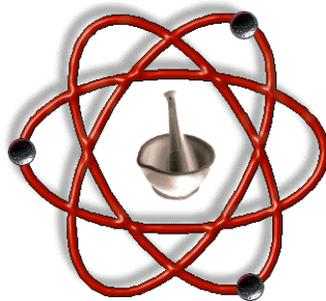


NUCLEAR PHARMACY COMPOUNDING GUIDELINES



Prepared by

Nuclear Pharmacy Compounding Practice Committee

Section on Nuclear Pharmacy Practice

Academy of Pharmacy Practice and Management (APPM)

American Pharmaceutical Association (APhA)

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ABBREVIATION LIST

ACARA:	as clean as reasonably achievable
ACS:	American Chemical Society
ANDA:	abbreviated new drug application
APhA:	American Pharmaceutical Association
APPM:	Academy of Pharmacy Practice and Management
AR:	analytical reagent
ASHP	American Society of Health-System Pharmacy
BET:	bacterial endotoxin testing
CFR:	Code of Federal Regulations
CGMP's:	current good manufacturing practices
FCC:	Food Chemicals Codex
FDA:	Food and Drug Administration
FDAMA:	Food and Drug Administration Modernization and Accountability Act of 1997
FFDCA	Federal Food, Drug, and Cosmetic Act
MOU:	memorandum of understanding
NABP	National Association of Boards of Pharmacy
NDA:	new drug application
NF:	National Formulary
PET:	positron emission tomography
RCP:	radiochemical purity
USP:	United States Pharmacopeia
USPCI	United States Pharmacopeial Convention, Inc.

DEFINITIONS

The following selective definitions apply to the *Nuclear Pharmacy Compounding Guidelines*:

ACARA (as clean as reasonably achievable) means making every reasonable effort to maintain clean conditions, as much as one can possibly achieve without significantly compromising radiation protection. When the ACARA principal is applied to nuclear pharmacy compounding practice, it should:

- (1) be consistent with the purpose for which the licensed activity is undertaken,
- (2) take into account the state of the technology, the economics of improvements with regard to benefits to the public health and safety, as well as other societal and socioeconomic considerations, and
- (3) be in relation to utilization of radiopharmaceuticals in the public interest.

Bulk Drug Substance means any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.

Component means any ingredient (active or non-active) intended for use in the compounding of a drug product, including those that may not appear in such product (i.e., intermediate).

Compounding means the preparation, mixing, assembling, packaging, or labeling of a drug (including a reagent kit or a radiopharmaceutical) (1) as the result of a practitioner's prescription order or initiative based on the practitioner/patient/pharmacist relationship in the course of professional practice, or (2) for the purpose of, or as an incident to, research, teaching, or chemical analysis and not for sale or dispensing. Compounding also includes the preparation of drugs (including radiopharmaceuticals) in anticipation of prescription orders based on routine, regularly observed prescribing patterns. Please also refer to the *General Provisions* section for further description regarding nuclear pharmacy compounding practices.

Compounding area means the physical space used for the compounding activity, such as the surface of a countertop, the interior of a laminar flow hood, or the interior of an enclosed glove box, etc.

Excipient means any non-active ingredient or intermediate of a drug product.

Intermediate means an ingredient (other than a bulk drug substance) intended for use in the compounding of a drug product that does not appear in the final drug product.

Nuclear Pharmacist means one that has state licensure as a pharmacist or nuclear pharmacist (as applicable), and meets the training requirements for an authorized or experienced nuclear pharmacist as stated in Title 10, Code of Federal Regulations (10 CFR), Part 35.980 *Training for an authorized nuclear pharmacist* (NRC 1999c) and 35.981 *Training for experienced nuclear pharmacists* (NRC 1999d).

Practitioner or Prescribing Practitioner means an individual licensed or otherwise authorized to prescribe and use radiopharmaceuticals. In the case where the practitioner is a veterinarian, "patient" means an animal under his/her care.

Prescription Order means an order for medication issued by a practitioner (prescribing practitioner) to be filled by a nuclear pharmacist for use in a specific patient of the prescriber.

Medication Order or Notation is similar to prescription order, but is intended for a patient in an institutional setting.

Radiopharmaceutical or Radioactive Drug means any substance defined as a drug in Section 201(g)(1) of the *Federal Food, Drug and Cosmetic Act* (FFDCA) (FDA 1998a) which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any non-radioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance, but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term “radiopharmaceutical” or “radioactive drug” includes any “radioactive biological product,” which is defined as a biological product that is labeled with a radionuclide or intended solely to be labeled with a radionuclide. For practical purposes, the term “radiopharmaceutical” or “radioactive drug” used in the Guidelines does not include the term “compounded positron emission tomography (PET) drug” as defined in Section 201(ii) of the FFDCA (FDA 1998a).

Reagent Kit means a sterile and pyrogen-free reaction vial containing the nonradioactive chemicals [e.g., complexing agent (ligand), reducing agent, stabilizer, or dispersing agent] that are required to produce a specific radiopharmaceutical after reaction with a radioactive component.

Stability means that extent to which a drug preparation maintains within specified limits, and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of compounding. As used here, the term “stability” does not apply to radioactive decay.

INTRODUCTION

Nuclear pharmacy compounding, like traditional pharmacy compounding, is an integral part of pharmacy practice and is essential to the provision of health care and delivery of a cost-effective radiopharmaceutical service. Both nuclear pharmacy and traditional pharmacy compounding practices are regulated by the individual state boards of pharmacy and other regulatory agencies. Nuclear pharmacists must be familiar with the statutes and regulations that govern compounding because these requirements vary from state to state.

Nuclear pharmacy compounding can be as simple as adding a radioactive liquid to a commercially available reagent kit, or as complex as the creation of a multi-component reagent kit or the synthesis of a radiolabeled compound via a multi-step preparation process. Compounding is different from manufacturing, which is guided by current good manufacturing practices (CGMP's) [see United States Pharmacopeia (USP) <1078> *Good Manufacturing Practices for Bulk Pharmaceutical Excipients* (USPCI 1999i)]. Some of the characteristics or criteria that differentiate compounding from manufacturing include the existence of specific practitioner-patient-pharmacist relationships; the quantity of medication prepared in anticipation of receiving a valid prescription or prescription order; and the conditions of sale, which are limited to specific prescription orders.

Section 127 of the *Food and Drug Administration Modernization and Accountability Act* (FDAMA) of 1997, which includes the addition of Section 503A to FFDCa (FDA 1998d), establishes various criteria and requirements with regard to pharmacy compounding (U.S. 105th Congress 1997b). However, Section 503A(e)(2) states that Section 503A does not apply to compounded positron emission tomography (PET) drugs and radiopharmaceuticals (i.e., non-PET radiopharmaceuticals) (FDA 1998d). Compounded PET drug products are not subject to the provisions of Section 503A, since Section 121 of the FDAMA has been developed to regulate these drugs (U.S. 105th Congress 1997a). However, no other section of the FDAMA was enacted to deal with compounded radiopharmaceuticals, and there is no mention as to why the compounding of radiopharmaceuticals was excluded from Section 503A.

In order to fill this “gap” with regard to the compounding of radiopharmaceuticals, the Section on Nuclear Pharmacy Practice, Academy of Pharmacy Practice and Management (APPM) – American Pharmaceutical Association (APhA), decided to establish the Nuclear Pharmacy Compounding Practice Committee, as suggested by Dennis Swanson in early 1998, to proactively develop a set of professional compounding guidelines for nuclear pharmacy. The main objective of this Committee was to establish a set of practical guidelines that closely follows the spirit of the *Nuclear Pharmacy Guideline Criteria for Determining When to Register as a Drug Establishment* (1984 Nuclear Pharmacy Guideline) (FDA 1984), as well as the provisions of Section 503A of the FFDCa (FDA 1998d). The *Nuclear Pharmacy Compounding Guidelines* have been designed and developed not only to address the various issues related to the compounding practices within the nuclear pharmacy/nuclear medicine community, but the Committee also hopes that the guidelines will assist the Food and Drug Administration (FDA) in the development of new regulatory guidance regarding the compounding of radiopharmaceuticals.

After three years of constant debate and revisions, the Committee has finally completed this draft version of the *Nuclear Pharmacy Compounding Guidelines* (version 7.2). The recommendations contained in the guidelines are designed to set up minimum good compounding practice of radiopharmaceuticals by a nuclear pharmacist. The *Nuclear Pharmacy Compounding Guidelines* are in addition to the *Nuclear Pharmacy Practice Guidelines* (Section on Nuclear Pharmacy Practice 1995) established by the Section on Nuclear Pharmacy Practice, APhA-APPM, as well as the other documents mentioned in these guidelines.

The FDA is currently developing its regulatory framework for PET drug products in accordance with Section 121 of the FDAMA (U.S. 105th Congress 1997a), which was issued by Congress and signed by the President into law on November 21, 1997. This act directs the FDA to develop procedures [i.e., new drug application (NDA) and abbreviated new drug application (ANDA)] for the approval of PET drugs, as well as CGMP's for their production. However, there are several controversial issues related to this law. Not only does the law fail to include the term "pharmacist" along with the term "practitioner" in the definition of a "compounded positron emission tomography drug", but it also stipulates that the compounding process of any PET drug must meet the NDA/ANDA and CGMP requirements which are normally associated with the manufacturing process (U.S. 105th Congress 1997a). Nevertheless, as the current law stands, the compounding of PET drug products shall be subject to PET compounding standards (USPCI 1999h), as well as the official monographs of the USP, until November 21st, 2001, or two years after the date on which the FDA establishes the procedures and requirements pursuant to Section 121 of FDAMA (U.S. 105th Congress 1997a), whichever is later.

Although Section 503A of the FFDCA provides for three statutory exemptions – CGMP's [§501(a)(2)(B)], "adequate directions for use" on the drug label [§502(f)(1)], and NDA/ANDA (§505) (FDA 1998e), with regard to drug products that are compounded in accordance with the requirements as stated in Section 503A, compounded radiopharmaceuticals are not eligible for those exemptions. This is mainly due to the fact that Section 503A does not apply to compounded radiopharmaceuticals (FDA 1998d), as well as the fact that the federal law at the time that the FDAMA was enacted did not exempt radiopharmaceuticals from the adulteration, misbranding, and new drug requirements of FFDCA (U.S. Congress 106th 2000). The FDA is currently evaluating radiopharmaceutical compounding according to the enforcement policies that were in place at the time of the enactment of Section 503A of the FFDCA (FDA 1998d). These FDA enforcement policies are the 1992 *Compliance Policy Guide* on pharmacy compounding (CPG 7132.16) (FDA 1992) and the 1984 Nuclear Pharmacy Guideline (FDA 1984).

Since CPG 7132.16 addresses mainly conventional drugs rather than radiopharmaceuticals, the document states that one must refer to the FDA guidelines and other CPGs for interpretation or clarification of the FDA's positions concerning nuclear pharmacy. The 1984 Nuclear Pharmacy Guideline is an enforcement policy issued by the FDA in May 1984, and is directly related to the operation of nuclear pharmacy, including the compounding of radiopharmaceuticals (FDA 1984). Consequently, we believe that our proposed guidelines should be based upon the principles as stated in the 1984 Nuclear Pharmacy Guideline (FDA 1984), as well as the provisions contained in Section 503A of the FFDCA (FDA 1998d).

The 1984 Nuclear Pharmacy Guideline (FDA 1984) indicated that if the operational activities of a nuclear pharmacy are consistent with Section 510(g)(1) of the FFDCA (FDA 1998f), that nuclear pharmacy is then exempt from registration as a drug establishment (Section 510) (FDA 1998f). Therefore, if a nuclear pharmacy that is not considered to be a drug establishment, it appears reasonable to assume that it should be exempted from compliance with other requirements that flow from registration, such as Section 501 (Adulteration Drugs and Devices) (FDA 1998b), Section 502 (Misbranded Drugs and Devices) (FDA 1998c), Section 505 (New Drugs) (FDA 1998e), and Section 704 (Factory Inspection) (FDA 1998g) of the FFDCA.

Consequently, it seems logical to surmise that a radiopharmaceutical which is compounded by a nuclear pharmacist, based on a valid prescription, while engaging in compounding activities which are in conformance with the normal practice of pharmacy, as governed by the board of pharmacy which licenses the practice site and as stated in Section 510(g)(1) of the FFDCA (FDA 1998f), that compounded radiopharmaceutical should be exempted from compliance with at least three provisions of the FFDCA, i.e., adulteration [e.g., CGMP requirements as stated in Section 501(a)(2)(B)] (FDA 1998b), misbranding [e.g., labeling of drugs with adequate directions for use as stipulated in Section 502(f)(1)] (FDA 1998c),

and the new drug provisions (i.e., NDA or ANDA regulation as described in Section 505) (FDA 1998e). As such, the design and development of the proposed *Nuclear Pharmacy Compounding Guidelines* were based upon the 1984 Nuclear Pharmacy Guideline (FDA 1984), and we have also closely followed the regulatory framework contained in Section 503A of the FFDCa (FDA 1998d).

However, the FDA does not think that the current law allows compounded radiopharmaceuticals to be eligible for the three statutory exemptions provided by Section 503A of the FFDCa: (1) Section 501(a)(2)(B) (concerning the CGMP requirements) (FDA 1998b); (2) Section 502(f)(1) (concerning the labeling of drugs with adequate directions for use) (FDA 1998c); and (3) Section 505 (concerning the approval of drugs under NDA or ANDA) (FDA 1998e) (Lana Ogram, FDA, written communication, April 2001). Consequently, in certain situations the FDA may exercise its enforcement discretion with regard to the aforementioned requirements (i.e., CGMP's, the labeling of drugs with adequate directions for use, and NDA/ANDA) (FDA 1998b, 1998c, 1998e) (Lana Ogram, FDA, written communication, April 2001).

Recently, FDA has established a working group to review their enforcement policies (i.e., CPG 7132.16 and the 1984 Nuclear Pharmacy Guideline) (FDA 1992, 1984) in light of Section 503A of the FFDCa (FDA 1998d), and intends to issue new guidance with regard to the compounding of radiopharmaceuticals (Lana Ogram, FDA, written communication, August 2001). When completed, the new guidance will be published in the *Federal Register* and the FDA will establish a docket for the receipt of comments from the general public (Lana Ogram, FDA, written communication, August 2001).

GENERAL PROVISIONS

1. The compounding of radiopharmaceuticals and the dispensing of compounded preparations shall be in compliance with the requirements established by the individual state boards of pharmacy and other pertinent regulatory agencies.
2. Based on the existence of a practitioner-patient-pharmacist relationship and the presentation of an unsolicited and valid prescription order or a notation, approved by the prescribing practitioner, which states that a compounded product is necessary for an identified individual patient, a nuclear pharmacist may compound radiopharmaceuticals in a nuclear pharmacy, a nuclear medicine laboratory, or a federal facility.
3. Nuclear pharmacy compounding does not include mixing, reconstituting, or other such acts that are performed in accordance or consistent with the directions contained in approved labeling or other manufacturer directions consistent with that labeling. Nuclear pharmacy compounding also does not include any deviation(s) from the directions contained in the approved product labeling or other manufacturer directions consistent with that labeling which result in a final radioactive drug product that is of the same quality and purity as that produced with adherence to the product labeling. The nuclear pharmacist should use his/her professional judgement, scientific knowledge, literature evidence, etc., as the basis to perform any deviation(s) from the manufacturer's recommended preparation process, and the final product should be checked by the appropriate quality control process as described in the *Quality Control* section or other reliable source(s).
4. Radiopharmaceuticals may also be compounded for the purpose of, or incidental to, research, teaching, or chemical analysis. However, these types of compounded preparations are not for sale or dispensing for patient use.
5. The compounding of non-radioactive drugs, except reagent kits, shall be subject to the provisions of Section 127 of the FDAMA (U.S. 105th Congress 1997b) [Section 503A of the FFDCA (FDA 1998d)] and the guidelines of the USP.
6. When a radiopharmaceutical is compounded by a nuclear pharmacist, based on a valid prescription, while engaging in compounding activities which are in conformance with the normal practice of pharmacy, as governed by the board of pharmacy which licenses the practice site and as stated in Section 510(g)(1) of the FFDCA (FDA 1998f), that compounded radiopharmaceutical has historically been exempted, by FDA enforcement policy guidelines (FDA 1984, 1992), from enforcement of at least three provisions of the FFDCA, i.e., adulteration [e.g., CGMP requirements as stated in Section 501(a)(2)(B)] (FDA 1998b), misbranding [e.g., labeling of drugs with adequate directions for use as stipulated in Section 502(f)(1)] (FDA 1998c), and the new drug provisions (i.e., NDA or ANDA regulation as described in Section 505) (FDA 1998e). The enforcement policy guidance for compounded radiopharmaceuticals is currently being reviewed by the FDA. In that guidance, the FDA may address and clarify situations where FDA could exercise its enforcement discretion for the aforementioned three statutory requirements (Lana Ogram, FDA, written communication, August 2001).
7. The nuclear pharmacist is responsible for compounding preparations of acceptable strength, quality, and purity, utilizing appropriate packaging and labeling in accordance with good compounding practice, official standards, and relevant scientific data and information.

8. The nuclear pharmacist may compound radiopharmaceuticals in limited quantities in anticipation of the receipt of a valid prescription order or a notation, approved by the prescribing practitioner. The quantity of compounded radiopharmaceuticals is based on the past history of the nuclear pharmacist receiving valid prescription orders or notations, approved by the prescribing practitioner, for the compounding of the drug products.
9. The nuclear pharmacist does not compound a radiopharmaceutical using, as a component, a drug product that appears on a list, published by the FDA in the Federal Register, of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective.
10. The nuclear pharmacist may compound a radiopharmaceutical that has been previously approved by the FDA, but is no longer commercially available [does not include a radiopharmaceutical that has been withdrawn or removed from the market because such drug product or component(s) of such drug product has been found to be unsafe or not effective].
11. The nuclear pharmacist does not compound regularly or in inordinate amounts (as defined by the FDA and/or state board of pharmacy) any radiopharmaceuticals that are essentially copies of a commercially available drug product. However, the term “essentially a copy of a commercially available drug product” does not apply to a drug product in which there is a change made for an identified individual patient which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product.
12. The nuclear pharmacist should not compound any patented radiopharmaceutical unless it is not reasonably available to meet the urgent medical need(s) of an identified individual patient. This is allowed only when the patented radiopharmaceutical cannot be readily obtained from a commercial source, and the prescriber shall be informed that a radiopharmaceutical will be compounded to replace the commercial product.
13. Nuclear pharmacists engaging in compounding should continually expand their compounding knowledge and enhance their compounding skills by participating in seminars and workshops, studying appropriate literature, and consulting with colleagues.
14. A practitioner may obtain compounded drug products from a nuclear pharmacy to administer to an identified individual patient under his/her care in the course of his/her professional practice. In addition to the labeling requirements of the state and federal regulations, the compounded drug products requested by the practitioner should also be labeled “For Office Use Only.”
15. Compounded radiopharmaceuticals are not for resale outside the prescriber and patient relationship involved with the prescription order or notation approved by the prescribing practitioner.

ORGANIZATION AND PERSONNEL

1. The nuclear pharmacist has the responsibility and authority to inspect and approve or reject all components, drug product containers, closures, in-process materials, labeling, as well as the authority to prepare and review all compounding records to assure that no errors have occurred in the compounding process. The nuclear pharmacist is also responsible for the proper maintenance, cleanliness, and use of all equipment used in prescription compounding practice.
2. All nuclear pharmacists who engage in compounding of drugs shall be proficient in the art of compounding and shall maintain proficiency through current awareness and training. Also, every nuclear pharmacist who engages in drug compounding must be aware of, and familiar with, all details of good compounding practices.
3. The practice of nuclear pharmacy compounding may also be performed by a nuclear pharmacist intern, who must be under the immediate and personal supervision of a nuclear pharmacist.
4. Nuclear pharmacy technicians may assist the nuclear pharmacist in nonprofessional (nonjudgmental) aspects of compounding. It is the responsibility of the nuclear pharmacist to train and monitor the nuclear pharmacy technician. For the training program specific to nuclear pharmacy technicians, it is recommended to refer to the *Guidelines for Nuclear Pharmacy Technician Training Programs* (Section on Nuclear Pharmacy Practice 2000) prepared by the Ad Hoc Committee on Nuclear Pharmacy Technicians, Section on Nuclear Pharmacy Practice, APhA-APPM. The duties of nuclear pharmacy technicians shall be consistent with the training received.
5. Nuclear pharmacists as well as all personnel involved with compounding should participate in programs designed to enhance and maintain competence in compounding. Procedures should be established to verify the ability of staff to meet established competencies. These procedures may include observation, written tests, or quality control testing of finished products.
6. To protect drug products from contamination, personnel engaged in nuclear pharmacy compounding practice should wear clean clothing appropriate to the operation being performed. To protect personnel from chemical exposure and medication or chemical contamination, personnel shall, as appropriate, wear protective apparel, such as coats/jackets, aprons, gowns, as well as head, face, hand, and arm coverings, safety goggles, and a mask or respirator, etc.
7. Only personnel authorized by the responsible nuclear pharmacist shall be in the immediate vicinity of the drug compounding operation. Any person shown at any time (either by medical examination or nuclear pharmacist determination) to have an apparent illness or open lesion(s) that may adversely affect the safety or quality of a drug product being compounded shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected, or determined by competent medical personnel not to jeopardize the safety or quality of the product(s) being compounded. All personnel who assist the nuclear pharmacist in compounding procedures shall be instructed to report to the nuclear pharmacist any health conditions that may have adverse effects on drug products.

8. For the compounding of radiopharmaceuticals that belong to the high-risk category II [as defined in the United States Pharmacopeia (USP) <1206> *Sterile Drug Products for Home Use* (USPCI 1999k)] and/or risk level 3 [as defined in the *American Society of Health-System Pharmacy Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* (ASHP 2000)], it is recommended to refer to USP <1206> monograph (USPCI 1999k) and *American Society of Health-System Pharmacy Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* (ASHP 2000) for further guidance regarding organization and personnel for these types of radiopharmaceuticals.

COMPOUNDING ENVIRONMENT

Facilities

1. Nuclear pharmacies engaging in compounding should have a specifically designated and adequate area with limited access for the orderly placement of equipment and materials to prevent mix-ups between ingredients, containers, labels, in-process materials, and finished preparations. The compounding area should also be designed, arranged, used, and maintained to prevent cross-contamination.
2. Adequate lighting, heating, ventilation, and air-conditioning systems should be provided in all drug-compounding areas. The compounding area should not contain dust-collecting overhangs (e.g., ceiling, utility pipes, hanging light fixtures) and ledges (e.g., windowsills). The area(s) used for the compounding of drugs shall be maintained in a good state of repair.
3. The area(s) used for the compounding of drugs should be maintained in a clean and sanitary condition. Adequate washing facilities, easily accessible to the compounding area(s) of the nuclear pharmacy, should be provided. These facilities should include, but not be limited to, hot and cold water, soap or detergent, and air-dryers or single-service towels. Compounding areas should be free of infestation by insects, rodents, and other vermin. Sewage, trash, and other refuse in the compounding area should be disposed of in a safe, sanitary, and timely manner.
4. Potable water should be supplied for hand and equipment washing. Potable water should be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any compounded drug product. Purified water must be used for compounding nonsterile drug preparations and must also be used for rinsing equipment and utensils. When water is used to prepare a sterile preparation, Water for Injection, Sterile Water for Injection, or Bacteriostatic Water for Injection must be used.
5. Areas in the nuclear pharmacy used for the compounding of sterile products should be separate and distinct from the compounding or dispensing of non-sterile drug products. The compounding of sterile products in a nuclear pharmacy should be performed using an aseptic technique. However, the concept of “as clean as reasonably achievable” (ACARA) should be applied to the compounding of sterile products in a nuclear pharmacy whenever both sterility and radiation safety issues are considerations.
6. To minimize dust and particulate matter, cartons and boxes should not be stored or opened in the compounding area. Computer entry, order processing, label generation, and record keeping should be performed outside the compounding area.
7. Storage areas should provide an environment suitably controlled to ensure quality and stability of bulk and/or excipients and finished preparations. Bulk drug substances and excipients used in the compounding of drugs must be stored in adequately labeled containers in a clean, dry, and temperature-controlled area or, if required, in proper refrigeration.

8. For the compounding of radiopharmaceuticals that belong to the high-risk category II [as defined in the United States Pharmacopeia (USP) <1206> *Sterile Drug Products for Home Use* (USPCI 1999k)] and/or risk level 3 [as defined in the *American Society of Health-System Pharmacy Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* (ASHP 2000)], it is recommended to refer to USP <1206> monograph (USPCI 1999k) and *American Society of Health-System Pharmacy Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* (ASHP 2000) for further guidance regarding facilities. However, the ACARA principle should be considered whenever radiation safety becomes an issue of concern for the compounding of these types of radiopharmaceuticals.

Equipment

1. It shall be the responsibility of the nuclear pharmacist to inspect the equipment and utensils for compounding immediately prior to use to determine if these items are suitable for usage.
2. Equipment used in the compounding of drug products shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use, as well as its cleaning and maintenance. The types and sizes of equipment will depend on the dosage forms and the quantities compounded. For further information, please refer to USP <41> *Weights and Balances* (USPCI 1999b), <1176> *Prescription Balances and Volumetric Apparatus* (USPCI 1999j), and equipment manufacturers' instruction manuals.
3. Equipment used in the compounding of drug products shall be of suitable composition so that surfaces which contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond that desired.
4. Equipment and utensils used for compounding shall be cleaned and sanitized to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond that desired. Previously cleaned equipment and utensils used for compounding drugs must be protected from contamination prior to use.
5. With regard to equipment, utensils, and containers/closures used in the compounding of sterile drug products, one can refer to the *Model Rules for Sterile Pharmaceuticals* (NABP 1999) published by the National Association of Boards of Pharmacy for the cleaning, sterilization, and maintenance procedures.
6. Automatic, mechanical, or electronic equipment, or other types of equipment or related systems that will perform a function satisfactorily may be used in the compounding of drug products. If such equipment is used, it shall be cleaned and sanitized prior to use, routinely inspected, calibrated (if necessary) or checked to assure proper performance.
7. The equipment used to perform quality control of the compounded drug preparations shall be routinely inspected, calibrated (if necessary) or checked to assure proper performance.
8. For the compounding of radiopharmaceuticals that belong to the high-risk category II [as defined in the United States Pharmacopeia (USP) <1206> *Sterile Drug Products for Home Use* (USPCI 1999k) and/or risk level 3 [as defined in the *American Society of Health-System Pharmacy Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* (ASHP 2000)], it is recommended to refer to USP <1206> monograph (USPCI 1999k) and *American Society of Health-System Pharmacy Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* (ASHP 2000) for further guidance regarding equipment. However, the ACARA principle should be considered whenever radiation safety becomes an issue of concern for the compounding of these types of radiopharmaceuticals.

SOURCES OF COMPOUNDING DRUG COMPONENTS

Bulk Drug Substance

Any bulk drug substance used in the compounding of a reagent kit or radiopharmaceutical is preferred to be one of the following (in descending order of preference):

- (1) a USP or National Formulary (NF) grade substance
 - (2) an active ingredient of an approved drug product
 - (3) a drug substance that appears on a list developed by the FDA and the United States Pharmacopeia Convention, Incorporated
 - (4) a high quality source of chemical substance, such as a substance which is an analytical reagent (AR), a substance which has been certified by the American Chemical Society (ACS), or a substance which is listed as Food Chemicals Codes (FCC) grade
- Any bulk drug substance used in the compounding of reagent kits or radiopharmaceuticals should preferably be manufactured by an establishment that meets Section 510 of the FFDCFA (FDA 1998f), and each bulk drug substance should be accompanied by a valid certificate of analysis if available.
 - Only manufactured substances from containers labeled with a batch control number and a future expiration date are acceptable as a potential source of bulk drug substances. When compounding with manufactured drug products, the nuclear pharmacist must consider all ingredients present in the substance relative to the intended use of the compounded preparation.
 - For a bulk drug substance used in compounding that is not purchased from a registered drug manufacturer, the nuclear pharmacist should establish identity and purity by reasonable means, which may include, but are not limited to, lot analysis, manufacturer reputation, or reliability of source.

Excipient

Any excipient used in the compounding of a reagent kit or radiopharmaceutical is preferred to be one of the following (in descending order of preference):

- (1) a USP or NF grade substance
- (2) a non-active ingredient or an intermediate of an approved drug product
- (3) a high quality source of chemical substance, such as a substance which is an AR, a substance which has been certified by the ACS, or a substance which is listed as FCC grade

- Any excipient used in the compounding of reagent kits or radiopharmaceuticals should preferably be manufactured by an establishment that meets Section 510 of the FFDCA (FDA 1998f), and each excipient should be accompanied by a valid certificate of analysis if available.
- Only manufactured substances from containers labeled with a batch control number and a future expiration date are acceptable as a potential source of excipients. When compounding with manufactured drug products, the nuclear pharmacist must consider all ingredients present in the substance relative to the intended use of the compounded preparation.
- For an excipient used in compounding that is not purchased from a registered drug manufacturer, the nuclear pharmacist should establish identity and purity by reasonable means, which may include, but are not limited to, lot analysis, manufacturer reputation, or reliability of source.

QUALITY CONTROL

Compounded Reagent Kits

1. If the radiolabeled product from the reconstituted compounded reagent kit is listed in the USP, the quality control of the compounded reagent kit can be conducted by testing the radiolabeled product to determine whether it meets all applicable USP standards as described in its monograph. If not, the radiolabeled product should meet professional standards of a similar nature appropriate for its safety and intended use.
2. If necessary, it is also recommended to follow the stipulations as stated in the Quality Control section of USP <795> *Pharmacy Compounding* (USPCI 2000) for the quality control of compounded reagent kits.
3. It is recommended that reagent kits compounded under high-risk category II [as defined in USP <1206> *Sterile Drug Products for Home Use* (USPCI 1999k)] and/or risk level 3 [as defined in the *American Society of Health-System Pharmacy Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* (ASHP 2000)] conditions shall be subject to quality control checks or tests as described in the *Finished Product Release Checks and Tests* under USP <1206> *Sterile Drug Products for Home Use* (USPCI 1999k).

Compounded Radiopharmaceuticals

It is recommended that radiopharmaceuticals compounded under high-risk category II [as defined in USP <1206> *Sterile Drug Products for Home Use* (USPCI 1999k)] and/or risk level 3 [as defined in the *American Society of Health-System Pharmacy Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* (ASHP 2000)] conditions shall be subject to quality control checks or tests as described in the *Finished Product Release Checks and Tests* under USP <1206> *Sterile Drug Products for Home Use* (USPCI 1999k).

Quality Control of ^{99m}Tc Eluate

For the quality control of ^{99m}Tc eluate, please refer to USP *Sodium Pertechnetate Tc 99m Injection* (USPCI 1999a).

Visual Inspection of Product

Visual inspection of the compounded radiopharmaceutical shall be conducted to ensure the absence of foreign matter and also to establish product identity by confirming that (1) a liquid product is a solution, a colloid, or a macroaggregated suspension, and that (2) a solid product has defined properties that identify it.

Assessment of Radioactivity

The amount of radioactivity in each compounded radiopharmaceutical should be verified and documented prior to dispensing, using a proper standardized radionuclide (dose) calibrator or other validated radiation measuring device. If there is substantial delay, relative to the radionuclide's half-life,

between the time of dose measurement and the time of administration, the dose should be decay-corrected.

Quality Control of Radionuclide (Dose) Calibrator

For the quality control of the radionuclide (dose) calibrator, please refer to 10 CFR Part 35.50 *Possession, use, calibration, and check of dose calibrators* (NRC 1999a) and Part 35.52 *Possession, use, calibration, and check of instruments to measure dosages of alpha- or beta-emitting radionuclides* (NRC 1999b).

Radionuclidic Purity

For non-technetium products, radionuclidic purity can be determined with the use of a suitable counting assembly [see *Selection of a Counting Assembly* under USP <821> *Radioactivity* (USPCI 1999g)]. In the absence of USP or equivalent standards, radionuclidic purity specifications should be established based on scientific data and sound rationale.

Radiochemical Purity

The radiochemical purity (RCP) of compounded radiopharmaceuticals should be monitored before administration to patients. The nuclear pharmacist must select an appropriate RCP testing method based on literature evidence, scientific data, and his/her professional judgement, etc. In the absence of USP or equivalent standards, radiochemical purity specifications should be established a priori based on scientific data and sound rationale. Appropriate and acceptable RCP value of the final compounded radiopharmaceutical should be confirmed using an established and/or validated procedure. In any event, clear, easy-to-follow descriptions of test methods should be readily available to all nuclear pharmacy staff.

While both the USP radiopharmaceutical monographs and manufacturer's package inserts provide standard methods for testing RCP, RCP testing procedures that may be more adaptable to a nuclear pharmacy setting can be found in the *Alternative Radiochemical Purity Testing Procedures for the Compounded Radiopharmaceuticals Approved from 1988-1997* which was published by the APhA (Section on Nuclear Pharmacy Practice 1998) or in the appropriate literature.

pH

The pH of the final compounded radiopharmaceutical preparation should be checked to ensure that its value is within the acceptable range as defined by the USP, package insert, or appropriate literature. In the absence of USP or equivalent standards, pH specifications should be established a priori based on scientific data and sound rationale.

Verification of Macroaggregate Particle Size and Number

The particle size of radiolabeled macroaggregates should be verified to be within the acceptable range, as defined by the USP, package insert, or appropriate literature, prior to use. The particle number of radiolabeled macroaggregates should be verified to be within the prescribed range.

Imprinted Labeling

At the completion of the compounding drug operation, the nuclear pharmacist shall examine the compounded drug product for correct labeling as required by the appropriate Nuclear Regulatory Commission and/or state statutes or regulations.

Microbiological Control and Bacterial Endotoxin Testing

Microbiological control (i.e., sterility testing) and bacterial endotoxin testing (BET) shall be performed according to written policies and procedures for specific compounded radiopharmaceuticals when these tests are required as release criteria. Retrospective sterility testing and BET should be conducted on randomly selected batches of the product to check the adequacy of aseptic technique. These tests should also be conducted at regular periodic intervals, depending on historic results and trends, and should be completed more frequently when new personnel are involved. Sterility testing and BET should be performed according to locally accepted test methodology, or with the use of procedures based on and adapted from those described in USP <71> *Sterility Tests* (USPCI 1999c) and USP <85> *Bacterial Endotoxins Test* (USPCI 1999d), respectively.

The endotoxin limit for intrathecally administered radiopharmaceuticals is significantly less than that for intravenously administered radiopharmaceuticals (maximum administration of 14 EU vs. 175 EU, respectively). Hence, a BET appropriate for detecting endotoxin concentrations at this lower limit should be performed by qualified personnel for each compounded radiopharmaceutical intended for intrathecal administration. As an alternative to BET of the final compounded radiopharmaceutical, acceptable limits of endotoxin can be ensured by limiting the intrathecal dose volume to no more than 8% of the maximum intravenous dose volume, in conjunction with strict adherence to aseptic technique.

STABILITY OF COMPOUNDED PREPARATIONS

1. Since compounded drug products are intended for immediate use or storage for a very limited time, stability evaluation and expiration dating are different for these drug products when compared with manufactured drug products. Thus, all stability data should be carefully interpreted in relation to the actual compounded formulation. Beyond-use times and dates should be assigned conservatively. In addition to consideration of all available stability information and reasonable patient needs with respect to the intended drug usage, the nuclear pharmacist should also apply his/her pharmaceutical education and experience.
2. All extemporaneously compounded parenteral radiopharmaceutical preparations should be used no more than 24 hours post compounding process unless data are available to support longer storage.
3. It is recommended to follow USP <1206> *Sterile Drug Products for Home Use* (USPCI 1999k) and/or *American Society of Health-System Pharmacy Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* (ASHP 2000) for the determination of expiration time and date for radiopharmaceuticals compounded in high-risk category II [as defined in USP <1206> *Sterile Drug Products for Home Use* (USPCI 1999k)] and/or risk level 3 [as defined in the *American Society of Health-System Pharmacy Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* (ASHP 2000)] conditions.
4. The beyond-use time/date limit of any compounded reagent kit or radiopharmaceutical may be extended when there is valid supporting scientific stability information that is directly applicable to the specific preparation (i.e., the same drug concentration range, pH, excipients, vehicle, water content, etc.)
5. All compounded drug products should be observed for signs of instability. Observation should be conducted during preparation of the drug product, as well as during any storage period that may occur before the compounded drug product is dispensed.

PRIMARY PACKAGING OF COMPOUNDED PREPARATIONS

1. Components, drug product containers, and closures used in the compounding of drugs shall be handled and stored in a manner to prevent contamination. Bagged or boxed components of drug product containers and closures used in the compounding of drugs shall be stored off the floor in such a manner as to permit cleaning and inspection.
2. Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the compounded drug beyond the desired result. Components, drug product containers, and closures for use in the compounding of drug products shall be rotated so that the oldest stock is used first. Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that could cause deterioration or contamination of the compounded drug product. Drug product containers and closures shall be clean and, where indicated by the intended use of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.
3. Methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures used in the preparation of sterile pharmaceuticals.
4. It is recommended that compounded preparations be packaged in containers meeting USP standards [see USP <661> *Containers* (USPCI 1999e) and <671> *Containers – Permeation* (USPCI 1999f)]. The container used depends on the physical and chemical properties of the compounded preparation. Container-drug interaction should be considered with substances such as phenolic compounds and sorptive materials (e.g., polypeptides and proteins).

IMPRINTED LABELING FOR COMPOUNDED PREPARATIONS

1. Compounded radiopharmaceuticals should be labeled with adequate identifying information to prevent errors during preparation, storage, and use. The labeling information shall include the complete list of components, the preparation date and/or time, the assigned expiration date and/or time, and storage requirements.
2. Additional labeling requirements may be specified in certain state or local regulations.

COMPOUNDING RECORDS AND DOCUMENTS

1. The formulation record, compounding record, and Material Safety Data Sheet file, similar to or as described in USP <795> *Pharmacy Compounding* (USPCI 2000), should be maintained for every compounded reagent kit and radiopharmaceutical, and the records should be retained for the same period of time as each state requires for the retention of prescription files.
2. Records required under the *Nuclear Pharmacy Compounding Guidelines* may be retained either as the original records or as true copies, such as photocopies, microfilm, microfiche, or other accurate reproduction of the original records.
3. All original records, or copies of such records, that are required to be kept under the *Nuclear Pharmacy Compounding Guidelines* shall be readily available for authorized inspection during the retention period at the facility where the activities described in such records occurred. The original records, or copies, shall be subject to photocopying or other means of reproduction as part of such an inspection.
4. Compounding records shall be kept in accordance with applicable state and federal regulations.

STORAGE

1. All bulk drug substances, excipients, compounded reagent kits, and compounded radiopharmaceuticals must be stored according to USP-NF, manufacturer specifications, or other credible reference sources.
2. All radioactive components and compounded radiopharmaceuticals should be stored inside appropriate radiation shielding.
3. Compounded radiopharmaceuticals, if applicable, not intended for prompt use should be stored at a temperature expected to inhibit microbial growth (e.g., 2-8°C). Compounded drug products may be frozen if adequate stability evidence to support freezing storage is available.
4. Temperature in refrigerators and freezers used to store bulk drug substances, excipients and compounded radiopharmaceuticals should be monitored every working day to ensure that storage requirements are met.
5. All light-sensitive bulk drug substances, excipients and compounded radiopharmaceuticals should be suitably protected from light from the time of receipt and/or preparation until the time of use or, when indicated, until the conclusion of administration of the compounded drug product.
6. To permit adequate floor cleaning, supplies and drugs should be stored on shelving areas above the floor.

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