

Explanations and Unresolved Issues Pertaining to the Development of the *Nuclear Pharmacy Compounding Guidelines*

Joseph C. Hung, Samuel C. Augustine, Kenneth T. Cheng, Richard L. Green, Wade M. Hopkins, David L. Laven, Brigette R. Nelson, Neil A. Petry, James A. Ponto, Timothy M. Quinton, and Dennis P. Swanson

Objectives: To provide background information related to the development of the *Nuclear Pharmacy Compounding Guidelines*, to discuss regulatory complexities related to radiopharmaceutical compounding practice, and to summarize the gaps in the current compounding regulations for radiopharmaceuticals. **Data Sources:** The *Guidelines* closely follow the provisions of section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the monographs and chapters related to pharmacy compounding in the *United States Pharmacopeia* (USP), and the recommended guidelines published by the American Society of Health-System Pharmacists. **Summary:** The Food and Drug Administration Modernization Act (FDAMA) of 1997 established parameters under which the compounding of drug products is appropriate and lawful, but these criteria expressly do not apply to radiopharmaceuticals. The Nuclear Pharmacy Compounding Practice Committee, a group of nuclear pharmacists convened by the American Pharmaceutical Association, developed the *Nuclear Pharmacy Compounding Guidelines* to establish a set of principles and guidelines for good radiopharmaceutical compounding practice. The intent of the new document is to provide guidance on radiopharmaceutical compounding practices that have evolved over the last 2 decades and to place them in an appropriate regulatory framework in accordance with previous enforcement policies and guidelines issued by the U.S. Food and Drug Administration (FDA) regarding the exemption of certain pharmacy practices from enforcement of adulteration, misbranding, and new drug requirements. **Conclusion:** The *Nuclear Pharmacy Compounding Guidelines*, recently released by APhA, is the first official document that provides realistic and practical compounding guidance for nuclear pharmacists. Even though the United States Court of Appeals for the Ninth Circuit recently ruled section 503A of the FD&C Act to be invalid in its entirety, and the Supreme Court upheld that ruling, the compliance policy guides issued by FDA in March 1992 and revised in May 2002 maintain guiding principles on pharmacy compounding similar to those stated in section 503A of the FD&C Act. The Nuclear Pharmacy Compounding Practice Committee is optimistic that the practical information contained in the *Guidelines* will assist state boards of pharmacy, FDA, and the United States Pharmacopeial Convention in setting appropriate standards for nuclear pharmacy compounding practice that will ensure the continued availability of high-quality compounded radiopharmaceuticals at reasonable cost.

J Am Pharm Assoc. 2002;42:789-98.

The *Nuclear Pharmacy Compounding Guidelines* were approved by the Board of Trustees of the American Pharmaceutical Association (APhA) in September 2001 and published by APhA in November 2001. This set of guidelines (see www.aphanet.org/nuclear_compounding.pdf) is the first nationally recognized document that provides realistic and practical

compounding guidance for nuclear pharmacy practice.

The Food and Drug Administration Modernization Act (FDAMA), enacted in late 1997, protects a pharmacist's professional prerogative to compound drug products; however, the provisions of the pharmacy compounding section of the act (i.e., section 127 of FDAMA, which added section 503A to the Federal Food, Drug, and Cosmetic Act [FD&C Act]) do not apply to radiopharmaceuticals.¹ The decision not to include radiopharmaceuticals was related to the complexities specifically associated with compounding radiopharmaceuticals, as well as the time constraint that Congress placed on the development and approval of the section 127 language.²

Nuclear pharmacy compounding, like traditional pharmacy compounding, is an integral part of pharmacy practice and is

Received February 12, 2002, and accepted for publication July 23, 2002.

Authors' affiliations are listed on pages 797-8.

Correspondence: Joseph C. Hung, PhD, BCNP, FAPhA Nuclear Medicine, Department of Radiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905-0001. Fax: 507-266-4461. E-mail: jhung@mayo.edu.

essential to the provision of high-quality, cost-effective patient care. However, neither federal drug laws nor the *United States Pharmacopeia* (USP) includes specific requirements or standards for compounding radiopharmaceuticals or for the strength, quality, and purity of most compounded radiopharmaceuticals used in routine clinical practice today.

To proactively develop a set of professional compounding guidelines for nuclear pharmacy, the APhA Academy of Pharmacy Practice and Management (APhA-APPM) Section on Nuclear Pharmacy Practice formed the Nuclear Pharmacy Compounding Practice Committee in early 1998. The group consisted of nuclear pharmacists from academic institutions, commercial nuclear pharmacies, and independent nuclear pharmacies. The approved guidelines represent the end product of a nearly 4-year effort by the committee.

This was not the first time that the Section had developed such guidelines. In 1993 APhA distributed a document on the compounding of radiopharmaceuticals for positron emission tomography (PET).³ That earlier endeavor served as the basis for compounding guidance as stated in the USP⁴ as well as the current regulation of these PET agents under FDAMA.⁵

The purpose of developing the *Nuclear Pharmacy Compounding Guidelines* was not to rewrite the various nuclear pharmacy practice acts or model state board regulations. Rather, the intent was to propose principles and standards for nuclear pharmacy practice based on the related regulations (i.e., section 503A of the FD&C Act)¹ as well as the recommended guidelines published in the USP and by the American Society of Health-System Pharmacists (ASHP).⁶⁻⁹ The intent of the *Guidelines* is to provide nuclear pharmacists with information on minimum good compounding practices for radiopharmaceuticals and to assist state boards of pharmacy, the U.S. Food and Drug Administration (FDA), and the United States Pharmacopeial Convention in developing new regulatory guidance pertaining to the compounding of radiopharmaceuticals.

Drafts of the *Guidelines* were posted on The Nuclear Pharmacy Web site (<http://nuclearpharmacy.uams.edu>) and distributed to various organizations (e.g., FDA, USP, National Association of Boards of Pharmacy, state boards of pharmacy, Council on Radionuclides and Radiopharmaceuticals, Inc. [CORAR]), with requests for comments and suggestions. Comments received were considered by the Nuclear Pharmacy Compounding Practice Committee and incorporated into the final guidelines as appropriate.

Objectives

The purpose of the present article is to provide background information relating to the development of the *Nuclear Pharmacy Compounding Guidelines*, to discuss issues related to the current state of radiopharmaceutical compounding, and to summarize any gaps that exist in the current compounding regulations with regard to radiopharmaceuticals. Certain sections of the *Guidelines* appear

as footnotes in this article to place into context the issues discussed. Headings throughout the text address specific regulatory issues related to radiopharmaceutical compounding.

FDA Enforcement Policy Guidance

From June 2000 through August 2001, the Nuclear Pharmacy Compounding Practice Committee received several pieces of correspondence from FDA's Pharmacy Compounding Steering Committee (PCSC) concerning the draft guidelines, principally with regard to FDA's "enforcement discretion" on the practice of radiopharmaceutical compounding. While PCSC indicated that the draft guidelines closely followed the provisions of section 503A of the FD&C Act,¹ current law does not exempt compounded radiopharmaceuticals from three provisions of the FD&C Act: section 501(a)(2)(B)—adulteration (concerning the current good manufacturing practice [CGMP] requirements),¹⁰ section 502(f)(1)—misbranding (concerning the labeling of drugs with adequate directions for use),¹¹ and section 505—new drug provisions (concerning the approval of drugs and requirements for New Drug Applications [NDA] and Abbreviated New Drug Applications [ANDA]).¹² On that basis, PCSC suggested that all references to any exemption from the above three statutory requirements with regard to radiopharmaceuticals be removed from item 6^a of the General Provisions section of the *Nuclear Pharmacy Compounding Guidelines*.

To help readers better understand this confusing issue, the following discussion is divided into subsections.

Section 503A of the FD&C Act

Section 503A of the FD&C Act stipulates that drug products that are compounded by a pharmacist or physician for an identified individual patient pursuant to a valid prescription order and that conform to other requirements listed in section 503A are exempted from the FD&C Act's adulteration, misbranding, and new drug provisions.^{1,10-12}

^aWhen 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).

Before FDAMA was enacted, federal drug law could have been strictly interpreted as requiring a pharmacist to obtain a new drug approval and to comply with the statutory requirements related to adulteration, misbranding, and NDA/ANDA¹⁰⁻¹² for all compounded prescription drugs. The NDA/ANDA process, required for manufacturing and marketing drug products, is not amenable to pharmacy compounding in terms of cost, document submission, and timeliness. Additionally, the enormous complexity and high costs associated with meeting CGMP requirements¹³ intended for large-scale manufacturing would almost certainly end small-scale pharmacy compounding practice.

Recognizing the importance of pharmacy compounding to patient care, FDA has traditionally allowed pharmacy compounding activities, practiced in compliance with state law, to proceed under its enforcement discretion guidance. Nevertheless, FDA contended that it retained the authority to regulate pharmacy compounding vis-à-vis the statutory requirements described above at any time it chooses to do so. Hence, many pharmacists were uncertain as to the legality of compounding. FDAMA finally established rules that clarify and formalize federal drug compounding practice regulation.¹

Exemption From Adulteration, Misbranding, and New Drug Provisions for Compounded Radiopharmaceuticals

Because section 503A of the FD&C Act expressly does not apply to radiopharmaceuticals,¹ these drugs are not eligible for the above three statutory exemptions provided by the federal laws.¹⁰⁻¹² To ensure clinical access to individual compounded radiopharmaceuticals, the Nuclear Pharmacy Compounding Practice Committee believes that FDA should continue its enforcement discretion policy with regard to radiopharmaceuticals, thereby permitting nuclear pharmacists to compound radiopharmaceuticals without requiring compliance with strict FD&C Act requirements regarding adulteration, misbranding, and new drug provisions.¹⁰⁻¹² As a result, item 6 of the General Provisions section of the *Nuclear Pharmacy Compounding Guidelines* is intended to reflect the current regulatory enforcement situation and to suggest a reasonable framework for developing future regulation of the compounding of radiopharmaceuticals.

Invalidation of Section 503A of the FD&C Act

After section 503A of the FD&C Act went into effect on November 21, 1998,¹ several compounding pharmacies joined together and initiated a lawsuit challenging the solicitation and advertising provisions of section 503A. These pharmacies argued that these subsections violated the First Amendment's guarantee of free speech.¹⁴ The United States District Court for the District of Nevada ruled in the pharmacists' favor. FDA appealed to the United States Court of Appeals for the Ninth Circuit. On February

6, 2001, the court of appeals delivered its opinion, agreeing with the ruling of the district court.¹⁴ However, the appeals court went further, declaring section 503A to be invalid in its entirety.¹⁴

FDA petitioned the U.S. Supreme Court for writ of certiorari, and, on February 26, 2002, the Court heard oral arguments in the appeal.¹⁵ On April 29, 2002, the Supreme Court upheld the decision of the court of appeals in affirming that the advertising ban was unconstitutional and that section 503A should be struck down in its entirety.¹⁵ Since the Supreme Court did not rule on the issue related to the advertising and promotion of compounded drug products, and did not remand the decision to the circuit court,¹⁵ section 503A in its entirety is now considered to be invalid.

CPG 460.200 and 1984 Nuclear Pharmacy Guideline

At the time FDAMA was enacted, two FDA enforcement policies were in place: the 1992 Compliance Policy Guide (CPG) on Pharmacy Compounding (CPG 7132.16, later renumbered as 460.200), *Manufacture, Distribution, and Promotion of Adulterated, Misbranded, or Unapproved New Drugs for Human Use by State-Licensed Pharmacies*; and the *Nuclear Pharmacy Guideline Criteria for Determining when to Register as a Drug Establishment* issued by FDA in 1984 (1984 Nuclear Pharmacy Guideline).^{16,17} After the U.S. Supreme Court upheld the decision of the court of appeals in the pharmacy compounding case,¹⁵ FDA issued a guidance for FDA staff and industry titled *Sec. 460.200 Pharmacy Compounding* on June 7, 2002, to address certain "ambiguous" issues related to pharmacy compounding that arose following the decision by the Supreme Court.¹⁸ Overall, the "new" guidance is very similar to 1992 CPG 460.200,^{16,18} and it provides guidelines for drug compounders, as well as FDA staff, as to what activities the agency will consider in exercising its enforcement discretion with regard to pharmacy compounding practice.¹⁸

Neither the 1992 version nor the 2002 version of CPG 460.200 includes specific guidance on nuclear pharmacy.^{16,18} The primary focus of either version of the CPG 460.200 is on nonradioactive drugs, rather than radiopharmaceuticals, and, as such, the 1992 and 2002 versions of CPG 460.200 specifically state that one must refer to FDA guidelines and other CPGs for interpretation or clarification of FDA's position concerning nuclear pharmacy issues.^{16,18} Because the 1984 Nuclear Pharmacy Guideline is directly related to nuclear pharmacy operations, including radiopharmaceutical compounding,¹⁷ the Nuclear Pharmacy Compounding Practice Committee contends that this document should be the primary legal reference for issues associated with radiopharmaceutical compounding.

The 1984 Nuclear Pharmacy Guideline indicates that if the operational activities of a nuclear pharmacy are consistent with section 510(g)(1) of the FD&C Act,¹⁹ then that nuclear pharmacy is not required to register as a drug establishment.¹⁷ Therefore, if a nuclear pharmacy is not considered a drug establishment, it appears reasonable to assume that it should be exempted from

compliance with federal adulteration, misbranding, and new drug provisions.^{10, 12}

Accordingly, it would also seem logical to surmise that a radiopharmaceutical that is compounded pursuant to a valid prescription by a nuclear pharmacist engaging in compounding activities that are in conformance with the normal practice of pharmacy as licensed and governed by the state board of pharmacy should be exempted from compliance with at least the three aforementioned statutory provisions.¹⁰⁻¹²

In actuality, however, the current drug laws simply offer no statutory exemptions for compounded radiopharmaceuticals. Even though the 1984 Nuclear Pharmacy Guideline implies that compounded radiopharmaceuticals are not subject to the adulteration, misbranding, or new drug provisions, it actually provides only for discretionary enforcement of these requirements. The *Nuclear Pharmacy Compounding Guidelines* used the above-referenced documents as a springboard to further refine the definitions of good compounding practice as they exist in today's practice arena.

FDA Working Group: New Radiopharmaceutical Guidance

Without statutory exemptions from adulteration, misbranding, and new drug provisions¹⁰⁻¹² or a discretionary enforcement policy being observed by FDA, the potential exists that nuclear pharmacy compounding practice will cease due to the imposition and over-enforcement of regulations not intended for the practice. That, in turn, would certainly pose a serious threat to proper and necessary care for certain groups of patients, which is dependent on the ready availability of cost-effective compounded radiopharmaceuticals.

The Nuclear Pharmacy Compounding Practice Committee members were pleased to learn that FDA recently established a working group to develop a new guidance on the compounding of radiopharmaceuticals (PCSC, personal communication, August 13, 2001). Currently, FDA is reexamining CPG 460.200¹⁶ and the 1984 Nuclear Pharmacy Guideline¹⁷ in light of FDAMA in the development of the new guidance on the compounding of radiopharmaceuticals. According to FDA, this working group includes pharmacists and nuclear pharmacists, and the new guidance will be published in the *Federal Register* with a request for comments from the public (PCSC, personal communication, August 13, 2001). Until new guidance is issued, FDA will continue to rely on these two documents to "regulate" nuclear pharmacy compounding practice (PCSC, personal communication, June 26, 1999).

Until FDA issues the new guidance to address and clarify the situations in which it may exercise its authority to enforce the three statutory requirements as they apply to compounded radiopharmaceuticals, the Nuclear Pharmacy Compounding Practice Committee feels that FDA should continue to follow its existing 1984 Nuclear Pharmacy Guideline.¹⁷ This course of action would allow nuclear pharmacists to continue providing proper patient care. It would also show that FDA is being reasonable in its

approach to regulating professional practice and sensitive to the needs of patients and health care providers.

Compounded Radiopharmaceuticals and PET Drugs

"Radiopharmaceutical or radioactive drug," as defined in the 1997 FDAMA²⁰ and reiterated in the *Nuclear Pharmacy Compounding Guidelines*, includes any nonradioactive reagent kit or radionuclide generator intended for use in the preparation of any such drug product. Hence, nonradioactive reagent kits, as well as the corresponding final radiolabeled products, are covered by the Nuclear Pharmacy Compounding Practice Committee's guidelines.

Radiopharmaceutical and compounded PET drugs are the only two drug categories excluded from the "sanctuary list" of the pharmacy compounding law as stated in section 503A of the FD&C Act.¹

Although PET drugs precisely fit the statutory definition of a radiopharmaceutical or radioactive drug, the Nuclear Pharmacy Compounding Practice Committee decided to exclude "compounded PET drug" from the definition of "radiopharmaceutical or radioactive drug" stated in the *Guidelines*. The main reason for this exclusion is that section 121 of FDAMA provides a separate and distinct regulatory framework for PET drug products, including compounded PET drugs.⁵ However, there are several controversial issues related to the law concerning compounding of PET drug products.¹⁷ When the rule sunsets, 2 years after the date on which FDA establishes the requirements, compounded PET drugs will likely be subject to the same type of regulation (e.g., CGMP, NDA/ANDA) that FDA currently applies to drug manufacturing and marketing activity.⁵

While the application of the "manufacturing" requirements of section 121 of FDAMA to the compounding of PET drugs is perplexing, one may wonder whether, following this precedent, FDA will eventually place compounded radiopharmaceuticals under the same regulatory framework, making them subject to the adulteration, misbranding, and new drug provisions of the FD&C Act.^{5,21}

Compounding of Radiopharmaceuticals

Preparation According to Manufacturer's Instructions

According to the definition stated in section 503A of the FD&C Act, the term "compounding" does not include mixing, reconstituting, or other such acts performed in accordance with directions contained in approved product labeling provided by manufacturers and other directions consistent with that labeling.¹ Thus, a drug product prepared via a process that is the same as that stated on FDA-approved labeling is not considered to be compounded.

Conversely, a drug product prepared via processes or proce-

dures that deviate even slightly from those described in a package insert would be considered a compounded product. Using this definition of compounding, the vast majority of the nearly 20 million radiopharmaceutical patient doses dispensed annually by nuclear pharmacists would be considered compounded drug products.²²

Deficiencies of Package Inserts for Radiopharmaceuticals

Within the field of nuclear pharmacy, it is common to find that a package insert contains inadequate information to permit the reconstitution and quality control (QC) of the radiopharmaceutical. The five categories of deficiencies identified by the Nuclear Pharmacy Compounding Practice Committee in the package insert instructions for the preparation of radiopharmaceuticals are absent or incomplete directions (e.g., QC procedure²³), restrictive directions (e.g., specific needle sizes,²⁴ particular QC techniques²⁵), inconsistent directions (e.g., conflicting expiration times,²⁶ differing reconstituted volumes for preparing the same radiopharmaceutical²⁴), impractical directions (e.g., unsafe particle number with regard to certain particulate radiopharmaceuticals,²⁷ unrealistically low activity limits for reconstituting various cold kits²⁸), and vague directions (e.g., can,²⁹ recommend,²⁸ should³⁰).

The poor quality of package insert instructions supports the notion that strictly adhering to manufacturer's directions is not always the best way to ensure quality patient care, radiation safety, or timely provision of radiopharmaceutical doses. Because of the aforementioned deficiencies, it is difficult, and sometimes impossible, to prepare a radiopharmaceutical by following the directions exactly as stated in the package insert. Unfortunately, manufacturers are not interested in either revising or augmenting the information contained in the package inserts because of the huge expense and extensive paperwork typically involved in gaining FDA approval for a revised insert. This situation creates a dilemma for nuclear pharmacists.

The Nuclear Pharmacy Compounding Practice Committee is of the opinion that the manufacturer's instructions should be viewed as guidance rather than required procedure. A nuclear pharmacist should have the professional prerogative to use alternative methods to prepare radiopharmaceuticals, provided those procedures have been proven to provide equivalent, or better, results and that he or she does not engage in activities that fall outside the normal practice of nuclear pharmacy. These beliefs of the Nuclear Pharmacy Compounding Practice Committee are reflected in item 3 of the General Provisions section of the *Guidelines*.^b

Strictly speaking, any radiopharmaceutical that is not prepared in accordance with the manufacturer's instructions could be classified as a compounded radiopharmaceutical. However, as implied above, deviations in procedure when preparing radiopharmaceuticals are, by and large, caused by deficiencies in package insert directions that make it impossible for nuclear pharmacists to adhere to manufacturer's instructions.

Copycat Drugs

Compounded drug products are not required to meet the adulteration, misbranding, and new drug provisions specified in section 503A of the FD&C Act. The section does place several restrictions on compounding practice¹ and will not be subjected to FDA's enforcement action, as per CPG 460.200,^{16,18} provided such drug products are compounded in accordance with state law and traditional compounding activity (e.g., extemporaneously compounding reasonable quantities of human drugs upon receipt of a valid prescription from a licensed practitioner for an individually identified patient). However, section 503A and CPG 460.200 nonetheless place several restrictions on the pharmacy compounding practice.^{1,16,18}

One restriction is that a pharmacist cannot copy any commercially available drug product on a regular basis or in inordinate amounts.¹ The main intent here is to limit the scope of compounding in order to prevent small-scale manufacturing under the guise of compounding. However, this copycat limitation does not apply to a drug product that may be similar to the commercially available drug when the change made to the drug product produces a "significant difference" in the care of the patient.¹ For example, the removal of a dye from a commercially available drug product for a particular patient who is allergic to the dye may be presumed to make a significant difference in that patient's care. Thus, compounding the above drug product without dye is not only permissible under current federal drug law but becomes a professional responsibility for both the compounding pharmacist and the prescribing physician.

"Deviations" From the Manufacturer's Instructions in the Preparation of Radiopharmaceuticals^b

The Nuclear Pharmacy Compounding Practice Committee feels that the definition of nuclear pharmacy compounding should not apply to a radiopharmaceutical prepared via deviation(s) from manufacturer's instructions, as long as the radiopharmaceutical maintains the same quality and purity as that produced by adherence to the manufacturer's directions. Therefore, if a radiopharmaceutical is not prepared in accordance with the manufacturer's directions, we maintain that it should not be considered a

^bNuclear 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).

compounded drug product as long as its quality and purity are the same as those drugs produced in compliance with the preparation instructions as provided by the manufacturer.

The committee's view with regard to the use of an alternative method for the preparation of a radiopharmaceutical is in line with the policy adopted by USP. The General Notices section of the USP indicates that the existence of an official test method in the USP does not preclude the use of a validated alternative method.³¹ However, when a difference appears, or in the event of dispute, the USP method is the referee method.³¹

Examples of Compounded Radiopharmaceuticals

Clearly, when a radiopharmaceutical is not commercially available, a nuclear pharmacist is allowed to compound that particular radioactive drug for an individual patient, based on a prescription order and medical need (i.e., items 2^c and 10^d of the General Provisions section of the *Nuclear Pharmacy Compounding Guidelines*). Examples of such compounded radiopharmaceuticals are technetium-99m (^{99m}Tc)-labeled human serum albumin and ^{99m}Tc(V)-labeled succimer.

In certain circumstances, a nuclear pharmacist may be required to compound a radiopharmaceutical that is only slightly different from an FDA-approved radiopharmaceutical that is commercially available (i.e., item 11^e of the General Provisions section of the *Nuclear Pharmacy Compounding Guidelines*). Again, the preparation of this compounded radioactive drug is permissible only when it is done for the legitimate medical needs of an individual, identified patient.^c Examples of this type of compounded radiopharmaceutical include ^{99m}Tc-labeled macro-aggregated albumin (^{99m}Tc-MAA) with a reduced number of particles/dose for a patient with severe pulmonary hypertension and ^{99m}Tc-labeled sulfur colloid with a smaller particle size for lymphoscintigraphy.

It is sometimes necessary to change an inactive ingredient because of the potential for sensitivity or allergic reaction in certain

^cBased 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.

^dThe 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].

^eThe 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.

patients^e (for example, ^{99m}Tc-labeled mebrofenin prepared from a Choletec reagent kit [Bracco Diagnostics] contains propylparaben, a preservative to which some patients are allergic).

A particular patient may require a specific dosage form that cannot be prepared using a commercially available drug product.^e Examples of this include a sodium iodide ¹³¹I capsule compounded for a patient who requires a dosage or capsule size that is not available from the manufacturer and a sodium iodide ¹²³I solution compounded for a pediatric patient, since it is often difficult for younger patients to swallow the commercially available radioactive iodine capsule(s).

Kit Splitting

Kit splitting, or vial fractionation, is a process that is generally applied to reagent kits. Kit splitting is usually accomplished when the lyophilized contents of a vial are reconstituted with physiological saline and the resulting solution is divided and transferred to a number of new vials and stored under frozen conditions for an extended period of time.

This practice has usually been carried out during drug shortages or for economic reasons and is typically similar to partial vial usage or multiple dosage dispensing from a single-use vial, both of which are common practice in hospital pharmacies. However, manufacturers (CORAR, personal communication, June 18, 2002) and others caution that kit splitting can have a significant adverse effect on sterility, drug content uniformity, and stability, especially for products that must be manipulated and stored in a special environment, such as low moisture or inert gas conditions.^{32,33}

The Nuclear Pharmacy Compounding Practice Committee spent a great deal of time discussing this difficult issue. Kit splitting is clearly a practice that deviates from package insert directions. One interpretation was that, when done carefully with verification of sterility, radiochemical purity (RCP), etc., kit splitting should not be considered compounding as long as the final product's quality and purity are the same as those produced in compliance with the manufacturer's preparation instructions. A second interpretation was that kit splitting should be considered compounding of limited quantities of drug in anticipation of receiving prescription orders. A third take was that this practice should be considered manufacturing because repackaging is typically considered a manufacturing activity.

Because of the lack of consensus, the committee decided not to address kit splitting in the text of the *Nuclear Pharmacy Compounding Guidelines*. However, given the recurring shortages of certain reagent kits and radiopharmaceuticals in recent years, kit splitting may be a viable option for prolonging the availability of radioactive drugs to meet patients' needs. If this practice is undertaken, it is important for the nuclear pharmacist to ensure that an adequate amount of any active ingredient is maintained in the smaller dosage forms so that the quality of the nuclear medicine procedure is not compromised and the final product complies with all applicable standards of quality and purity. It is also critical for

the nuclear pharmacist to base any kit splitting practice on his or her professional judgment and knowledge and to ensure that such a practice is in compliance with the applicable law.

Other Restrictions Under Section 503A of the FD&C Act and CPG 460.200

Withdrawn or Removed Drug Products

Since section 503A of the FD&C Act and the 1992 and 2002 versions of CPG 460.200 do not apply to radiopharmaceuticals,^{1,16,18} FDA has no statutory responsibility to include radiopharmaceuticals on its list of unsafe or ineffective drug products. Nonetheless, any drugs included on this list probably should not be used as components when compounding radiopharmaceuticals. Item 9^f of the General Provisions section of the *Nuclear Pharmacy Compounding Guidelines* reflects this reasoning.

Demonstrably Difficult to Compound Drug Product

Section 503A of the FD&C Act indicates that a pharmacist cannot compound a drug product if the difficulty of the compounding process may potentially compromise the safety or effectiveness of that drug product.¹ Since the section's provisions do not apply to radiopharmaceuticals,¹ the Demonstrably Difficult to Compound Drug Product list issued by FDA does not include a listing of such radiopharmaceuticals. Additionally, the criteria used by FDA to identify drugs that present demonstrable difficulties in compounding may be too subjective or restrictive. Furthermore, the 1992 and 2002 versions of CPG 460.200 do not list the aforementioned restriction as one of the pharmacy acts that may "trigger" FDA's enforcement action, although the list of "inappropriate" acts as stated in the 1992 and 2002 CPG 460.200 is not exhaustive and other acts may be considered by FDA on a case-by-case base.^{16,18} As a result, the Nuclear Pharmacy Compounding Practice Committee decided not to include the phrase "demonstrably difficult to compound drug product" in the text of the *Nuclear Pharmacy Compounding Guidelines*.

Pharmacy Compounding Memorandum of Understanding

The intent of the memorandum of understanding (MOU) between the state and FDA as described in section 503A of the FD&C Act is to provide guidance concerning the distribution of inordinate quantities of compounded drug products outside the state in which the compounding pharmacy is located.¹ As stated in the previous sections, compounded radiopharmaceuticals are not covered by the MOU regarding interstate distribution since the provisions of section 503A are not applicable to radiopharmaceu-

ticals. In addition, neither the 1992 nor the 2002 CPG 460.200 addresses the MOU issue. As such, the MOU item is not included in the *Nuclear Pharmacy Compounding Guidelines*.

Advertising and Promotion

Section 503A of the FD&C Act prohibits pharmacists from advertising or promoting the drugs they compound.¹ Those pharmacists are, however, permitted to advertise or promote their compounding service. Some pharmacists have argued that these regulations violate the First Amendment's guarantee of free speech. In its decision on a lawsuit brought by Western States Medical Center of Nevada against FDA, the United States Court of Appeals for the Ninth Circuit ruled in a statement dated February 6, 2001, that not only are points (a) and (c) of section 503A in violation of the First Amendment, but, further, that section 503A in its entirety is invalid since, as determined by the court, points (a) and (c) of section 503A may not be severed from the rest of the provisions in section 503A.¹⁴ As stated earlier in this article, the Supreme Court has affirmed the decision made by the court of appeals. However, the Supreme Court failed to address whether pharmacy compounding was legal before FDAMA.¹⁵ Therefore, the only ruling with regard to section 503A is the one issued by the court of appeals, in which the court declared the advertising ban in section 503A to be unconstitutional and that it could not be severed from the rest of section 503A. As such, the court concluded that section 503A of the FD&C Act was invalid in its entirety.

The Nuclear Pharmacy Compounding Practice Committee chose not to include this restriction within the *Nuclear Pharmacy Compounding Guidelines*. This decision was based not only on section 503A's inapplicability to radiopharmaceuticals but also on the fact that the issue of advertising and promotion with regard to pharmacy compounding is not mentioned in CPG 460.200.^{1,16,18}

ACARA (As Clean As Reasonably Achievable)

Since the majority of radiopharmaceuticals are administered intravenously and all package inserts for parenteral radiopharmaceuticals require the use of aseptic technique during preparation, it seems reasonable to stipulate that radiopharmaceutical compounding practice be performed in a clean and controlled environment (e.g., an M3.5 [Class 100] laminar flow hood located in a clean room). More than 25 years of history have proven that nuclear pharmacy practice yields incredibly safe products; problems associated with lack of sterility and pyrogenicity have been exceedingly rare. Although theoretical improvements could be made if all radiopharmaceuticals were compounded in a clean and controlled area, the value could be negative based on the law of diminishing returns and decreased use because of increased costs.

USP 1191, "Stability Considerations in Dispensing Practice," states that "because of potential unobservable problems with respect to sterility and chemical stability, all extemporaneous parenteral preparations should be used within 24 hours unless data are avail-

^fThe 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.

able to support longer storage.”⁷ Therefore, the Nuclear Pharmacy Compounding Practice Committee believes that the practice of compounding parenteral radiopharmaceuticals outside of a laminar flow hood or a clean room can be further justified by the short expiration times (typically hours) of virtually all radiopharmaceuticals.

However, if compounding certain radiopharmaceuticals poses greater than usual potential risk for patients (e.g., drug products compounded from nonsterile ingredients or compounded with nonsterile components, containers, or equipment, or if “open system” transfer or nonsealed reservoirs are used in the compounding process), the committee suggests that nuclear pharmacists refer to USP 1206⁸ and an article titled “ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products” published in the *American Journal of Health-System Pharmacy*⁹ for further guidance.

It is not a simple task to adequately manage both aseptic technique and radiation safety when compounding radiopharmaceuticals. In fact, nuclear pharmacists typically have to make some compromise between the two considerations in order to complete the preparation of a radiopharmaceutical. This has led us to adopt the standard of ACARA (as clean as reasonably achievable) as a companion to ALARA (as low as reasonably achievable), the common standard for radiation protection.³⁴ To clarify the requirements for ACARA, three additional criteria were added to the definition of ACARA in the Definitions section of the *Nuclear Pharmacy Compounding Guidelines*. These three new criteria for ACARA are similar to the conditions set for ALARA in the Definitions section of Part 35.2 of Title 10 of the *Code of Federal Regulations*.³⁴

Other Minor Issues Related to Nuclear Pharmacy Compounding Practices

Patented Radiopharmaceuticals

As indicated in section 503A of the FD&C Act, exemptions from the adulteration, misbranding, and new drug requirements granted to compounded pharmaceuticals do not apply to compounded drugs that are essentially copies of commercially available drug products when those drugs are compounded on a regular basis or in inordinate amounts.¹ In addition, the recently issued CPG 460.200 indicates that FDA would seriously consider enforcement action against any pharmacy conducting the aforementioned activity.¹⁸ These restrictions suggest that copying commercially available drugs for economic reasons is permissible as long as it is not done regularly or in inordinate amounts. The Nuclear Pharmacy Compounding Practice Committee believes that any patented drug product, including radiopharmaceuticals, should receive more protection due to the research and development efforts involved, as well as the cost invested by the pharmaceutical manufacturer, in acquiring the patent. As a result, the Committee’s *Guidelines* place more stringent requirements on the compounding of patented radioactive drugs.

As stated in item 12^g of the General Provisions section of the *Nuclear Pharmacy Compounding Guidelines*, a nuclear pharma-

gist is allowed to compound a patented radiopharmaceutical only when it cannot be readily obtained from a commercial source and provided it is to be used to meet the urgent medical need(s) of an identified individual patient.

One may argue that copying a patented drug is no different from photocopying an article from a scientific journal for one’s own use, and, thus, that a nuclear pharmacist should be permitted to copy a patented radiopharmaceutical for in-house patient use. However, as long as the patient is charged for the compounded patented radiopharmaceutical, that money exchange will be in violation of copyright or patent law. However, were the compounding of a patented radiopharmaceutical to be performed in an emergency to meet the medical needs of an identified individual patient, the Nuclear Pharmacy Compounding Practice Committee does not believe that the pharmaceutical company that owns the patent rights of the radiopharmaceutical would pursue any legal challenge concerning the nuclear pharmacist’s actions.

Sources of Compounding Drug Components

Using an alternative high-quality source of compounding drug components as stated in item 4 of the Bulk Drug Substance^h and item 3 of the Excipientⁱ subsections of the *Nuclear Pharmacy Compounding Guidelines* is not specifically identified in section 503A of the FD&C Act or in the 1992 and 2002 versions of CPG 460.200.^{1,16,18} Section 503A does mention that the bulk drug substances and any other drug substances used in compounding a drug product must also comply with standards as stated in the USP chapter on pharmacy compounding (i.e., USP 795).^{1,6}

According to USP 795, a USP- or a *National Formulary*-grade substance is the preferred source of substances for compounding all other drug preparations.⁶ If such a product is not available, however, then the use of a high quality substance (i.e., analytical reagent-, certified American Chemical Society-, or Food Chemicals Codes-grade) substance is acceptable.⁶

Radiochemical Purity Testing

With regard to compounded radiopharmaceuticals that are similar to radiopharmaceuticals prepared in accordance with manufacturer’s directions (e.g., ^{99m}Tc-MAA with a reduced particle number), USP radiopharmaceutical monographs and package inserts may provide adequate information for completion of the

^gThe 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.

^hA 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

ⁱA 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

required RCP testing. However, if the RCP testing information, as stated in a USP monograph or package insert, is inadequate or inappropriate, nuclear pharmacists can refer to the *Alternative Radiochemical Purity Testing Procedures for the Compounded Radiopharmaceuticals Approved from 1988–1997*, which was published by APhA in 1998,³⁵ or they can use their professional judgment in selecting a suitable RCP testing method from the literature.^j

Bacterial Endotoxin Limit for Intrathecally Administered Radiopharmaceuticals

Because intrathecally administered radiopharmaceuticals bypass the blood–brain barrier and enter the brain directly via the cerebrospinal fluid, the bacterial endotoxin limit for this type of radiopharmaceutical is considerably lower than that for intravenously administered radiopharmaceuticals.³⁷ As a result, the *Nuclear Pharmacy Compounding Guidelines* suggest that bacterial endotoxin testing at a sensitivity appropriate for intrathecal administration should be performed by qualified personnel or that, in lieu of this testing, the dose volume should be limited to no more than 8% of the maximum intravenous dose volume in conjunction with meticulous aseptic technique in the compounding of the radiopharmaceutical for this use.

Conclusion

The exclusion of radiopharmaceuticals from section 503A of the FD&C Act places the practice of compounding radiopharmaceuticals by nuclear pharmacists in a state of regulatory limbo. Because compounded radiopharmaceuticals are ineligible for the statutory exemptions from the adulteration, misbranding, and new drug provisions of the FD&C Act provided by section 503A,¹ and are not specifically addressed in the 1992 and 2002 versions of CPG 460.200, nuclear pharmacists must continue to rely on FDA's enforcement discretion as described in its 1984 Nuclear Pharmacy Guideline. If FDA revises its enforcement compliance policies to eliminate this discretion for radiopharmaceutical compounding,

^jThe 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.

such activities would, by default, be viewed as manufacturing. This would place the compounding of radiopharmaceuticals in the same predicament as the compounding of PET drug products.^{5,21}

Either underregulating (i.e., excluding radiopharmaceuticals from section 503A of the FD&C Act) or overregulating (i.e., applying CGMP and NDA/ANDA requirements to compounded pharmaceuticals) the practice of radiopharmaceutical compounding will only serve to escalate the cost of compounded radiopharmaceuticals and force many nuclear pharmacists out of the practice of compounding. These alternatives are clearly inconsistent with the general public's welfare or benefit. To ensure the continued availability of compounded radiopharmaceuticals at reasonable cost, and to maintain adequate quality of those drug products, it is imperative that current federal law be revised to provide a statutory exemption for compounded radiopharmaceuticals.

Until the federal compounding regulation for radiopharmaceuticals is changed, the availability of the *Nuclear Pharmacy Compounding Guidelines* will assist state boards of pharmacy in appropriately evaluating and regulating nuclear pharmacy compounding practices. The realistic and practical compounding principles and procedures provided in the *Nuclear Pharmacy Compounding Guidelines* are also offered as a blueprint for FDA to follow in developing new radiopharmaceutical guidance.

Joseph C. Hung, PhD, BCNP, FAPhA, is chair, Nuclear Pharmacy Compounding Practice Committee, American Pharmaceutical Association Academy of Pharmacy Practice and Management (APhA-APPM) Section on Nuclear Pharmacy Practice; director, Nuclear Pharmacy Laboratories and PET Radiochemistry Facility, Nuclear Medicine, Department of Radiology, Mayo Clinic; and professor of pharmacy and professor of radiology, Mayo Medical School, Rochester, Minn. Samuel C. Augustine, PharmD, BCNP, FAPhA, is associate professor, Department of Pharmacy Practice, College of Pharmacy, Department of Pathology and Microbiology, College of Medicine, University of Nebraska Medical Center, and director, Nebraska Drug Information Network, Omaha, Neb. Kenneth T. Cheng, PhD, BCNP, FAPhA, is associate professor and director, Nuclear Pharmacy Program, Department of Pharmaceutical Sciences, College of Pharmacy, Medical University of South Carolina, Charleston, S.C. Richard L. Green, RPh, BCNP, is adjunct associate professor of bionucleonics, College of Pharmacy and Health Sciences, Butler University, Indianapolis, Ind., and program manager–pharmacy practice, Quality & Regulatory Department, Syncor International Corporation, Woodland Hills, Calif. Wade M. Hopkins, BCNP, is pharmacy manager, Syncor International Corporation, Houston, Tex. David L. Laven, NPh, CRPh, FASHP, FAPhA, is owner, Gammascan Consultants, Longwood, Fla. Brigitte R. Nelson, MS, PharmD, BCNP, is staff nuclear pharmacist, Regulatory Support Central Pharmacy Services, Inc., Jacksonville, Fla. Neil A. Petry, MS, BCNP, FAPhA, is assistant professor of radiology and director, Radiopharmacy and Nuclear Medicine Laboratory, Duke University Medical Center, Durham, N.C. James A. Ponto, MS, BCNP, FAPhA, is chief nuclear pharmacist and professor (clinical), Division of Nuclear Medicine, Department of Radiology, University of Iowa Hospitals and Clinics, Iowa City, Iowa. Timothy M. Quinton, PharmD, MS, BCNP, FAPhA, is president, Radiopharmacy, Inc., Evansville, Ind. Dennis P. Swanson, MS, BCNP, FAPhA, is professor of pharmacy and therapeutics, School of Pharmacy, University of Pittsburgh, and director, Research Conduct and Compliance Office, University of Pittsburgh, Pittsburgh, Pa.

None of the authors of this article or members of their immediate families have conflicts of interest or financial interests (i.e., grants [pending or received], employment, gifts, stock holdings or options, honoraria, consultancies, expert testimony, patents, and royalties) with regard to any product or service mentioned in this article, with the following exceptions: Hung supervises radiopharmaceutical compounding services at the Nuclear Pharmacy Laboratories of Mayo Clinic and serves as chair, APhA-APPM Section on Nuclear Pharmacy Practice. Augustine served as member at large, APhA-APPM Section on Nuclear Pharmacy Practice, and

serves as a member of the Expert Committee on Parenteral Products—Compounding and Preparation General Policies and Requirements Division, United States Pharmacopeial Convention (USP). Cheng provides drug compounding services as director of the Nuclear Pharmacy Division of the Department of Pharmaceutical Sciences at the Medical University of South Carolina and served as chair, APhA–APPM Section on Nuclear Pharmacy Practice, 1999–2000. Nelson served as member-at-large, APhA–APPM Section on Nuclear Pharmacy Practice, 1999–2000. Petry supervises and performs radiopharmaceutical compounding services at the Radiopharmacy and Nuclear Medicine Laboratory of the Duke University Medical Center and served as chair, APhA–APPM Section on Nuclear Pharmacy Practice, 2000–2001. Ponto served as a consultant for the Office of Compliance, U.S. Food and Drug Administration (FDA), 2000, performs radiopharmaceutical compounding services for University of Iowa Hospitals and Clinics, and serves as a member of the Expert Committee on Radiopharmaceuticals, Information Division, USP. Laura L. Ponto, his wife, serves as a member of the Expert Committee on Radiopharmaceuticals, Information Division, USP. consultant to the Medical Imaging Drug Advisory Committee, FDA, and member-at-large, APhA–APPM Section on Nuclear Pharmacy Practice. Quinton served as chair, APhA–APPM Section on Nuclear Pharmacy Practice, 1998–1999. Swanson serves on the Expert Committee on Radiopharmaceuticals, Information Division, USP, and as a member of the Expert Committee on Radiopharmaceuticals and Medical Imaging Agents, Noncomplex Actives and Excipients Division, USP.

Acknowledgments: The authors thank Susan C. Winckler, Susan K. Bishop, and Anne L. Burns, American Pharmaceutical Association, for their kind assistance in securing the approval of the *Guidelines* from APhA's Board of Trustees. We also express our sincere thanks to Vicki S. Krage, Mayo Clinic, for her assistance in the proofing and submission of the manuscript.

Parts of this paper were presented by Hung at the Nuclear Pharmacists' Breakfast and Business Meeting on March 7, 1999, during the Annual Meeting of the American Pharmaceutical Association.

References

1. Application of federal law to practice of pharmacy compounding. Food and Drug Administration Modernization Act of 1997, Pub L No. 105-115 §127, 11 Stat 2296.
2. Kotz D. Congress passes FDA reform act: nuclear medicine community stands to gain [news]. *J Nucl Med.* 1998;39:15N–8N.
3. *Nuclear Pharmacy Guidelines for the Compounding of Radiopharmaceuticals for Positron Emission Tomography.* Washington, DC: American Pharmaceutical Association; 1993.
4. Radiopharmaceuticals for positron emission tomography—compounding. In: *USP25–NF20: United States Pharmacopeia and National Formulary.* Rockville, Md: United States Pharmacopeial Convention, Inc; 2002:2068–71.
5. Positron emission tomography. Food and Drug Administration Modernization Act of 1997, Pub L No. 105-115 §121, 11 Stat 2296.
6. Pharmacy compounding. In: *USP25–NF20: United States Pharmacopeia and National Formulary.* Rockville, Md: United States Pharmacopeial Convention, Inc; 2002:2053–7.
7. Stability considerations in dispensing practice. In: *USP25–NF20: United States Pharmacopeia and National Formulary.* Rockville, Md: United States Pharmacopeial Convention, Inc; 2002:2231–4.
8. Sterile drug products for home use. In: *USP25–NF20: United States Pharmacopeia and National Formulary.* Rockville, Md: United States Pharmacopeial Convention, Inc; 2002:2234–47.
9. ASHP guidelines on quality assurance for pharmacy-prepared sterile products. American Society of Health-System Pharmacy. *Am J Health Syst Pharm.* 2000;57:1150–69.
10. Adulterated drugs and devices. Federal Food, Drug and Cosmetic Act §501(a)(2)(B), 21 USC §301 (1998).
11. Misbranded drugs and devices. Federal Food, Drug and Cosmetic Act §502(f)(1), 21 USC §301 (1998).
12. New drugs. Federal Food, Drug, and Cosmetic Act §505, 21 USC §301 (1998).
13. Current good manufacturing practice for finished pharmaceuticals, 63 *Federal Register* 14355–6 (1998) (codified at 21 CFR §211).
14. *Western States Medical Center v Shalala* 238 F3d 1090 (9th Cir 2001). Available at: www.ca9.uscourts.gov/ca9/newopinions.nsf/F48E2BCB53CC88FD882569EB0062542F5file/9917424.pdf?openelement. Accessed July 31, 2002.
15. *Thompson, Secretary of Health and Human Services, et al. v Western States Medical Center et al.* 535 US (2002). Available at: <http://a257.g.akamaitech.net/7/257/2422/29apr20021100/www.supremecourtus.gov/opinions/01pdf/01-344.pdf>. Accessed August 3, 2002.
16. Manufacture, distribution, and promotion of adulterated, misbranded, or unapproved new drugs for human use by state-licensed pharmacies. In: *Compliance Policy Guides Manual.* Bethesda, Md: U.S. Food and Drug Administration; 1992:§460.200 [formerly §7132.16].
17. *Nuclear Pharmacy Guideline Criteria for Determining When to Register as a Drug Establishment.* Washington, DC: Food and Drug Administration; 1984.
18. Sec. 460.200 pharmacy compounding. In: *Guidance for FDA Staff and Industry Compliance Policy Guides Manual.* Rockville, Md: U.S. Food and Drug Administration; May 2002. Available at: www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460.200.html. Accessed August 5, 2002.
19. Registration of producers of drugs and devices. Federal Food, Drug and Cosmetic Act §510(g)(1), 21 USC §301 (1998).
20. Requirements for radiopharmaceuticals—definition. Food and Drug Administration Modernization Act of 1997, Pub L No. 105-115 §122, 11 Stat 2296.
21. Hung JC. Regulation of the compounding of positron emission tomography drugs. *Am J Health Syst Pharm.* 2001;58:134–9.
22. Fast facts about nuclear medicine. Society of Nuclear Medicine Web site. Available at: www.snm.org/nuclear/new_whats_nm_1.html. Accessed February 10, 2002.
23. CIS-SULFUR COLLOID [package insert]. Bedford, Mass: CIS-US, Inc; 1999.
24. Ceretec [package insert]. Arlington Heights, Ill: Amersham Healthcare; 1996.
25. TechneScan MAG3 [package insert]. St. Louis, Mo: Mallinckrodt Inc; 2000.
26. Choletec [package insert]. Princeton, NJ: Bracco Diagnostics Inc; 2000.
27. Macrotec [package insert]. Princeton, NJ: Bracco Diagnostics Inc; 2000.
28. Cardiolite [package insert]. N. Billerica, Mass: Bristol-Myers Squibb Medical Imaging, Inc; 2001.
29. Myoview [package insert]. Arlington Heights, Ill: Amersham Health; 2001.
30. OncoScint CR/OV [package insert]. Princeton, NJ: CYTOGEN Corporation; 1996.
31. General notices and requirements. In: *USP25–NF20: United States Pharmacopeia and National Formulary.* Rockville, Md: United States Pharmacopeial Convention, Inc; 2002:1–11.
32. Hung JC, Ponto JA, Hammes RJ. Radiopharmaceutical-related pitfalls and artifacts. *Semin Nuc Med.* 1996;26:208–55.
33. Hnatowich DJ, Coupal JJ [moderators]. Cost-containment and the practice of pharmacy. *J Nucl Med.* 1995;36:285N.
34. ALARA program, 10 CFR §35.20 (2001).
35. *Alternative Radiochemical Purity Testing Procedures for the Compounded Radiopharmaceuticals Approved from 1988–1997.* Washington, DC: American Pharmaceutical Association; 1998.
36. Bacterial endotoxins test. In: *USP25–NF20: United States Pharmacopeia and National Formulary.* Rockville, Md: United States Pharmacopeial Convention, Inc; 2002:1889–93.