The SNMMI/ACNM Practice Guideline for the Use of Radiopharmaceuticals 5.0

Kara Weatherman[1], Erin Elizabeth Grady[2], Nic Mastascusa[3], Sara Johnson[4], George H. Hinkle[5], Richard Laforest[6], Chloee Wendorf[7], and Kathy S. Thomas[8]

[1]Purdue University College of Pharmacy, West Lafayette, Indiana; [2]Department of Radiology, Stanford University, Stanford, California; [3]University of Iowa Hospitals & Clinics, Iowa City, Iowa; [4]Veteran Affairs San Diego Healthcare System, San Diego, California; [5]The Ohio State University, Columbus, Ohio; [6]Mallinckrodt Institute of Radiology, Washington University, St. Louis, Missouri; [7]Department of Radiology, UC San Diego Health, San Diego, California; and [8]Retired

PREAMBLE

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international scientific and professional organization founded in 1954 to promote the science, technology, and practical application of nuclear medicine. Its 15,000 members are physicians, technologists, and scientists specializing in the research and practice of nuclear medicine. In addition to publishing journals, newsletters, and books, the SNMMI also sponsors international meetings and workshops designed to increase the competencies of nuclear medicine practitioners and to promote new advances in the science of nuclear medicine.

The SNMMI will periodically define new standards/guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service to patients. Existing standards/guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated. Starting February 2014, the SNMMI guidelines have been referred to as procedure standards. Any practice guideline or procedure guideline published before that date is now considered an SNMMI procedure standard.

Each standard/guideline, representing a policy statement by the SNMMI, has undergone a thorough consensus process in which it has been subjected to extensive review. The SNMMI recognizes the safe and effective use of radiopharmaceuticals requires specific training, skills, and techniques, as described in each document.

The SNMMI have written and approved these standards/guidelines to promote the use of nuclear medicine procedures with high quality. These standards/guidelines are intended to assist practitioners in providing appropriate nuclear medicine care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, the SNMMI cautions against the use of these standards/guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the appropriateness of any specific procedure or course of action must be made by medical professionals considering the unique circumstances of each case. Thus, there is no implication that an approach differing from the standards/guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the standards/guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the standards/guidelines.

The practice of medicine involves not only the science but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized adherence to these standards/guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these standards/guidelines is to assist practitioners in achieving this objective.

I. INTRODUCTION/GOALS

This guideline was developed by the SNMMI to describe important factors common for radiopharmaceuticals used in diagnostic nuclear medicine, Positron Emission Tomography (PET), and therapeutic nuclear medicine procedures. It is

For correspondence or reprints, contact Kara Weatherman (kdwman@purdue.edu).

Published online Apr. 1, 2025.

intended to guide nuclear medicine professionals in establishing policies and procedures for the use of radiopharmaceuticals in clinical practice. This guideline is intended to be concordant with the regulations of state and federal agencies.

II. DEFINITIONS

A. Diagnostic Radiopharmaceuticals

Diagnostic radiopharmaceuticals (also known as radioactive drugs) are drugs containing radionuclides capable of emitting radiation in the range of 80 keV to 511 keV. The distribution of the radiopharmaceutical within the body is determined by the physiochemical properties of the drug, the stability of the radiolabel, the purity of the radiopharmaceutical preparation, the pathophysiologic state of the patient, the presence or absence of interfering drugs, and the route of administration. Dynamic, static, whole body, and single photon emission computed tomography (SPECT) images of the biodistribution of the radiopharmaceutical within the body can be obtained using a gamma camera with or without computed tomography (CT) or other suitable instruments appropriate for the radiopharmaceutical being imaged. Radioactivity in specified sites of accumulation in situ or biologic samples can be collected and measured for nonimaging procedures. The safe handling of diagnostic radiopharmaceuticals requires applying the three principles of radiation protection, appropriate shielding based on the keV range of the radiopharmaceutical (e.g. lead/tungsten shielding), minimum handling time, and increased distance where possible and appropriate.

- Elution of Generators – Traditional radionuclide generators provide a continuous supply of radioactivity that can be used for the preparation of radiopharmaceutical kit formulations and in some instances, for direct administration to patients. USP <825> requires the elution of radionuclide generators to be carried out in an area validated to meet ISO 8 standards at minimum. The projected yield of radioactivity from a generator can be calculated based on calibration activity and previous elution history. The volume of eluate used should be chosen to optimize the assay of the generator elution, based on the projected radioactivity level to be eluted. Following elution, the total activity should be determined by dose calibrator measurement and the resulting assay (mCi/mL) calculated. Each elution must be evaluated to determine radionuclidic purity, and the concentration of parent isotope breakthrough compared to the Nuclear Regulatory Commission (NRC) regulatory limits. Other quality control tests for radiochemical and chemical purity may also be performed per accepted procedures. Generator elutions may be used up to manufacturer-specified expiration times, although an extension of this time may be implemented following in-house validation processes. The final activity, total volume, date and time of elution, and elution expiration should be documented, along with the identity of the person performing the elution. Radiation safety procedures and aseptic techniques must be used and maintained throughout the process.
- On-site Kit Preparation – Radiopharmaceuticals available as kit formulations should be prepared according to the manufacturer's product labeling instructions in an ISO Class 5 environment (laminar flow hood) located in a clean room or segregated radiopharmaceutical processing area (SRPA). If these engineering controls are not available, radiopharmaceutical kit preparation can occur under immediate use designation, with preparation in an ambient environment, assuring the prepared product is limited to use for one patient and all manipulations and patient administration are concluded within one hour of starting the preparation procedure. The prescribing physician or nuclear pharmacist may introduce minor deviations from package insert instructions, as defined by the Food and Drug Administration (FDA), to meet patient needs. Radiopharmaceutical kit preparation deviating from product labeling standards radiopharmaceutical compounding requires a validated master formulation record (MFR) on file, per USP <825>. It is the responsibility of the person preparing the radiopharmaceutical kit to assess final product quality. This can be achieved through the development and implementation of a comprehensive quality control program evaluating radionuclidic, radiochemical, and chemical purity, biologic purity (sterility and apyrogenicity), and pharmaceutical purity (pH, particle size, absence of foreign particulate matter).

B. PET Radiopharmaceuticals

Positron-emitting isotopes emit a positron ($\beta+$), which is the antiparticle of an electron. Positrons have all the characteristics of an electron but with a positive charge. Like β particles ($\beta-$), positrons are emitted from nuclei with a range of energies up to a maximum characteristic energy (Emax). Positrons travel in a tortuous path upon emission, depositing most of their energy before interacting with a negatively charged electron in the environment. At the end of the positron's travelled distance, an annihilation reaction occurs within a very short time ($\sim 10^{-10}$ seconds) resulting in the production of two 511 keV photons at nearly 180° angles which can be imaged via coincidence detection on a stand-alone PET system or hybrid scanner (PET/CT or PET/MRI). Positrons have a short range in soft tissue, which is dependent on the initial positron energy. They travel only a few millimeters from the nucleus and have low linear energy transfer (LET) (0.2–3 keV/μm).

PET radiopharmaceuticals are typically used to evaluate metabolic and biochemical activity in various cells in the body. The shorter half-life of most PET isotopes in typical clinical use provides an advantage in minimizing patient exposure while obtaining quality diagnostic information. Isotope half-life must be considered in conjunction with the physiologic distribution and uptake of the PET radiopharmaceuticals. Several PET isotopes (O-15, C-11, N-13) are natural substrates commonly used to label biological molecules. However, there has been increasing interest in radiopharmaceutical development using other PET isotopes (usually with longer half-life) to form a theranostic pair with α or β-emitting isotopes, usually of the same element or chelated to yield similar pharmacokinetics.

Manipulation of positron-emitting isotopes requires emphasis on radiation safety practices due to the 511 keV gamma photons produced. Adequate shielding of positron-emitting

isotopes is a significant consideration in maintaining ALARA safety for radiation workers and patients. Lead is an economical and readily available shielding material, but denser materials like tungsten are more effective and allow for thinner shielding and increased ease for operator use. Minimizing handling time and incorporating remote manipulator and dispensing technologies can help maintain appropriate ALARA considerations when handling positron-emitting radiopharmaceuticals.

- Generator Elution & Infusion Systems: Positron-emitting isotopes can be produced using radionuclide generator technology, allowing for on-site production and availability of short-lived isotopes without the need for a cyclotron. PET-producing generators have parent isotopes with long half-lives, allowing for extended periods of clinical use compared to the traditional generator systems, but produce PET-emitting radiopharmaceuticals with very short half-lives. PET generator eluates can be used for direct patient administration (Rb-82) or for radiolabeling kit formulations (Ga-68). Like traditional Mo-99/Tc-99m generators, the eluates from the PET generators must be evaluated for radionuclidic purity before administration to patients, per directions outlined in manufacturer-provided instructions for use, while meeting specified regulatory standards. PET generators and infusion systems are subject to USP <825> storage and elution requirements. Non-direct generators, i.e., Ge-68/Ga-68, must meet a minimum of ISO Class 8 criteria for storage and elution, and an ISO Class 5 environment is required for subsequent PET radiopharmaceutical kit preparation, i.e., PSMA kit preparation. Direct generators, such as Rb-82, and PET infusion systems do not require an ISO Class environment but are limited to a single puncture and 10-hour beyond-use-date (BUD). As with other PET agents, the 511 keV gamma photons from these isotopes require adequate shielding to maintain ALARA for the radiation safety worker and patients.
- Cyclotron Production: Many of the commercially available PET radiopharmaceuticals are produced in FDA-regulated manufacturing facilities, while research agents at a minimum must meet the requirements set forth by USP. Cyclotrons are characterized by the energy of the particle beam attained at the end of acceleration, and following irradiation of a stable target through a nuclear reaction, a proton-rich positron-emitting material is generated. Cyclotron Production: Many of the commercially available PET radiopharmaceuticals are produced in FDA-regulated manufacturing facilities, while research agents at a minimum must meet the requirements set forth by USP. Cyclotrons are characterized by the energy of the particle beam attained at the end of acceleration, and following irradiation of a stable target through a nuclear reaction, a proton-rich positron-emitting material is generated. The isotope produced is incorporated into a final radiopharmaceutical, generally via an automated synthesis process which carries out all radiolabeling, purification, and sterilization steps. Manufacturing facilities are required to follow current good manufacturing practice (cGMP) during all production steps, and all products undergo rigorous quality control testing before final product release. Many cyclotron-produced PET radiopharmaceuticals are ultimately transferred to a nuclear pharmacy for unit dose dispensing.

C. Therapeutic Radiopharmaceuticals

Theranostic isotopes can be produced via nuclear reactors, particle accelerators, or via naturally occurring decay processes in a radionuclide generator system. Production occurs in FDA regulated facilities under guidelines for active pharmaceutical ingredients and are generally covered by a drug master file (DMF) submitted to and authorized by the FDA. The isotopes are incorporated into a final radiopharmaceutical, generally via an automated synthesis process, which carries out all radiolabeling, purification, and sterilization steps. Manufacturing facilities are required to follow current good manufacturing practice (cGMP) during all production steps, and all products undergo rigorous quality control testing before final product release. The final theranostic radiopharmaceutical is provided as a single patient dose and delivered to the end user for dispensing and administration.

Radiopharmaceuticals with therapeutic efficacy emit α or β− emissions with a particle decay pathway, effective range in tissue, and biological effectiveness specific to tumor size or abnormal tissue. β-emitting radioisotopes are most effective in medium to large tumors based on their long particle path length (≤12 mm) and low LET (~0.2 keV/μm). α-particles, with their short path length (50 μm–100 μm) and high LET (100 keV/μm) are more suitable for small neoplasms or micrometastases (*1*). Similar to diagnostic radiopharmaceuticals, the biodistribution of therapeutic radiopharmaceuticals is determined by the physiochemical properties of the drug, the stability of the radiolabel, the purity of the radiopharmaceutical preparation, the pathophysiologic state of the patient, the presence or absence of interfering drugs, and the route of administration. Imaging is possible but difficult with some therapeutic radionuclides due to the low amount of activity injected leading to few counts in the keV range visible to a gamma camera (see current guidelines). The safe handling of therapeutic radiopharmaceuticals is critically important when applying the three principles of radiation protection, appropriate shielding based on the particle emissions and keV range of the radiopharmaceutical (e.g. acrylic/lead or tungsten shielding or lead/tungsten shielding), minimum handling time, and increased distance where possible and appropriate. These concerns are of high importance due to the emission of high energy gamma rays concomitant with the therapy β or α particles emitted.

Patient imaging following the administration of therapeutic radiopharmaceuticals enables dosimetric calculations of the radiation dose delivered to organs and tumors. Dosimetry methodology and nomenclature has been described and has been the subject of numerous MIRD reports, including the recent MIRD 2022 Primer (*2*). However, dosimetry in radiopharmaceuticals therapy is evolving and publications such as ICRU-96 propose recommendations on methodology, nomenclature and reporting.

D. Physiologic and Pharmacologic Interventions

Physiologic and pharmacologic interventions increase the sensitivity or specificity of a nuclear medicine procedure by affecting the distribution and pharmacokinetics of the administered radiopharmaceutical through an alteration in

organ physiology. Preparation of these pharmacologic agents for intravenous administration must follow requirements outlined in USP <797>. Non-radioactive interventions are not covered in USP <825> which is limited to radioactive agents only.

III. PRACTICAL CONSIDERATIONS

A. Clinical Use and Administration of Radiopharmaceuticals

1. The administration of a radiopharmaceutical to a patient must be prescribed by an authorized user, either by an individually written prescription or a standardized protocol. The radiopharmaceutical identity, amount or infusion rate, and route of administration (e.g., oral, inhalation, subcutaneous, intravenous, intradermal) must be expressly stated.
2. The authorized user is ultimately responsible for the safety, quality, and correctness of all radiopharmaceuticals prepared and dispensed for administration under their direction.
3. According to applicable state and local laws, appropriately trained personnel are responsible for the safety, quality, and correctness of the radiopharmaceuticals prepared and dispensed under their supervision.
4. The preparation, quality control, dispensing, and administration of radiopharmaceuticals and adjunct drugs to patients may be delegated to qualified personnel, according to applicable state and local laws (*3*,*4*).
5. There must be a signed and dated written directive for each patient for all therapeutic radiopharmaceuticals, including but not limited to I-125- or I-131-sodium iodide in quantities of 1.11 MBq (30 μCi) or more.
6. Patients of childbearing potential and breastfeeding patients must be identified before the administration of any radioactive material. Pregnancy testing must be performed before administration of any radiopharmaceutical that could potentially result in a dose to an embryo or fetus of 50 mSv (5 rem) or more. When performing pregnancy testing, serum pregnancy tests should be performed prior to therapeutic nuclear medicine procedures given the enhanced sensitivity. Timing of pregnancy testing is per institutional protocol.
7. The identity of the radiopharmaceutical, amount of radioactivity, and route of administration must be verified before administration and consistent with the written prescription or standard protocol. The goal is to ensure the right patient receives the right exam with the right radiopharmaceutical or medication at the right time with the right dose and by the right route of administration. Syringes and outer shielding or containers must be accurately labeled for verification of contents.
8. The quantity of radioactivity to be administered must be assayed using a dose calibrator before administration. Alternatively, for sites using unit doses, where permitted by state or federal regulation, the radioactivity may be determined using decay correction of the unit dose based on the activity determined by the radiopharmacy or manufacturer. The amount of radioactivity must fall within the tolerance levels of applicable state and federal regulations (e.g. 10% of the prescribed dose and the actual quantity administered within ±20% unless otherwise directed by the authorized user) or within the prescribed range and be documented in the patient's medical record (*4*).
9. Before administration, the expiration date and time of the radiopharmaceutical must be verified to ensure the dose is administered before expiration.
10. Proper administration of any radiopharmaceutical is essential to image quality and quantification. Best practices for administering radiopharmaceuticals should be followed. 'Straight sticking' should not be performed. Verifying venous patency before, during, and following injection is essential to avoid misadministration, which includes a careful evaluation of backflow following initial catheter placement and immobilization of the injection site. Radiopharmaceutical misadministration can affect tracer kinetics and uptake. Although rare, extravasation of therapeutic radiopharmaceuticals may potentially cause damage to the tissue surrounding the injection site. The injection should be immediately discontinued if resistance is felt, swelling at the injection site is observed, or the patient complains of pain or discomfort at the injection site. Documentation of infiltration should include the estimated volume and location of the infiltration as well as immediate or follow-up care, as needed (*4*).

B. Recordkeeping

1. Records on the receipt, preparation, use, administration, and disposal of all radiopharmaceuticals and non-radioactive pharmacologic interventions should comply with the Radioactive Materials license conditions, USP Chapters <797> and <825>, and medical and radiation control protocols (*5*,*6*).
2. Records on the receipt of packages containing radioactive material should include the identity of contents and the results of inspection for physical damage, measurement of the radiation dose rate emanating from the package, and testing for removable contamination, as required by the regulatory agencies. Records on the receipt of radioactive material should be maintained and stored per local, state, and federal regulations. Records should include the identity of the radiopharmaceutical, its source, the amount of the activity received, and the results of radiation surveys and contamination testing. Any discrepancies must be reported to the manufacturer or the regulatory agency.
3. For all radiopharmaceuticals prepared on-site, records should be USP <825> compliant and should include the date and time of preparation; the quantity, volume, and concentration of radioactivity used; reagent lot numbers; quality control data; the expiration time; waste disposition; and the name or initials of the individual responsible for the preparation.
4. For all radiopharmaceuticals, the identity of the radiopharmaceutical, the amount of radioactivity administered, the identity of the patient and the individual performing the administration; the route of administration; date and time of use must be recorded.
5. Records on testing of the radionuclide dose calibrator for constancy, accuracy, linearity, and geometric variation must be maintained.
6. All radioactive material must be disposed of per institutional, state, and federal regulations. Policies and procedures should be developed to ensure radioactive material does not enter the normal waste stream of the institution, except in exempt quantities on exempt forms (e.g., patient excreta).

C. Adverse Reactions/Product Problems

Adverse drug reactions (ADR) are unintended, harmful events or side effects related to the administration of a medication or specifically for this context a radiopharmaceutical.

Although ADRs for diagnostic radiopharmaceuticals are relatively uncommon as compared to conventional drugs, the most common reactions to these radiopharmaceuticals are rash, nausea, and vomiting. With the advent of many novel therapeutic radiopharmaceuticals, adverse effect reporting (AE) has become more common and necessary. The United States (US) Food and Drug Administration (FDA) defines AEs by degree of seriousness. However, any known or suspected AEs following the administration of a diagnostic or therapeutic radiopharmaceutical should be managed according to USP <825>. Establishing facility standard operating procedures (SOPs) addressing known or suspected AEs should be implemented as a best practice. Adverse reactions associated with the administration of radiopharmaceuticals should be investigated and documented in accordance with facility SOPs and all applicable regulations. Reporting AEs to the US FDA is a critical part of drug pharmacovigilance (*7*).

D. Medical Events Involving Radiopharmaceuticals

Medical events involving radiopharmaceuticals are defined by federal and state regulatory agencies and accreditation bodies (e.g., Joint Commission). An event is described as a radiopharmaceutical dose to the wrong patient, wrong radiopharmaceutical, wrong route of administration, or an administered dose varying from the prescribed dose. A dose that varies from a prescribed dose is defined as one that exceeds the effective dose equivalent (EDE) of 5 rem, 50 rem to the organ, tissue, or shallow dose equivalent (SDE) to the skin or the dose delivered differs from the prescribed dose by 20% or greater. Medical Events must be reported in accordance with USNRC or Agreement State regulations (*8*).

E. Diagnostic Dose Reduction Guidelines

1. The radiation dose for all nuclear medicine and molecular imaging procedures should be optimized so the patient receives the smallest possible amount of radioactivity that will provide the appropriate diagnostic information. In the pediatric population, the North American Consensus Guidelines for administered activity are based on body weight, except for radionuclide cystogram and gastric-emptying studies (*9*,*10*).
2. Policies and procedures should be in place to ensure the qualified personnel administering the radiopharmaceutical must follow the five rights of medication administration.
3. To ensure the appropriate use of radiopharmaceuticals, comprehensive quality control measures should be in place.
4. The authorized user, nuclear medicine physician(s), and technologist(s) must be appropriately trained and certified/licensed according to state and institutional guidelines and participate in annual competency assessments, as appropriate, to maintain up-to-date training in the safe use and handling of radiopharmaceuticals.

IV. ISSUES REQUIRING FURTHER CLARIFICATION

All radiopharmaceuticals (sterile and non-sterile) and any adjunct agents for pharmacologic interventions should be prepared following USP <797> (Pharmaceutical Compounding: Sterile Preparations) USP <825> (Radiopharmaceuticals – Preparation, compounding, dispensing, and repackaging), following the state board of pharmacy and other state and local requirements.

V. ACKNOWLEDGEMENTS

This guideline was revised through the collaborative efforts of the SNMMI and SNMMI-TS Quality Committee. Comments and suggestions from relevant SNMMI Councils and committees are appreciated and have been considered in this guideline. We thank Julia K. Trigger, MS, Associate Director of Evidence and Quality of SNMMI, for her efforts in organizing the update of this procedure standard.

VI. LIABILITY STATEMENT

This guideline summarizes the views of the SNMMI/ACNM. It reflects recommendations for which the SNMMI/ACNM cannot be held responsible. The recommendations should be taken into context of good practice of nuclear medicine and not substituted for national and international legal or regulatory provisions.

VII. BIBLIOGRAPHY/REFERENCES

1. Poty S, Francesconi LC, McDevitt MR, Morris MJ, Lewis JS. α-emitters for radiotherapy: from basic radiochemistry to clinical studies–part 1. *J Nucl Med.* 2018;59:878–884.
2. MIRD Committee of the SNMMI. *MIRD Primer 2022: A Complete Guide to Radiopharmaceutical Dosimetry*. SNMMI; 2022.
3. Wallner PE, Yoo DC, Calais J, et al. ACR–ACNM–ARS–ASTRO–SNMMI practice parameter for the performance of therapy with radiopharmaceuticals. *Am J Clin Oncol*. 2024;47:169–176.
4. Farrell, MB, Thomas, KS, eds. *Quick-Reference Protocol Manual for Nuclear Medicine Technologists*, 2nd ed. Reston, VA, SNMMI; 2024: 5–6.
5. USP. Pharmaceutical Compounding – Sterile Preparations <797>. In: USP-NF. Rockville, MD: USP; November 2023.
6. USP. Radiopharmaceuticals – Preparation, Compounding, Dispensing and Repackaging <825>. In: USP-NF. Rockville, MD: USP; November 2023
7. Meher BR, Agrawal K, Gnanasegaran G. Review of adverse reactions associated with the use of common diagnostic radiopharmaceuticals. *Indian J Nucl Med.* 2021;36:163–167.
8. https://www.nrc.gov/reading-rm/doc-collections/cfr/part035/part035-3045.html
9. SNMMI Position Statement on Dose Optimization for Nuclear Medicine and Molecular Imaging Procedures, 2012. https://snmmi.org/common/Uploaded%20files/Web/Clinical%20Practice/SNM_Position_Statement_on_Dose_Optimization_FINAL_June_2012.pdf.
10. Gelfand MJ, Parisi MT, Treves T. Pediatric radiopharmaceutical administered doses: 2010 North American Consensus Guidelines. *J Nucl Med.* 2011;52:318–322.