GUIDANCE FOR FDA STAFF AND INDUSTRY

COMPLIANCE POLICY GUIDE
Sec. _____ RADIOPHARMACEUTICAL COMPOUNDING

I. INTRODUCTION

Section 503A was added to the Federal Food, Drug, and Cosmetic Act (FDC Act) by the Food and Drug Administration Modernization Act of 1997. Section 503A describes conditions that must be satisfied in order for drug products compounded by a licensed pharmacist or licensed physician to be exempt from certain requirements of the FDC Act. Radiopharmaceuticals and positron emission tomography (PET) drugs (as defined in FDC Act Section 201(ii)) were exempt from Section 503A. The conditions of Section 503A included restrictions on the advertising or promotion of the compounding of any particular drug, class of drug, or type of drug and the solicitation of prescriptions for compounded drugs. These provisions were challenged in court and held unconstitutional by the U.S. Supreme Court in 2002. Therefore, in May 2002, FDA issued Compliance Policy Guide (CPG) 460.200, which described how FDA intended “to address pharmacy compounding of human drugs in the immediate future” as a result of the Supreme Court decision. CPG 460.200 applied to pharmacy compounding of all human drugs, including radiopharmaceuticals. On November 27, 2013, the Drug Quality and Security Act (DQSA) was enacted. Among other things, the DQSA amended Section 503A by removing the advertising, promotion, and solicitation provisions. Because the DQSA amendment to Section 503A rendered it enforceable, CPG 460.200 was superseded and was withdrawn by FDA on December 4, 2013.

Because Section 503A exempts radiopharmaceuticals and PET drugs, and CPG 460.200, which covered these products, has been withdrawn, it is necessary to explain FDA’s current policy with regard to the compounding of radiopharmaceuticals. ¹

II. BACKGROUND

Nuclear pharmacies play an essential role in the preparation and distribution of radiopharmaceutical products. Radiopharmaceuticals are radioactive drugs, in both sterile and non-sterile form, that are used in nuclear medicine procedures to diagnose and/or treat diseases such as cancer, cardiovascular disease, and neurological disorders. They have short radioactive half-lives – typically from several minutes to several days – and therefore must reach the patient soon after being prepared. Sometimes they are shipped rapidly by the manufacturer to the end user (imaging center or hospital). However, more frequently, they are shipped by the manufacturer in “hot” (radioactive) ¹

¹ For purposes of this Compliance Policy Guide, the term radiopharmaceutical includes a PET drug as defined in Section 201(ii) of the FDC Act.
multidose containers or as approved non-radioactive “cold kits” to a nuclear pharmacy, which then processes them as necessary for patient use, draws them into patient-ready containers, and ships these rapidly to the end user.

Much of the activity of a nuclear pharmacy consists of mixing, reconstituting, eluting, radio-labeling (i.e., combining a radioisotope, which is often sourced on-site from a generator or cyclotron, with a non-radioactive compound), or otherwise manipulating approved radiopharmaceuticals in accordance with the instructions in the approved labeling, and packaging them into containers suitable for dispensing and administration to the patient. FDA does not consider these operations performed in accordance with the manufacturer’s instructions to be compounding, and this Compliance Policy Guide does not apply to this type of activity. In addition, because a radiopharmaceutical is in a constant state of decay after preparation, nuclear pharmacists routinely make minor deviations from the manufacturer’s instructions to account for variations in time and distance between the pharmacy and the point of patient use that have not been anticipated or provided for in the manufacturer’s instructions. FDA does not consider minor deviations from the manufacturer’s instructions with regard to radioactivity, volume, or stability to be compounding, and such activity is also not covered by this Compliance Policy Guide.

Like conventional pharmacies, nuclear pharmacies sometimes compound products that are not approved, or that differ significantly from an approved product, in order to meet the medical needs of an identified individual patient. A compounded radiopharmaceutical may differ from an approved radiopharmaceutical in its active or inactive ingredients, dosage form, radioactive dose, or mass dose. However, because of the unique features of radiopharmaceuticals, typical nuclear pharmacy practice involves many activities that differ from the ordinary practice of pharmacy for conventional drugs, and these differences affect compounding and other dispensing activities alike.

One such difference lies in the prescription ordering procedure. The laws of most states permit nuclear pharmacies to prepare or compound a radiopharmaceutical on the order of a physician before receiving the patient’s name, or, in some states, without ever receiving the patient’s name. Because of the short radioactive half-life of radiopharmaceuticals, hospitals and imaging centers typically place orders for a certain number of nuclear medicine procedures to be conducted during the day or (on Friday) during the weekend. Often, the hospital or imaging center needs to have radiopharmaceutical doses ready in case of emergency, or have them on hand for evening or weekend hours, when the nuclear pharmacy is closed. In these situations, the facility does not know the patient’s name at the time that the radiopharmaceutical is ordered from the nuclear pharmacy, but the patient’s name is provided to the pharmacy a day or several days later, as specified by state law.

Another difference between nuclear pharmacy practice and conventional pharmacy practice is the limited supply chain, which frequently necessitates interstate shipment. Nuclear pharmacies are far fewer in number than conventional pharmacies, and many nuclear pharmacies serve a geographical area that extends across state lines.
Because, as described above, time is of the essence in the dispensing and shipping of a radiopharmaceutical, a hospital or imaging center may need to rely on an out-of-state nuclear pharmacy that is geographically closer than an in-state nuclear pharmacy.

In formulating the guidance below, FDA has taken into account these differences in routine practice between nuclear pharmacies and traditional pharmacies.

III. DEFINITIONS

**Bulk drug substance** means any substance that is represented for use in a radiopharmaceutical and that, when used in the manufacturing, processing, or packaging of a radiopharmaceutical, becomes an active ingredient, or becomes incorporated into an active ingredient, in the finished dosage form of the radiopharmaceutical. A bulk drug substance may or may not be radioactive, and may be a component of a non-radioactive reagent kit that is used in the preparation of a radiopharmaceutical.

**Compounding** means the combining, admixing, mixing, diluting, reconstituting, or otherwise altering of an FDA-approved radiopharmaceutical, or preparing a radiopharmaceutical from bulk drug substances. Compounding does not include the reconstituting, diluting, mixing, or other such activities performed in accordance with specific directions contained in the approved labeling provided by the product’s manufacturer and other manufacturer directions consistent with that labeling. Compounding also does not include a minor deviation from such directions with regard to radioactivity, volume, or stability, which is made by or under the supervision of a licensed nuclear pharmacist or a physician, and which is necessary in order to accommodate circumstances not contemplated in the manufacturer’s instructions, such as the rate of radioactive decay or geographical distance from the patient. For purposes of this Compliance Policy Guide, compounding also does not include preparation of a radiopharmaceutical by an outsourcing facility registered with FDA pursuant to FDC Act Section 503B, and this Compliance Policy Guide does not apply to such a radiopharmaceutical.

**Radiopharmaceutical** means any substance defined as a drug in Section 201(g) of the FDC Act, 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 that contain trace quantities of naturally occurring radionuclides. The term includes a radioactive biological product as defined in 21 C.F.R. § 600.3(ee).

IV. POLICY

This section clarifies how FDA will exercise enforcement discretion with respect to the compounding of radiopharmaceuticals. FDA will not take action against nuclear

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2 See 21 C.F.R. § 310.3(n).
FDA will exercise its discretion not to initiate enforcement if a compounded radiopharmaceutical meets the following conditions:

1. **Licensed Nuclear Pharmacy**

   The radiopharmaceutical is compounded by, or under the supervision of:

   (a) a licensed pharmacist in a state-licensed pharmacy that also holds a radioactive materials license issued by the Nuclear Regulatory Commission (NRC) or by a State pursuant to an agreement with the NRC under Section 274 of the Atomic Energy Act of 1954 (42 U.S.C. § 2021) (an “Agreement State”), or

   (b) a physician who is authorized to compound drugs under State law and is recognized as an Authorized User on a radioactive materials license issued by the NRC or an Agreement State.

2. **Valid Prescription or Order**

   The radiopharmaceutical is compounded and dispensed based on a valid prescription order that identifies an individual patient, and that is received from a licensed practitioner authorized by state law to prescribe drugs. A radiopharmaceutical may also be compounded and dispensed pursuant to an order that does not identify an individual patient if such order is received from a health care practitioner within a physician’s office, hospital, or other health care facility, and if the name of the patient is later submitted to the pharmacist if required by, and as required by, State law.

3. **USP Compounding Chapters**

   The radiopharmaceutical is compounded in accordance with the chapters on pharmacy compounding in the United States Pharmacopoeia (USP).
4. Bulk Drug Substances

Bulk drug substances (including radioisotopes) used in the compounding of the radiopharmaceutical are FDA-approved products or components of FDA-approved products, or comply with an applicable USP or National Formulary (NF) monograph, if one exists. In addition, each bulk drug substance must be manufactured in an establishment registered with FDA under FDC Act Section 510, and should be accompanied by a valid certificate of analysis.

5. Inactive ingredients

Inactive ingredients used in the compounded radiopharmaceutical product comply with an applicable USP or NF monograph, if one exists.

6. Copies of Approved Products

The radiopharmaceutical compound is not essentially a copy of a commercially available radiopharmaceutical. The term “essentially a copy of a commercially available radiopharmaceutical” does not include:

(a) A compounded radiopharmaceutical product in which there is a change that produces for an identified individual patient a clinical difference, as determined and documented by the prescribing practitioner, between the compounded radiopharmaceutical and the comparable approved radiopharmaceutical. Examples of such changes could include the following:

- A change in inactive ingredients is necessary for a particular identified patient because of the potential for sensitivity or allergic reaction.

- A particular identified patient requires a dosage form, a radioactive dose, or a mass dose that cannot be prepared using commercially available product – for example, an I-131 NaI capsule compounded for a patient who requires a dosage that is not available from the manufacturer; or a reduced particle count Tc-99m MAA compounded for a one-lung adult; or an I-123 oral solution compounded for a pediatric patient.

(b) A radiopharmaceutical product that appears on the drug shortage list established under FDC Act Section 506E.

(c) A radiopharmaceutical product that is the same as a product that was approved by FDA but was withdrawn from the market by the manufacturer for reasons unrelated to safety or efficacy.
7. Interstate Distribution

The nuclear pharmacy does not distribute inordinate amounts of compounded radiopharmaceuticals interstate. FDA considers interstate distribution of compounded radiopharmaceuticals to be inordinate if the number of compounded radiopharmaceutical prescriptions that are distributed annually to locations that are not within the state in which the nuclear pharmacy is located, or an immediately contiguous state, is greater than 20% of the total number of prescriptions dispensed or distributed (including both intrastate and interstate) by the nuclear pharmacy. This limitation on interstate distribution does not apply to inter-company transfers.

8. Drugs on “Withdrawn or Removed” List

Neither the radiopharmaceutical, or any of its components, appears on FDA’s list of drug products that have been withdrawn or removed from the market because they have been found to be unsafe or not effective (21 C.F.R. § 216.24).

9. Resale

The compounded radiopharmaceutical is not offered at wholesale or to other entities for resale. This does not prohibit a nuclear pharmacy from selling a compounded radiopharmaceutical to a health care entity for administration to a patient.

10. Demonstrated Difficulties for Compounding

The compounded radiopharmaceutical is not identified (directly or as part of a category of drugs) on a list, published by FDA pursuant to FDC Act Section 503B(a)(6), of drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients.