized with General Chapter <797>.

Comment Summary #15: Commenters requested clarification about the requirements for air and surface monitoring for non-classified areas.

Response: Comment not incorporated. Proposed chapter text only refers to requirements for classified areas. End-users are encouraged to use their discretion about this aspect with patient safety and access considerations in mind.

Comment Summary #16: Commenters requested that all areas in the facility be included in viable airborne particle monitoring program.

Response: Comment not incorporated. Proposed text includes classified areas and SRPAs which are relevant for ensuring patient safety. Inclusion of all areas would be more restrictive.

Comment Summary #17: Commenters requested additional qualifying criteria for dynamic and simulated operating conditions.

Response: Comment not incorporated. Proposed text requires facilities to develop their own SOPs for describing these conditions.

CLEANING AND DISINFECTING

Comment Summary #1: Commenters requested inclusion of the requirement for cleaning and disinfecting to be completed at the end of the compounding day and in the classified areas.

Response: Comment not incorporated. The proposed text is considered appropriate to minimize radioactive contamination.

Comment Summary #2: Commenters requested that the frequency of cleaning and disinfecting PECs be revised from a monthly schedule to daily, at the beginning and end of each shift.

Response: Comment not incorporated. Requested change would be restrictive.

Comment Summary #3: Commenters requested that Table 5 be revised with more individual specifications.

Response: Comment not incorporated. The proposed Table 5 includes the minimum requirements for cleaning and disinfecting.

Comment Summary #4: Commenters requested changes to the proposed language to specify a certain time for cleaning and disinfecting during continuous use.

Response: Comment not incorporated. This is out of scope for the chapter and should be delineated by facility SOPs.

Comment Summary #5: Commenters requested a change to Table 5 to indicate a more frequent cleaning requirement.

Response: Comment not incorporated. Proposed text requires facilities to develop SOPs regarding cleaning schedules.

Comment Summary #6: Commenters requested an expansion of Table 5 to clarify the cleaning of the PEC and equipment separately.

Response: Comment not incorporated. The requirements listed in Table 5 meet the current practices of the radiopharmaceutical community and are consistent with General Chapter <797>.

Comment Summary #7: Commenters requested deletion of the phrase “shown to be effective against *Bacillus* species” as this is not a part of an EPA label claim.

Response: Comment incorporated.

Comment Summary #8: Commenters requested that dedicated equipment be used in blood-handling areas to avoid cross-contamination.

Response: Comment not incorporated. This is expected to be controlled by institutional policies and SOPs.

Comment Summary #9: Commenters requested clarification on the restrictions on introducing shipping carton(s) or other corrugated or uncoated cardboard into classified rooms or the SRPA.

Response: Comment incorporated by including the phrases such as, “clean side of the ante room”, and “perimeter of a SRPA” as examples.

Comment Summary #10: Commenters requested the deletion of proposed language requiring the complete drying of disinfected items.

Response: Comment incorporated.

Comment Summary #11: Commenters requested deletion of the phrase “within the PEC” from the subsection, *Disinfecting Critical Sites within the PEC* to ensure that immediate use sterile preparations are covered.

Response: Comment incorporated. The revised title of the subsection is “*Disinfection of Critical Sites.*”

Comment Summary #12: Commenters indicated that the current text regarding the prohibition on returning the syringe to classified areas or SRPA for assay would pose an undue burden.

Response: Comment partially incorporated. Additional language was added to allow the return of a used syringe to a classified area for re-assay under specific conditions.

Comment Summary #13: Commenters requested expansion of the cleaning and disinfection procedures to include facility SOPs in addition to RAM license.

Response: Comment incorporated.

Comment Summary #14: Commenters requested adding the design of equipment used within a hot-cell to Table 5.

Response: Comment incorporated.

Comment Summary #15: Commenters requested the deletion of proposed text requiring a disinfected surface not to be disturbed following application of the disinfectant.

Response: Comment not incorporated. Text is harmonized with General Chapter <797>.

Comment Summary #16: Commenters requested clarification regarding whether all disinfectants need to be sterile.

Response: Comment partially incorporated. Proposed language was altered to state that only 70% isopropyl alcohol (IPA) needs to be sterile.

Comment Summary #17: Commenters requested the removal of "sponges" as an acceptable example of a cleaning supply.

Response: Comment incorporated.

Comment Summary #18: Commenters requested that the disposal of all cleaning supplies be mandatory.

Response: Comment not incorporated. This would make the chapter too restrictive.

Comment Summary #19: Commenters requested inclusion of the need to monitor the radioactive contamination of used cleaning supplies to minimize accidental disposal of radioactive waste to ensure radiation safety.

Response: Comment incorporated.

Comment Summary #20: Commenters requested inclusion of radioactive decontamination prior to cleaning and disinfection of the PEC to maintain radiation safety.

Response: Comment incorporated.

Comment Summary #21: Commenters requested stressing the need to ensure sufficient contact time (as recommended by the manufacturers) of cleaning and disinfecting agents to ensure adequate disinfection to enhance patient safety.

Response: Comment incorporated.

Comment Summary #22: Commenters requested that low-lint wipers be used to disinfect any container or package entering into a classified area or SRPA.

Response: Comment incorporated.

Comment Summary #23: Commenters requested the inclusion of low-lint wipers to disinfect surfaces of items transferred to the PEC.

Response: Comment not incorporated. The proposed text is consistent with current practice.

Comment Summary #24: Commenters requested inclusion of provisions to allow flexibility in the use of remote handling of radiopharmaceuticals.

Response: Comment incorporated. Provisions consistent with nuclear pharmacy practice have been included without compromising the radiation safety and patient safety aspects.

Comment Summary #25: Commenters requested that language regarding the cleaning and disinfecting of items going from classified areas or the SRPA to the PEC be deleted.

Response: Comment not incorporated. Proposed language is consistent with current practice.

Comment Summary #26: Commenters requested the inclusion of “immediate-use SRPA” in the subsection on *Cleaning and Disinfecting Patient Care Area*.

Response: Comment not incorporated. This proposed revision is outside the scope of the CLEANING AND DISINFECTION section.

ASSIGNING BUD

Comment Summary #1: Commenters requested a statement on the difference between immediate use times and BUD.

Response: Comment not incorporated. Immediate-use times and BUD are defined in the *Glossary*.

Comment Summary #2: Commenters requested increasing the BUD to 6 hours for immediate use sterile radiopharmaceuticals when they are refrigerated after preparation.

Response: Comment not incorporated. The Expert Committee determined that there is no supporting data to allow the extension of BUD. The Expert Committee will consider the BUD extension upon receipt of supporting data.

Comment Summary #3: Commenters requested clarification of the term “vial puncture” with regard to the beginning of a BUD.

Response: Comment incorporated. Language was updated to reflect either the first vial puncture or exposure of a critical site to ambient air.

Comment Summary #4: Commenters requested the extension of a BUD based on the results from sterility testing.

Response: Comment not incorporated. The request is beyond the scope of the chapter.

Comment Summary #5: Commenters requested additional language clarifying that the maximum BUDs are listed in Table 7.

Response: Comment not incorporated. The statement is already present in Section 7.

Comment Summary #6: Commenters requested cross-referencing Table 7 in Section 10.1, *Sterile Preparations*.

Response: Comment incorporated.

Comment Summary #7: Commenters requested PEC and secondary engineering control (SEC) specifications for immediate use blood labeling to be included in Table 7 in the section assigning BUD.

Response: Comment not incorporated. Including specific requirements for PEC/SEC use in immediate use preparations would make the chapter more restrictive.

Comment Summary #8: Commenters requested clarification on the need to perform sterility testing on a compounded material using non-sterile components.

Response: Comment partially incorporated. Added "sterile components" to the 96-hour BUD classification to Table 7. Sterility testing prior to product release is out of scope for determining BUD.

Comment Summary #9: Commenters requested addition of BUDs to Table 7 that are based on: 1) storage conditions, such as refrigeration or freezing; 2) inclusion of a separate type of radionuclide generator system which contains built-in sterilization/bubble point testing capabilities; and 3) harmonization of Table 7 completely with General Chapter <797>.

Response: Comment not incorporated. There are insufficient data available to add this provision at this time. The Expert Committee will consider future revisions to the chapter upon the receipt of supporting data.

Comment Summary #10: Commenter requested that all repackaging or preparation with minor deviations of radiopharmaceuticals take place within an ISO classified environment.

Response: Comment not incorporated. Requested language would make the proposed chapter more restrictive though facilities have the option of writing their own SOPs to include more restrictive text.

Comment Summary #11: Commenter requested additional language to allow for a longer BUD for a manufacturer-specific radionuclide generator.

Response: Comment not incorporated. There are insufficient data available to add this provision at this time. The Expert Committee will consider future revisions to the chapter upon the receipt of supporting data.

Comment Summary #12: Commenter requested the removal of an example that highlights the use of a PET system.

Response: Comment not incorporated. Proposed language in the INTRODUCTION notes that further processing of PET radiopharmaceuticals is within the scope of this chapter.

Comment Summary #13: Commenters requested the specification of ISO air quality in place of ISO classification.

Response: Comment partially incorporated. Additional language was added in the FACILITY AND ENGINEERING CONTROLS section to clarify storage and elution of generators.

Comment Summary #14: Commenter requested alteration to Table 7 to allow for longer BUDs for drugs that are not commercially available.

Response: Comment not incorporated. Rationale of commenter is focused on the determination of a BUD based on General Chapter <797> conditions while in General Chapter <825>, the BUD determination is based on the balance of radiation safety, patient safety, and radionuclide half-life.

Comment Summary #15: Commenter requested clarification on the number of needle punctures allowed with a direct infusion system

Response: Comment incorporated. Table 7 was clarified to allow "one puncture" without a qualifier of total needle punctures used.

Comment Summary #16: Commenter requested the change to Table 7 so that simultaneous elution and preparation of radionuclide generators must take place within an ISO Class 5 PEC.

Response: Comment not incorporated. Table 7 requires that any preparation beyond immediate use be performed in an ISO Class 5 environment.

Comment Summary #17: Commenter requested that the BUD for dispensing, repackaging, preparation, and preparation with minor deviations be based on the package insert.

Response: Comment not incorporated. Package inserts do not provide sufficient detail on the environment required for dispensing, repackaging, preparation, and preparation with minor deviations.

Comment Summary #18: Commenters requested clarifying factors such as: 1) sterility; 2) radionuclidic purity; 3) radiochemical purity; 4) age of the radionuclide generator; 5) specific activity; 6) container type; and 7) cell viability of radiolabeled blood cells to be considered during BUD assignment.

Response: Comment incorporated.

Comment Summary #19: Commenter requested additional language clarifying cell viability in blood labeling.

Response: Comment incorporated. New bullet was added with proposed revision.

Comment Summary #20: Commenter requested a provision to allow considerations for technology and automation when assigning a BUD.

Response: Comment not incorporated. Request is out of scope and there are insufficient data available to support the revision. The Expert Committee will consider future revisions to the chapter upon the receipt of supporting data.

Comment Summary #21: Commenter requested clarification on the assignment of the final BUD based on the BUD of individual components.

Response: Comment incorporated.

Comment Summary #22: Commenters requested clarification on the start time for the BUD of radiolabeled blood components.

Response: Comment incorporated.

Comment Summary #23: Commenter requested that: 1) microbial contamination; 2) radiopharmaceutical chemical and physical stability; 3) purity; and 4) the container–closure system be considered simultaneously when determining the BUD.

Response: Comment not incorporated. BUDs are assigned primarily based on contamination concerns and then adjusted based on the other factors listed above.

Comment Summary #24: Commenters requested clarification of BUD assignments of radiopharmaceutical preparations starting with non-sterile components.

Response: Comment not incorporated. Section 11.3 in the *Sterile Compounding Using a Nonsterile Drug Substance or Components* section considers BUD assignments for preparations with non-sterile ingredients.

Comment Summary #25: Commenter requested clarification on the start time of a BUD regarding a container puncture.

Response: Comment incorporated.

Comment Summary #26: Commenters requested changes to the proposed text that would put the chapter out of alignment with General Chapter <795>, General Chapter <797>, or General Chapter <800>.

Response: Comment not incorporated. Whenever possible, language was maintained in its proposed form to make the section consistent with General Chapter <795> and General Chapter <797>.

Comment Summary #27: Commenter requested inclusion of intravascular devices with "Sterile Preparations."

Response: Comment incorporated.

Comment Summary #28: Commenter requested inclusion of "Maximum" in Table 7 column for BUD.

Response: Comment not incorporated. This is stated within the text.

Comment Summary #29: Commenter requested revising the text in Table 7 from "SRPA with ISO Class 8" to "SRPA within ISO Class 8."

Response: Comment not incorporated. The requested change would not provide any additional clarification.

Comment Summary #30: Commenter requested inclusion of additional language regarding chemical and radiochemical purity in determining BUD.

Response: Comment not incorporated. BUDs are assigned primarily based on contamination concerns and then adjusted based on the other factors. The chapter allows for other appropriate testing parameters to be determined by facility SOPs.

Comment Summary #31: Commenter requested removal of the words "suggest" or "suggested" with regard to the manufacturer's use-by-date.

Response: Comment not incorporated. Removal of these words could cause the chapter to become more restrictive and reduce patient access to these drugs.

Comment Summary #32: Commenter requested the addition of the phrase "FDA-approved" as an adjective to the kits used in radiopharmaceutical preparation, compounding, dispensing and repackaging.

Response: Comment partially incorporated. "FDA-approved" was revised to "conventionally manufactured," consistent with language used in <797>

Comment Summary #33: Commenter requested consideration of the maintenance of sterility in addition to other applicable parameters for use-by time.

Response: Comment partially incorporated. Revised the text from "manufacturer suggested" to "manufacturer stated/suggested" when referring to the use-by time from the manufacturer instructions. The Expert Committee has determined addition of maintenance of sterility would make the chapter restrictive.

Comment Summary #34: Commenter requested clarification on the inclusion of the frequency of sterility testing for BUD extension.

Response: Comment not incorporated. There are insufficient data available to support this provision at this time. The Expert Committee will consider future revisions to the chapter upon the receipt of supporting data.

Comment Summary #35: Commenter requested the addition of oxygen as an additional parameter influencing radiochemical purity.

Response: Comment not incorporated. The listed parameters should not be considered a comprehensive list.

Comment Summary #36: Commenter requested assignment of BUD be based on purity studies instead of stability studies.

Response: Comment not incorporated. Other parameters in a stability study may have an impact on patient safety.

Comment Summary #37: Commenter requested an explicit statement that radionuclidic purity may decrease over time due to longer half-lives of impurities.

Response: Comment not incorporated. Current text is a reflection of a well-understood relationship between purity and impurities.

Comment Summary #38: Commenter requested a specific notation of radionuclidic impurities based on Nuclear Regulatory Commission (NRC) requirements.

Response: Comment not incorporated. Language in INTRODUCTION states that all regulatory requirements must be met.

Comment Summary #39: Commenter requested inclusion of radionuclidic impurity Mo-99 not to exceed 0.15 $\mu\text{Ci}/\text{mCi}$ of Tc-99m at the time of administration for non-nuclear regulators.

Response: Comment not incorporated. Current language is an appropriate reflection of the Tc-99m radiopharmaceutical monographs.

Comment Summary #40: Commenter requested the replacement of "container type" with "container characteristics" and replacement of the listed example.

Response: Comment partially incorporated. Revised text as requested, but retained existing example because the proposed example lacks appropriate supporting data.

Comment Summary #41: Commenter requested additional inclusion of "FDA-approved PET drug monographs" when discussing radiopharmaceuticals prepared from kits.

Response: Comment partially incorporated by making the bullet state radiopharmaceutical rather than PET and non-PET.

Comment Summary #42: Commenter requested additional language to allow the use of a conventionally manufactured single-dose container to prepare multiple preparations (with or without minor deviations).

Response: Comment not incorporated. There are insufficient data available to add this provision at this time, and the Expert Committee has concerns regarding the impact of such a provision on patient safety. The Expert Committee will consider future revisions to the chapter upon the receipt of supporting data.

Comment Summary #43: Commenter requested an additional subsection for a single facility that handles low volume and low-risk radiopharmaceutical preparations with BUDs less than 12 hours.

Response: Comment not incorporated. The proposed text is reflective of current practices related to immediate use sterile radiopharmaceuticals.

DOCUMENTATION

Comment Summary #1: Commenters indicated that the proposed text in the introductory paragraph of the DOCUMENTATION section about maintaining policies is not clear and can possibly be misinterpreted.

Response: Comment incorporated. Clarifications to the text have been added to the chapter.

Comment Summary #2: Commenters requested clarifications and additional mandatory requirements be added to the list in the introductory paragraph under the DOCUMENTATION section.

Response: Comment partially incorporated. Requests to add mandatory requirements were not incorporated at the present time as this would make the chapter restrictive. The Expert Committee will consider including the revisions in a future revision if appropriate.

Comment Summary #3: Commenters requested the deletion of the reference to AU or ANP

Response: Comment not incorporated. AU and ANP are included as possible examples of supervising personnel and they are not all inclusive. Each facility may have a designated person(s).

Comment Summary #4: Commenters requested inclusion of: 1) distributed doses; 2) final disposition of a radiopharmaceutical; and 3) details of the specific purpose of the containers included in the Master Formulation Record (MFR).

Response: Comment not incorporated as the request is outside the scope of the chapter.

Comment Summary #5: Commenters requested exclusion explicitly stating that MFRs are not required for preparations following the manufacturer's instructions in the subsection, *Master Formulation Record*.

Response: Comment not incorporated. The Expert Committee determined that the current text allows the exclusion of preparation following manufacturer's instructions.

Comment Summary #6: Commenters requested removal of reference to the MFR when preparing minor deviations.

Response: Comment not incorporated. It is necessary to have traceability of all components when compounding.

Comment Summary #7: Commenters requested clarification on the phrase "remedial action" and the specific types of personnel referred to in the DOCUMENTATION section listed within the *Master Formulation Record and Records for Preparation with Minor Deviation/Compounding* subsection.

Response: Comment incorporated by changing "remedial action" to "corrective action."

Comment Summary #8: Commenters requested inclusion of training records of personnel on: 1) aseptic processing training; 2) hand hygiene; 3) glove fingertip; and 4) thumb sampling.

Response: Comment incorporated.

PREPARATION

Comment Summary #1: Commenter recommended including only radiochemical purity, in the introductory paragraph of the PREPARATION section to match the industry standard.

Response: Comment not incorporated. The Expert Committee determined that other parameters may be needed. The current text provides flexibility to choose the parameters.

Comment Summary #2: Commenter requested including the phrase "according to manufacturer's instructions" in the introductory paragraph of the PREPARATION section.

Response: Comment incorporated.

Comment Summary #3: Commenter requested categorization of specific radioactive bio-resins in the PREPARATION section.

Response: Comment not incorporated because the current language is appropriate to cover all the possible situations.

Comment Summary #4: Commenter requested kit-splitting to be included in the section, *Preparation with Minor Deviations*.

Response: Comment not incorporated. Kit-splitting is captured in the section on *Compounding Using Conventionally Marketed Products*.

Comment Summary #5: Commenter requested replacing the phrase “universal precautions” with “standard precautions” in the section on *Preparation of Radiolabeled Blood Components*.

Response: Comment incorporated.

Comment Summary #6: Commenters requested clarification of the dedicated rooms for labeling blood components.

Response: Comment incorporated by including additional details consistent with accepted nuclear pharmacy practice with patient safety considerations.

Comment Summary #7: Commenters requested that the time of the blood sample collection be considered in the BUD assignment of radiolabeled blood components.

Response: Comment incorporated.

Comment Summary #8: Commenter recommended removing the requirement of ISO Class 5 BSC located in an ISO Class 7 buffer area for blood labeling processes.

Response: Comment not incorporated. The Expert Committee determined that removing the requirement could compromise patient safety.

Comment Summary #9: Commenter requested allowing using dividers in a BSC to accommodate more than one labeling action within a workstation.

Response: Comment not incorporated. Such an allowance could lead to cross-contamination and compromise patient safety.

Comment Summary #10: Commenter requested clarification regarding the steps necessary if the use of dedicated dose calibrators during radiolabeling blood components is not feasible.

Response: Comment partially incorporated. Clarifications to the text have been added to the chapter.

Comment Summary #11: Commenters indicated that the use of dedicated dose calibrators should be made mandatory.

Response: Comment not incorporated. Requiring dedicated dose calibrators would make the chapter restrictive.

Comment Summary #12: Commenter requested removal of the labeling of the syringes and tubes in contact with patient blood components.

Response: Comment not incorporated. Labeling of syringes and tubes is needed to ensure patient safety.

Comment Summary #13: Commenter requested clarification of the garbing needs beyond what is in the chapter when handling blood components.

Response: Comment not incorporated. Additional garbing requirements would make the chapter restrictive. These requirements should be addressed by individual facility SOPs.

Comment Summary #14: Commenter requested replacing the examples of “pigs” and “ammo cases” with syringe transport shields and delivery cases.

Response: Comment incorporated.

Comment Summary #15: Commenter requested clarification about the start time for labeling blood components in order to establish consistent BUD assignment and also ensure that BUD of 1 hour is stated in the subsection for *Preparation of Radiolabeled Blood Components for Immediate Use* in the section, PREPARATION.

Response: Comment incorporated by including more details. Also, the reference to Table 7 for BUD for immediate use of radiolabeled blood components has been included in the section.

Comment Summary #16: Commenter requested a change of the subsection title from “*Immediate Use of Red Blood Cell Labeling*” to “*Preparation of Radiolabeled Red Blood Cells for Immediate Use.*”

Response: Comment incorporated.

Comment Summary #17: Commenter requested the removal of the requirements for dedicated space for blood handling to reduce cost.

Response: Comment not incorporated. Use of dedicated space is necessary to ensure patient safety.

Comment Summary #18: Commenter requested allowance of the use of other disinfecting agents besides sterile 70% IPA.

Response: Comment not incorporated. Sterile 70% IPA is common in nuclear pharmacy practice. The Expert Committee will consider future revisions to the chapter upon the receipt of supporting data. Also, the proposed text in the INTRODUCTION allows for the use of alternative methods if they are validated.

Comment Summary #19: Commenter requested changing the phrase “cleaning and disinfecting products” to “cleaning and disinfecting agents”, and to also include some examples for cleaning and disinfecting agents. Commenter felt that “products” belong to specific companies whereas agents represent a general class.

Response: Comment partially incorporated by changing the word “product” to “agent” without including the examples.

Comment Summary #20: Commenter requested including a table with tests necessary for preparations in the introductory paragraph of the section on PREPARATION.

Response: Comment not incorporated. Adding a table would make the requirements vary with the nature of the preparations. The Expert Committee determined that facility SOPs should address this.

Comment Summary #21: Commenter requested the word “should” be revised to “must” in the subsection on *Nonsterile Preparations* in the section on *Preparation Following Manufacturer Instruction*.

Response: Comment not incorporated. Requested revision would make the chapter more restrictive.

Comment Summary #22: Commenter requested including a dedicated room for complex-level, nonsterile compounding to be consistent with the Massachusetts draft regulation under *Nonsterile Preparations*.

Response: Comment not incorporated. The requirement would increase the burden on the end-users and may not be necessary in other states.

Comment Summary #23: Commenter requested adding a statement regarding the need to have a facilities procedure for cleaning the nonsterile preparations area daily.

Response: Comment not incorporated. Addition of such a statement would make the language restrictive. The existing text requires ensuring cleanliness to ensure quality.

Comment Summary #24: Commenters requested clarifications to the space requirements to ensure quality of the prepared nonsterile preparations.

Response: Comment incorporated.

Comment Summary #25: Commenter requested providing reference to Table 7 for BUD assignment in the PREPARATION section at appropriate places.

Response: Comment incorporated.

Comment Summary #26: Commenter requested clarifying the text regarding varying proportion of the ingredients in the section on *Preparation with Minor Deviations*.

Response: Comment incorporated.

Comment Summary #27: Commenter requested clarifying the test methods used in *Preparations with Minor Deviations*.

Response: Comment incorporated by specifying quality control (QC) test methods to be used.

Comment Summary #28: Commenter requested clarifying the introductory paragraphs in the section on *Preparation of Radiolabeled Blood Components* to emphasize the need to avoid biological contamination.

Response: Comment incorporated.

Comment Summary #29: Commenter requested replacement of “should” with “must” in the statement, “equipment and supplies should never be shared”.

Response: Comment not incorporated. The requested text would make the section PREPARATION restrictive.

Comment Summary #30: Commenter requested clarifications of the dedicated supplies for each labeling process of the blood components.

Response: Comment incorporated.

Comment Summary #31: Commenter suggested referencing the *Hand Hygiene* section in the section for *Preparation of Radiolabeled Blood Components*.

Response: Comment incorporated.

Comment Summary #32: Commenter requested exemption for PEC requirements for denatured Ultra-Tag® Red blood cells to save time during labeling.

Response: Comment not incorporated. The Expert Committee determined that shorter viable protocols are readily available.

Comment Summary #33: Commenter suggested following General Chapter <797> standards for high-risk sterile compounding for labeling blood components.

Response: Comment not incorporated. The proposed General Chapter <797> revision no longer has a section for high-risk compounding.

Comment Summary #34: Commenter expressed concern about the need to have permanent dedicated space for labeling blood components.

Response: Comment not incorporated. The proposed language does not require dedicated permanent space for blood labelling.

Comment Summary #35: Commenter requested emphasis on cleaning and disinfecting the area where the radiolabeling of blood components takes place for immediate use.

Response: Comment incorporated.

COMPOUNDING

Comment Summary #1: Commenter requested revising the introductory paragraph under the section on COMPOUNDING to clarify the criteria necessary for sterile compounding, such as using aseptic techniques in ISO 5 PEC.

Response: Comment incorporated.

Comment Summary #2: Commenter requested reference to The Joint Commission meal preparation guidelines in the section for compounding nonsterile radiopharmaceuticals.

Response: Comment not incorporated. The Joint Commission guidelines are out of the scope of the chapter.

Comment Summary #3: Commenters requested replacement of the word “compound” with “radiopharmaceuticals” as BUD applies to the prepared radiopharmaceuticals and not the compound.

Response: Comment incorporated.

Comment Summary #4: Commenters requested reference to the need to have validation data included to support kit-splitting.

Response: Comment not incorporated. The Expert Committee determined that the current text is sufficient to address validation requirements.

Comment Summary #5: Commenters requested removing the kit-splitting provision from the chapter.

Response: Comment not incorporated. The removal of kit-splitting provision would adversely affect patient access.

Comment Summary #6: Commenter requested explicitly calling out the need to ensure sterility in the COMPOUNDING section that has an impact on BUD.

Response: Comment not incorporated. Table 7 contains sufficient detail about BUD assignment.

Comment Summary #7: Commenter requested deletion of the reference to General Chapter <85> as it is not referenced in General Chapter <797>.

Response: Comments not incorporated. Reference to General Chapter<85> is necessary to ensure patient safety.

Comment Summary #8: Commenter requested allowing the use of ingredients for which no *USP-NF* monograph exists in the section *Sterile Compounding Using Nonsterile Components*.

Response: Comment incorporated by inserting the phrase “if one exists” at the appropriate place in the text.

Comment Summary #9: Commenter requested replacing “radioisotope” with “radionuclide”.

Response: Comment incorporated.

Comment Summary #10: Commenter requested inclusion of Tc99m sulfur colloid as an additional example in *Compounding Nonsterile Radiopharmaceuticals* in addition to meal preparations.

Response: Comment incorporated.

Comment Summary #11: Commenter requested replacing the phrase, “areas intended” with “area designated” in the subsection, *Compounding Nonsterile Radiopharmaceuticals* under the COMPOUNDING section.

Response: Comment incorporated.

Comment Summary #12: The commenter requested the inclusion of a provision that will allow compounding of a radiopharmaceutical that has been withdrawn from the market as part of the institutional review board approved investigational study.

Response: Comment incorporated.

Comment Summary #13: Commenter requested inclusion of additional ingredient sources such as *USP-NF* and *Food Chemicals Codex (FCC)* in the components for compounding purposes.

Response: Comment not incorporated. The current language is sufficient to provide information on the sources for the ingredients.

Comment Summary #14: Commenters requested clarification on how to establish identity of the oral meal components such as eggs, for which no public standards exist.

Response: Comment incorporated.

Comment Summary #15: Commenter requested clarifying the phrase “commercially marketed drug product” as it is not clear that regulatory agency approval is needed for use in sterile compounding.

Response: Comment incorporated.

Comment Summary #16: Commenter requested changing the title of the subsection, *Compounding Using Conventionally Marketed Drug Products* to *Sterile Compounding* as that reflects the subsection content more accurately.

Response: Comment incorporated.

Comment Summary #17: The commenter requested the addition of a reference to Category 1 Compounded Sterile Product from the General Chapter <797> proposal.

Response: Comment not incorporated. Classification based on categories similar to General Chapter <797> is out of scope for General Chapter <825>.

Comment Summary #18: Commenter requested inclusion of examples of commercially marketed products such as I-131 in section for *Sterile Compounding Using A Nonsterile Drug Substance or Components*.

Response: Comment not incorporated as such revision could lead to misunderstanding that only the specified radionuclides are allowed.

Comment Summary #19: Commenter noted concerns about high-risk for radiation contamination and exposure to personnel resulting from bubble point testing prior to dispensing.

Response: Comment partially incorporated by removing the phrase “prior to dispensing.”

Comment Summary #20: Commenter requested replacing the phrase “individual responsible” with “designated person.”

Response: Comment incorporated.

Comment Summary #21: Commenter requested mandating that bulk drug substances be manufactured by establishments registered with the FDA by changing the word “should” to “must.”

Response: Comment not incorporated. The requested language would be restrictive.

DISPENSING

Comment Summary #1: Commenter requested the inclusion of an introductory paragraph describing all activities that can be considered as dispensing.

Response: Comment not incorporated. The Expert Committee determined that generating an all-inclusive list would require time and resources to ensure comprehensiveness. The Expert Committee will consider this for a future revision.

Comment Summary #2: Commenters requested adding a reference to NRC 1556 vol 9.18 to dispensing PET drugs without re-assay.

Response: Comment not incorporated. The Expert Committee will consider this for inclusion in a future revision after ensuring that requested NRC guidance is appropriate for inclusion.

Comment Summary #3: Commenter requested making the section on *Repackaging* a subsection of DISPENSING.

Response: Comment not incorporated. The Expert Committee determined that keeping *Repackaging* will alleviate the potential misinterpretation that repackaging is allowed only when the task of *Dispensing* is considered.

Comment Summary #4: Commenter requested the inclusion of the route of administration on the outer label to ensure patient safety.

Response: Comment incorporated by adding a bullet on route of administration to the list.

Comment Summary #5: Commenter requested including radioactivity at the date and time of calibration.

Response: Comment incorporated.

Comment Summary #6: Commenter requested correcting the statement that implies *Direct Infusion System* is an FDA-approved medical device. According to the FDA, some direct infusion systems are diagnostic radiopharmaceuticals.

Response: Comment incorporated to be consistent with FDA designation.

Comment Summary #7: Commenter requested the portable PET direct infusion device example be replaced with a non-PET direct infusion system in the *Direct Infusion Systems*,

Response: Comment not incorporated. The portable PET direct infusion device is provided only as an example.

Comment Summary #8: Commenter requested inclusion of the environmental requirements for the use of *Direct Infusion Systems*.

Response: Comment not incorporated. The environmental requirements are best defined by the institutional SOPs because of the variable designs of direct infusion devices.

Comment Summary #9: Commenter requested clarification of the specific parts of the direct infusion systems that need to be sterilized.

Response: Comment incorporated by specifying the nonsterile parts of the direct infusion devices.

Comment Summary #10: Commenter requested to include the requirement to use ISO Class 5 PEC in case of problems with the infusion device.

Response: Comment not incorporated. The additional requirement will be considered in a future revision.

Comment Summary #11: Commenter recommended deletion of the subsection, *Transporting Generators Between Facilities*, which will ensure that each facility has its own generator alleviating the need to transfer between facilities.

Response: Comment not incorporated as deletion of the subsection will make the text more restrictive, add cost, and adversely affect patient access.

Comment Summary #12: Commenter requested to replace the word “guideline” with the word “standard” because the chapter is a public standard.

Response: Comment incorporated.

Comment Summary #13: Commenter requested replacement of the text “maintain sterility of the generator and prevent damage” with the phrase “maintain integrity” which includes sterility also in the subsection, *Transporting Generators Between Facilities*.

Response: Comment partially incorporated by inserting the word “integrity” and removing the phrase “prevent damage.”

Comment Summary #14: Commenter requested simplifying the definition of “dispensing” in the *Glossary* and making the text in the section on DISPENSING consistent with the *Glossary*.

Response: Comment incorporated.

Comment Summary #15: Commenter recommended deletion of the section, DISPENSING as a cross-reference to <797> because <797> would be sufficient.

Response: Comment not incorporated. This chapter (<825>) has been harmonized with <795> and <797> to the extent possible. The Expert Committee determined that dispensing requirements for this chapter take into account unique requirements of radiopharmaceuticals such as short half-life and radiation safety, which are not addressed in <797>.

Comment Summary #16: Commenter requested the replacement of the phrase “single-use” with “single-dose” in the section on *Dispensing and Radioassay* to be consistent with the package insert.

Response: Comment incorporated.

Comment Summary #17: Commenter requested deletion of “needle change” from the DISPENSING section.

Response: Comment not incorporated. Needle change belongs in DISPENSING section.

Comment Summary #18: Commenter requested replacing the phrase “final patient-specific dose” with “individual unit dose” in the subsection, *Dispensing and Radioassay*, as it may be interpreted as requiring patient names to be included on the label, which may be in conflict with pharmacy regulations.

Response: Comment partially incorporated. “Final patient dose” has been replaced with “final dose” in the subsection, *Dispensing and Radioassay*.

Comment Summary #19: Commenter requested clarification of the opening sentence in the subsection, *Labeling* under the section on DISPENSING to consider jurisdictions that may either do not have any laws or have more stringent ones.

Response: Comment not incorporated. The existing text is clear and sufficient. The proposed change would not have a significant impact on the chapter.

Comment Summary #20: Commenter requested deletion of the word “final” from the phrase “final container” which implies there may be an interim container.

Response: Comment incorporated.

Comment Summary #21: Commenter requested revision of the outer container labeling to be in compliance with regulatory agency requirements.

Response: Comment incorporated.

Comment Summary #22: Commenter requested making the labeling requirement of the inner container and the outer shielding consistent with each other.

Response: Comment incorporated.

Comment Summary #23: Commenter indicated that the information in the section, *Direct Infusion Systems* uses the phrase “in this chapter” and “strictly” in the first sentence as this should apply only to DISPENSING.

Response: Comment incorporated. The phrase, “in this chapter” has been changed to “in this section” and “strictly” has been deleted.

Comment Summary #24: Commenter requested the word “eluent” be added to the *Direct Infusion Systems* section along with diluent as the terms are interchangeable.

Response: Comment incorporated.

Comment Summary #25: Commenter requested the addition of the word “Injection” to Rubidium Chloride RB82 to make it consistent with the approved title.

Response: Comment incorporated.

Comment Summary #26: Commenters requested widening the BUD for direct infusion systems from 10 hours to up to 24 hours.

Response: Comment not incorporated. Ten hours is the maximum BUD in current practice. Additional supporting data is needed to widen the BUD.

Comment Summary #27: Commenter requested shortening the BUD for direct infusion systems from 10 hours to 4 hours to minimize the risk of cross-contamination from bloodborne pathogens, and also to make a corresponding change to Table 7.

Response: Comment not incorporated. Tightening the BUD would make the chapter more restrictive. The Expert Committee will consider this request in a future revision

Comment Summary #28: Commenter requested the saline concentration used in direct infusion systems be noted.

Response: Comment incorporated by replacing saline with 0.9% Sodium Chloride.

Comment Summary #29: Commenters indicated that the saline bags can be punctured more than once if they are used in an environment that is ISO 5 Class.

Response: Comment incorporated by qualifying the first occurrence of direct infusion systems with the statement, “direct infusion generators without an ISO 5 environment.”

Comment Summary #30: Commenter requested inclusion of the disinfection requirement of the septa with sterile 70% IPA prior to puncturing.

Response: Comment incorporated.

Comment Summary #31: Commenter requested not including the requirement of capping the generator needles and or ports as they are not required by the FDA approved or recognized generators.

Response: Comment not incorporated. The procedure ensures sterility and patient safety.

Comment Summary #32: Commenter requested inclusion of the need to comply with all local regulations and Department of Transportation (DOT) requirements.

Response: Comment not incorporated. The introduction to the chapter states that all the regulatory requirements must be followed.

REPACKAGING

Comment Summary #1: Commenter indicated that Thallous Chloride TI-201 Injection is defined as a sterile product, whereas the text says it is nonsterile.

Response: Comment incorporated. The word nonsterile has been changed to sterile to be consistent with the definition of the dosage from the USP monograph.

Comment Summary #2: Commenter requested replacement of the phrase, “FDA-approved” with “conventionally manufactured” in the first sentence of the section on REPACKAGING as this is reflective of the repackaging operation.

Response: Comment incorporated.

Comment Summary #3: Commenters requested removing the phrase, “FDA-approved” from the first sentence of the section REPACKAGING as some of the radiopharmaceuticals are not available from manufacturers.

Response: Comment not incorporated. The proposed text is consistent with the current FDA guidance.

Comment Summary #4: Commenter requested deletion of the introductory paragraph from the REPACKAGING section.

Response: Comment not incorporated. The Expert Committee determined this information is important to provide a context for activities that are considered as repackaging in the nuclear pharmacy practice.

Comment Summary #5: Commenters requested inclusion of the statement that labels must meet the statutory and regulatory requirements defined by federal, state, and local agencies.

Response: Comment partially incorporated. The necessary labeling requirements were clarified in a manner that does not add any additional requirements for practitioners.

Comment Summary #6: Commenter requested inclusion of dose-splitting in this section.

Response: Comment not incorporated here as dose-splitting is covered in the IMMEDIATE USE STERILE RADIOPHARMACEUTICALS section

Comment Summary #7: Commenter requested explicit reference to 10 CFR 32.72 to be consistent with NRC regulations.

Response: Comment not incorporated. The INTRODUCTION section of the chapter notes that all regulations of the NRC must be followed.

QUALITY ASSURANCE AND QUALITY CONTROL

Comment Summary #1: Commenter requested inclusion of reporting requirements as a part of the quality assurance (QA)/QC program.

Response: Comment not incorporated. Details of the reporting requirements are out of scope for the chapter. The introduction to the chapter states that all the regulatory requirements must be followed.

Comment Summary #2: Commenter requested merging the section on *Adverse Event Reporting* with the *Complaint Handling* section.

Response: Comment not incorporated. Keeping the two subsections separate aids in clarity.

Comment Summary #3: Commenter requested moving the cross-reference (see General Chapter <1163> *Quality Assurance in Pharmaceutical Compounding*) to the end of the sentence.

Response: Comment incorporated.

Comment Summary #4: Commenter requested revising the phrase “all aspects of the preparation of radiopharmaceuticals,” as it appears to exclude compounding, dispensing, and repackaging.

Response: Comment incorporated by replacing the word “preparation” with “handling.”

Comment Summary #5: Commenter requested deletion of the word, “duties” from the phrase, “roles and duties” as the two terms mean the same.

Response: Comment not incorporated. The words are specific to the tasks performed by individuals.

Comment Summary #6: Commenter requested revision of the opening sentence in the section, *Notification About and Recall of Out-of-Specifications Dispensed Radiopharmaceuticals*, as the current text implies all tests must be completed prior to administration.

Response: Comment not incorporated. The current text does not imply that all tests must be completed prior to administration.

Comment Summary #7: Commenter requested deletion of the redundant phrase “of distribution” from the sentence “determine the distribution of any affected radiopharmaceutical, including the date and quantity of distribution.”

Response: Comment incorporated.

Comment Summary #8: Commenter requested the deletion of the phrase “sterile process” from the phrase “sterile process facility,” as the tasks apply to the entire facility.

Response: Comment incorporated.

Comment Summary #9: Commenter requested specifying the agencies which must receive the recall notification and harmonization of the text with General Chapter <797>.

Response: Comment incorporated, and text made consistent with General Chapter<797>.

Comment Summary #10: Commenter requested making it clear that labeling referred to in the *Complaints Handling* section pertains to a container.

Response: Comment incorporated.

Comment Summary #11: Commenter requested simplifying the role of the designated person in the *Complaint Handling* section by removing adjectives such as “thorough” in the existing text.

Response: Comment incorporated.

Comment Summary #12: Commenter requested additional details and instructions regarding when, how, and where to send the adverse event reports.

Response: Comment not incorporated. The current text includes examples of the agencies such as state boards of pharmacy and FDA’s Medwatch program. Additional instructions should be included in the facility SOPs.

GLOSSARY

Comment Summary #1: Commenters requested the *Glossary* be placed at the beginning of the chapter.

Response: Comment not incorporated. USP Format and Style Guidelines require the *Glossary* to be at the end of the document.

Comment Summary #2: Commenter requested the addition of food "ingestion" as an administration route.

Response: Comment incorporated.

Comment Summary #3: Commenter requested alteration of the name "BUD" to be specific to radiopharmaceuticals.

Response: Comment not incorporated. Current term "BUD" is acceptable.

Comment Summary #4: Commenter requested alteration of the name "buffer room" to be specific to radiopharmaceuticals.

Response: Comment incorporated. "Room" was replaced throughout the document with "area" to distinguish from <797>.

Comment Summary #5: Commenter requested clarification of the definition of compounding.

Response: Comment not incorporated. The definition in <825> was revised to be consistent with FDA guidance.

Comment Summary #6: Commenters requested the inclusion of definitions for ANP, AU, Container–closure, Direct Infusion System, Dose-pooling, Dose-splitting, MFR, Molar mass, QA, QC.

Response: Comment incorporated.

Comment Summary #7: Commenters requested the removal of the words "commercially manufactured."

Response: Comment incorporated. Replaced with "conventionally manufactured."

Comment Summary #8: Commenter requested providing examples of types of tasks such as changing the needles that fall under administration in the definition of *Administration*.

Response: Comment not incorporated. Description of such examples is out of scope for this chapter.

Comment Summary #9: Commenter requested alignment of the definition of "Administration" with <797>.

Response: Comment not incorporated. Routes of administration in <797> are not similar enough to <825> to allow for harmonization.

Comment Summary #10: Commenter requested deletion of the definition for ALARA.

Response: Comment not incorporated. ALARA principles are necessary to ensure radiation safety practices.

Comment Summary #11: Commenter requested clarification of cleaning agent, critical site, designated person, disinfectant, expiration date, garb, HEPA, Hot-Cell, Hot-lab, Immediate use, ISO class, Ligand, Line of demarcation, Media-fill test, Multiple-dose container, Pass-through, Preparing, Preparing with minor deviations, Radioassay, Repackaging, SEC, Shielding, Specific activity, Start of preparation, Unclassified, Unrestricted area space, and Use-by time in the *Glossary*.

Response: Comment incorporated.

Comment Summary #12: Commenter requested the revision of the definition of "Blood components" as the phrase, "used to be radiolabeled" is confusing.

Response: Comment incorporated by revising the definition.

Comment Summary #13: Commenter requested the revision of the definition of BSC to generalize the term.

Response: Comment incorporated.

Comment Summary #14: Commenter requested the incorporation of "prepare with minor deviations" into the definition of BUD.

Response: Comment incorporated.

Comment Summary #15: Several commenters requested revision of the definition of "buffer room."

Response: Comment not incorporated. Definition is harmonized with General Chapter <797>.

Comment Summary #16: Several commenters requested the removal of "patient specific" and "FDA-approved" from the definition for "Dispensing."

Response: Comment incorporated.

Comment Summary #17: Commenter requested the revision or deletion of First air, Sporicidal agent, SRPA, and BSC.

Response: Comment not incorporated. The terms maintain harmonization with General Chapter <797>.

Comment Summary #18: Commenter requested revision of "designated person" to restrict to one person per facility.

Response: Comment not incorporated. This revision would make the chapter more restrictive and inconsistent with <797>.

Comment Summary #19: Commenter requested expanding and adding more detail to the definition for "Media-fill test."

Response: Comment not incorporated. This information is found in the section, *Media-fill Testing*.

Comment Summary #20: Commenter requested that the definition of multiple-dose and single-dose containers be consistent with General Chapter <797>.

Response: Comment partially incorporated. Definitions are harmonized with General Chapter<797> to the extent possible, taking into account the unique requirements of radiopharmaceuticals, especially with respect to radiation safety.

Comment Summary #21: Commenter requested replacing current "pass-through" language with an alternate system.

Response: Comment not incorporated. The definition for pass-through is consistent with engineering designs of nuclear pharmacies and radiopharmaceutical processing areas.

Comment Summary #22: Commenter requested deletion of "Patient-specific dose" to prevent confusion during inspections.

Response: Comment incorporated.

Comment Summary #23: Commenter requested clarification on the actions to be taken in the event of the failure of a radiochemical purity test.

Response: Comment not incorporated. Requested change is beyond the scope of the chapter.

Comment Summary #24: Commenter requested revision to the definition of "Radiopharmaceutical" by including their use in therapy, diagnosis and including how they are prepared.

Response: Comment not incorporated. The Expert Committee determined that the definition is sufficient.

Comment Summary #25: Commenter requested revision of SRPA from "...ISO Class 8 air quality..." to "...ISO Class 8 particle count specifications."

Response: Comment partially incorporated. Change to "...ISO Class 8 non-viable particle count" incorporated.

Comment Summary #26: Commenter requested the deletion of the one-hour requirement in the immediate use definition.

Response: Comment not incorporated. This requirement is necessary to ensure patient safety.

APPENDIX 1

Comment Summary #1: Commenter requested inclusion of the definitions for the acronyms not more than (NMT) and no less than (NLT).

Response: Comment not incorporated. Both are defined in Section 8.110 of the *General Notices*.

Comment Summary #2: Commenter requested deletion of Cleaning Equipment Trade Association (CETA) from the acronyms list as CETA is not a standards organization.

Response: Comment not incorporated. Inclusion of this in the chapter is as an explanation for what CETA stands for and does not imply that CETA is a standards organization.

Appendix 2

Comment Summary #1: Commenters requested alterations to the figures to increase clarity and provide additional examples of room types.

Response: Comment partially incorporated. Appendix 2 has been removed from the chapter to minimize the risk of potential confusion by regulators that these examples are USP requirements.