Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Edisa L. Gozun, CDER Office of Unapproved Drugs and Labeling Compliance (OUDLC) at 301-796-3110.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Compliance/OUDLC

December 2016
Compounding and Related Documents

Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities

Guidance for Industry

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Compliance/OUDLC

December 2016
Compounding and Related Documents

TABLE OF CONTENTS

Guidance for Industry[1]
Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or the Agency) on this topic. It does not create any rights for any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION AND SCOPE

This guidance sets forth the FDA's policy regarding the compounding and repackaging of radiopharmaceuticals for human use by State-licensed nuclear pharmacies and Federal facilities that are not registered as outsourcing facilities.[2]

Under current law, radiopharmaceuticals that are compounded by entities that are not registered with FDA as outsourcing facilities, and radiopharmaceuticals that are repackaged, are subject to all applicable provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) related to the production of drugs. Because Congress explicitly excluded radiopharmaceuticals from section 503A of the FD&C Act,[3] compounded radiopharmaceuticals are not eligible for the exemptions under section 503A from section 505 (concerning new drug approval requirements), section 502(f)(1) (concerning labeling with adequate directions for use), and section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP) requirements). In addition, Congress did not exempt repackaged radiopharmaceuticals from any provisions of the FD&C Act.

FDA is issuing this guidance to describe the conditions under which the Agency does not intend to take action for violations of sections 505, 502(f)(1), and 501(a)(2)(B) of the FD&C Act when

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER) in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

[2] *Outsourcing facility* refers to a facility that meets the definition of an outsourcing facility under section 503B(d)(4) of the FD&C Act.

[3] Section 503A of the FD&C Act describes the conditions that must be met for drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to qualify for exemptions from sections 505, 502(f)(1), and 501(a)(2)(B) of the FD&C Act. Section 503A(d)(2) of the FD&C Act states that "this section shall not apply to . . . radiopharmaceuticals."

a State-licensed nuclear pharmacy or a Federal facility that is not an outsourcing facility compounds or repackages radiopharmaceuticals for human use.[4]

This guidance ***does not address*** the following:

- Mixing, reconstituting, combining, diluting, or repackaging of a radiopharmaceutical, or other such acts, performed in accordance with directions contained in the FDA-approved labeling.
- Production of positron emission tomography (PET) drugs.
- Drug products that are not radiopharmaceuticals.[5]
- Radioactive biological products that are subject to licensure under section 351 of the Public Health Service (PHS) Act.
- Radiopharmaceuticals for use in animals.
- Compounding or repackaging of radiopharmaceuticals by entities that are not State-licensed nuclear pharmacies or Federal facilities.
- Compounding or repackaging of radiopharmaceuticals by outsourcing facilities. See FDA's draft guidance document, *Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities*.
- This guidance does not alter FDA's current regulations and guidances addressing investigational new drugs.

In May 1984, FDA issued guidance for industry on *Nuclear Pharmacy Guideline Criteria for Determining When to Register as a Drug Establishment* to describe activities of a nuclear pharmacy that would require the pharmacy to register as a drug establishment under section 510 of the FD&C Act. When finalized, this guidance will supersede the May 1984 guidance, and FDA intends to withdraw the May 1984 guidance in the *Federal Register* notice announcing the availability of the final version of this guidance.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[4] In addition, the definition of "product" in section 581(13) of the FD&C Act excludes radioactive drugs from the drug supply chain security requirements of the FD&C Act, including section 582.

[5] FDA has issued guidance documents concerning its policies for compounding non-radiopharmaceutical drug products under section 503A of the Act. See, for example, FDA's guidance, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

All FDA guidances are available on the FDA guidance web page. FDA updates guidances regularly. To make sure you have the most recent version of a guidance, always consult the guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

A. Radiopharmaceuticals, Generally

Radiopharmaceuticals are radioactive[6] sterile and non-sterile drugs that are used in nuclear medicine procedures to diagnose, monitor, and treat diseases. Radiopharmaceuticals are used in diagnostic procedures and for therapeutic purposes. For example, during certain diagnostic procedures involving radiopharmaceuticals, the body is exposed to small amounts of radiation to observe organ function. Radiopharmaceuticals used for therapeutic purposes are generally administered in larger amounts to ensure that therapeutic doses of radiation are delivered to specific disease sites.

Some radiopharmaceuticals are produced by a conventional manufacturer and shipped in *hot* (radioactive) multi-dose containers directly to an imaging center or hospital for patient administration. The imaging center or hospital's nuclear pharmacy transfers the radiopharmaceuticals from the multi-dose containers into unit-dose, patient-ready containers, and sometimes manipulates the radiopharmaceuticals in other ways, such as by diluting or pooling them. Other radiopharmaceuticals are produced at the nuclear pharmacy by combining radioactive materials eluted from a generator with non-radioactive *cold kits*. The nuclear pharmacy prepares the radiopharmaceutical product using the components of the kit and adding radioactive material eluted from a generator for administration to a patient.

Because radioactive drugs generally have short half-lives (e.g., minutes, hours, or up to a few days), they must reach the patient for administration soon after they are produced. Therefore, hospitals and imaging centers often place orders with a nuclear pharmacy for delivery of radiopharmaceutical unit-doses for procedures scheduled for the following day or in anticipation of unscheduled nuclear medicine procedures that might take place during the evening or weekend when the nuclear pharmacy is closed.

There are legal restrictions as to who is permitted to obtain, transport, manipulate, and use radioactive drugs. At the Federal level, the Nuclear Regulatory Commission (NRC) has established rules to protect the general public, patients, and radiation workers from unnecessary exposure to radiation.[7] The NRC and those States that have entered into certain agreements with

[6] As used in this guidance, *radiopharmaeutical* and *radioactive drug* have the same meaning and refer to a drug that meets the definition in 21 CFR 310.3(n): "any substance defined as a drug in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive 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 'radioactive drug' includes a 'radioactive biological product' as defined in 600.3(ee) of this chapter." *Radioactive biological product* is defined in 21 CFR 600.3(ee) as "a biological product which is labeled with a radionuclide or intended solely to be labeled with a radionuclide." As stated previously, this guidance does not apply to radioactive biological products.

[7] See 10 CFR parts 19, 20, and 35.

the NRC (Agreement States)[8] issue radioactive materials (RAM) licenses that describe who is licensed to possess radioactive materials and the type of radioactive material that may be possessed under the license. An authorized nuclear pharmacist, as defined by the NRC,[9] must be identified on a RAM license issued to a nuclear pharmacy where radiopharmaceuticals are prepared. Transport of radioactive materials is regulated by the NRC or the Agreement State and the U.S. Department of Transportation.[10]

Separate from the RAM licenses issued by the NRC or an Agreement State, State boards of pharmacy may issue pharmacy permits to holders that receive, prepare, repackage, and/or dispense radioactive drugs. Certain States specifically recognize a separate category of pharmacists who practice as nuclear pharmacists and issue credentials specific for this practice.

B. Terminology

1. Compounding

In this guidance, FDA regards *compounding* as the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug.

In some cases, State-licensed nuclear pharmacies compound a radiopharmaceutical from an FDA-approved drug product with one or more minor deviations (as described below) that are necessary to accommodate circumstances not contemplated in the FDA-approved labeling, such as the rate of radioactive decay or geographical distance from the patient.

For purposes of this guidance, FDA regards a *minor deviation* as a change from the approved labeling in radioactivity, volume, and/or the step-by-step procedures made when compounding the radiopharmaceutical from an FDA-approved drug product in a patient-ready dose. For example:

- A minor deviation in radioactivity may include the addition of a supplemental amount of Tc-99m sodium pertechnetate to an FDA-approved kit already containing that ingredient, so that the radiopharmaceutical can be provided to a geographically distant patient with a later use time.
- A minor deviation in volume may include the use of an additional quantity of normal saline to reduce the concentration of the radiopharmaceutical in cases in which a supplemental amount of Tc-99m sodium pertechnetate has been added, as described above. In such cases, the additional radioactivity may necessitate a corresponding increase in volume so that the quantity of the radiopharmaceutical to be drawn up into a unit-dose syringe can be more precisely measured.

[8] The NRC defines an Agreement State in part as one that has entered into an agreement with the NRC under section 274 of the Atomic Energy Act of 1954 (42 U.S.C. 2021).

[9] See 10 CFR 35.2

[10] See 10 CFR 71.5, 49 CFR parts 107, 171 through 180, and 390 through 397.

- A minor deviation in the step-by-step procedures for preparation may be one that results in the same finished radiopharmaceutical, but incorporates improvements in technology, enhanced quality control procedures, or decreased radiation exposure to pharmacy personnel.

In other circumstances, manipulations of a radiopharmaceutical involve more significant deviations from the directions in FDA-approved labeling, or a radiopharmaceutical might be produced from a bulk drug substance. For example, to meet the needs of an identified individual patient, such as a patient with an allergy to a particular ingredient, a nuclear pharmacist might compound a radiopharmaceutical that differs from an FDA-approved radiopharmaceutical in its inactive ingredients, dosage form, or mass dose.

There are also circumstances in which nuclear pharmacists compound radiopharmaceuticals from bulk drug substances when the FDA-approved radiopharmaceutical is discontinued or appears on the FDA drug shortage list.

2. Repackaging

FDA regards *repackaging* as the act of removing an FDA-approved radiopharmaceutical from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the product. Repackaging also includes the act of placing the contents of multiple containers (e.g., vials) of the same finished drug product into one container, as long as the container does not include other ingredients. If a radiopharmaceutical is manipulated in any other way, including if it is reconstituted, diluted, mixed, or combined with another ingredient, that act is not considered repackaging.

III. POLICY

As stated above, radiopharmaceuticals are generally not exempt from provisions of the FD&C Act related to the production of drugs.[11] For example, radiopharmaceuticals are subject to the premarket approval, misbranding and adulteration provisions of the FD&C Act, including section 505, section 502(f)(1), and section 501(a)(2)(B).

FDA recognizes that, although radiopharmaceuticals are not eligible for the exemptions in section 503A of the FD&C Act, there are circumstances in which State-licensed nuclear pharmacies and Federal facilities compound or repackage radiopharmaceuticals to meet patient needs. FDA has developed this guidance to explain the conditions under which it does not intend to take action regarding violations of certain requirements of the FD&C Act when radiopharmaceuticals are compounded or repackaged by State-licensed nuclear pharmacies or Federal facilities that are not outsourcing facilities.

[11] But see section 503B of the FD&C Act. FDA has addressed compounding of radiopharmaceuticals by outsourcing facilities under section 503B of the FD&C Act in the draft guidance document, *Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities*.

Although radiopharmaceuticals addressed by this guidance are subject to the adulteration, misbranding, and new drug approval provisions of the FD&C Act, FDA does not intend to take action for violations of sections 505, 502(f)(1), and 501(a)(2)(B) of the Act if a State-licensed nuclear pharmacy or a Federal facility that is not an outsourcing facility compounds or repackages radiopharmaceuticals in accordance with the conditions described in Section A or B below, whichever is applicable, and any other applicable requirements.[12]

A. Radiopharmaceutical Compounding That Involves Manipulation Other Than *Minor Deviations*

The conditions referred to above for compounding of a radiopharmaceutical other than *minor deviations* are as follows:

1. The radiopharmaceutical is compounded by or under the direct supervision of a licensed, authorized nuclear pharmacist[13] in a State-licensed nuclear pharmacy or a Federal facility that holds a RAM issued by the NRC or by an Agreement State.

2. The radiopharmaceutical is distributed[14] after the receipt of a valid prescription order for an identified individual patient (which includes an order or a notation in the patient's health record (e.g., chart) in a health care setting).

3. If the radiopharmaceutical is compounded in advance of receipt of a valid patient-specific prescription, it is compounded in a quantity that does not exceed the expected demand for the radiopharmaceutical within the beyond use date (BUD) of the product, based on a history of receipt of prescriptions for the radiopharmaceutical for that time period. The radiopharmaceutical is not distributed before the receipt of a valid prescription for an identified individual patient.

4. If the radiopharmaceutical is compounded using bulk drug substance(s), the bulk drug substance(s) comply with the standards of an applicable United States Pharmacopoeia (USP) or National Formulary (NF) monograph, if a monograph exists. If a monograph does not exist, the bulk drug substance(s) are components of a drug product approved under section 505 of the FD&C Act. For purposes of this condition, a bulk drug substance includes a radioisotope, a ligand, or other substance, such as a precursor that becomes an active ingredient.[15]

[12] Applicable requirements include, for example, the requirement that manufacturers not adulterate a radiopharmaceutical by preparing, packing, or holding the drug product under insanitary conditions. See section 501(a)(2)(A) of the FD&C Act.

[13] See definition of an *authorized nuclear pharmacist* at 10 CFR 35.2.

[14] *Distributed* means that the compounded or repackaged radiopharmaceutical has left the facility in which it was compounded or repackaged.

[15] FDA considers cold kits to be finished drug products. Therefore, a radiopharmaceutical compounded from the components of a cold kit is not subject to conditions of this guidance concerning bulk drug substances.

5. If the radiopharmaceutical is compounded using bulk drug substance(s), the original manufacturer of the bulk drug substance(s) and any subsequent manufacturers, including repackers, are establishments that are registered under section 510 of the FD&C Act (including a foreign establishment that is registered under section 510(i) of the FD&C Act), and each bulk drug substance is accompanied by a valid certificate of analysis. For purposes of this condition, *original manufacturer* means the entity that originally produced the bulk drug substance and not a subsequent packer, repacker, labeler, or distributor.

6. Radiopharmaceuticals may also contain other inactive ingredients such as a buffer, a stabilizer, or a preservative. If the radiopharmaceutical is compounded using ingredient(s) other than bulk drug substances, the ingredients comply with the standards of an applicable USP or NF monograph, if a monograph exists.

7. The radiopharmaceutical is compounded in compliance with the following USP Chapters:
    - If it is a non-sterile radiopharmaceutical, it is compounded in accordance with USP Chapter <795> (except for the BUD); or
    - If it is sterile radiopharmaceutical, it is produced in accordance with USP <797> (except for the BUD).

8. The compounded radiopharmaceutical does not appear on a list of drug products that have been withdrawn or removed from the market because they have been found to be unsafe or not effective. For purposes of this condition, refer to the "withdrawn or removed list" at 21 CFR 216.24.

9. The compounded radiopharmaceutical is not essentially a copy of a marketed FDA-approved radiopharmaceutical.

    FDA considers a compounded radiopharmaceutical to be essentially a copy of a marketed FDA-approved radiopharmaceutical if:

    - the compounded radiopharmaceutical has the same active ingredient(s) as the approved radiopharmaceutical;
    - the active ingredient(s) in the compounded radiopharmaceutical have the same or similar dosage strength (i.e., radioactive dose)[16] as the active ingredient(s) in the approved radiopharmaceutical;
    - the approved radiopharmaceutical can be used by the same route of administration as prescribed for the compounded radiopharmaceutical;
    - the approved radiopharmaceutical is not on FDA's drug shortage list (see section 506E of the FD&C Act) at the time of compounding and distribution; and
    - the approved product has not been discontinued and is currently marketed,

[16] *Similar strength* means that the strength of the compounded radiopharmaceutical is within 10% of the strength of the approved radiopharmaceutical.

unless there is a change that produces for an identified individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded radiopharmaceutical and the comparable FDA-approved radiopharmaceutical, and the prescriber's determination is documented in writing on the prescription or order by either (1) the prescribing practitioner, or (2) the compounder, reflecting a conversation with the prescribing practitioner.

If a compounder intends to rely on such a determination, the determination is documented on the prescription. This condition will be satisfied provided that the prescription makes clear that the prescriber identified the relevant change and the clinical difference produced for the patient, regardless of format. For example, the following would be sufficient for this condition:

- "No Dye X, patient allergy" (if the comparable approved drug contains the dye)

However, if a prescription identifies only a patient name and radiopharmaceutical formulation, this would not be sufficient to establish that the prescriber made the determination described in this condition. Note also that to satisfy this condition, the clinical difference that the prescriber identifies must be produced by the change the compounder will make to a radiopharmaceutical (i.e., a change in drug product formulation). Other factors, such as a lower price, are not sufficient to establish that the compounded radiopharmaceutical is not essentially a copy of the approved radiopharmaceutical.

10. The radiopharmaceutical that is being compounded is not identified (directly or as part of a category of drugs) on a list 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. For purposes of this condition, refer to the list in FDA regulations at 21 CFR part 216.[17]

11. The compounded radiopharmaceutical is not sold or transferred by an entity other than the entity that compounded such radiopharmaceutical. For purposes of this condition, a sale or transfer does not include administration of a compounded radiopharmaceutical in a health care setting.

12. The compounded radiopharmaceutical is distributed only in States in which the compounding of the radiopharmaceutical meets all applicable State requirements.

13. The radiopharmaceutical is compounded in accordance with all applicable requirements of the NRC (e.g., labeling requirements[18]) in a facility that meets all applicable

[17] This list has not yet been developed.

[18] See 10 CFR 20.1904.

requirements of the NRC, and the nuclear pharmacist who compounds or supervises the compounding of the radiopharmaceutical meets all applicable NRC requirements.

B. Radiopharmaceutical Compounding that Constitutes *Minor Deviations*, and Repackaging

The conditions referred to above for compounding of a radiopharmaceutical that is limited to *minor deviations*, as defined above, or to the repackaging of a radiopharmaceutical, are as follows:

1. The radiopharmaceutical is compounded or repackaged from a drug product approved under section 505 of the FD&C Act.

2. No substances are added to the radiopharmaceutical unless they are specified in the FDA-approved labeling for the radiopharmaceutical being compounded.

3. If the radiopharmaceutical is compounded (and not repackaged), the compounding constitutes a *minor deviation(s)*, as that term is defined above.

4. The radiopharmaceutical is compounded or repackaged by or under the direct supervision of a licensed authorized nuclear pharmacist in a State-licensed nuclear pharmacy or a Federal facility that also holds a RAM license issued by the NRC or an Agreement State.

5. The radiopharmaceutical is compounded or repackaged in compliance with the following USP Chapters:
    - If it is a non-sterile radiopharmaceutical, it is compounded or repackaged in accordance with USP Chapter <795> (except for the BUD); or
    - If it is sterile radiopharmaceutical, it is compounded or repackaged in accordance with USP <797> (except for the BUD).

6. The radiopharmaceutical is compounded or repackaged in accordance with all applicable requirements of the NRC (e.g., labeling requirements[19]) in a facility that meets all applicable requirements of the NRC, and the nuclear pharmacist who compounds or repackages, or who supervises the compounding or repackaging of the radiopharmaceutical, meets all applicable NRC requirements.

7. The compounded or repackaged radiopharmaceutical is distributed only in States in which the compounding or repackaging of the radiopharmaceutical meets all applicable State requirements.

8. The compounded or repackaged radiopharmaceutical is not sold or transferred by an entity other than the entity that compounded or repackaged such radiopharmaceutical.

[19] See 21 CFR 20.1904.

For purposes of this condition, a sale or transfer does not include administration of a compounded or repackaged radiopharmaceutical in a health care setting.

C. Establishment Registration and Drug Listing

Under section 510(b)(1) of the FD&C Act, between October 1 and December 31 of each year, every person who owns or operates any establishment in any State engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs is required to register with FDA, and under section 510(j) of the FD&C Act, every person who registers with FDA under section 510(b) must list its drugs with the Agency. Pharmacies that compound or repackage radiopharmaceuticals may qualify for an exemption from registration and thus not be required to list. Specifically, under section 510(g)(1), the registration and listing requirements do not apply to:

> pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail.

With respect to entities that do not qualify for the exemptions from registration under section 510 of the FD&C Act,[20] FDA does not intend to take action under section 502(o) of the FD&C Act for failure to register and list radiopharmaceuticals that are compounded or repackaged in accordance with this guidance.

[20] *See* also, 21 CFR 207.10.