Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities

Guidance for Industry

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

September 2018
Compounding and Related Documents

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Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION AND SCOPE

This guidance sets forth the FDA's policy regarding compounding and repackaging of radiopharmaceuticals for human use by entities that are registered with FDA as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act). This guidance describes how FDA generally intends to apply section 503B of the FD&C Act to radiopharmaceuticals compounded by outsourcing facilities. It also describes the conditions under which FDA generally does not intend to take action for violations of sections 505 and 502(f)(1) of the FD&C Act when an outsourcing facility repackages radiopharmaceuticals.

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
- Positron emission tomography (PET) drugs
- Drug products that are not radiopharmaceuticals[2]
- Radioactive biological products that are subject to licensure under section 351 of the Public Health Service (PHS) Act
- Radiopharmaceuticals for use in animals

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

[2] FDA has issued several guidance documents concerning its policies for compounding drug products that are not radiopharmaceuticals under sections 503B of the FD&C Act. See, for example, *Guidance For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B 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.

- Compounding or repackaging of radiopharmaceuticals by entities that are not registered with FDA as outsourcing facilities. See FDA guidance o *Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies, Federal Facilities, and Certain Other Entities*

This guidance does not alter FDA's current guidances addressing investigational new drugs.

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.

II. BACKGROUND

A. Radiopharmaceuticals, Generally

Radiopharmaceuticals are radioactive[3] sterile and non-sterile drugs that are used to diagnose, monitor, and treat diseases. Radiopharmaceuticals are used in diagnostic procedures and for therapeutic purposes. For example, during 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's "hot lab" 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 radionuclide generator with non-radioactive "cold kits." The nuclear pharmacy prepares the radiopharmaceutical product using the components of the kit and by adding radioactive material eluted from a radionuclide generator for eventual administration to a patient.

[3] As used in this guidance, *radiopharmaceutical* 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.

Because radioactive drugs generally have short half-lives (e.g., hours, 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.[4] The NRC and those states that have entered into certain agreements with the NRC (Agreement States)[5] issue radioactive materials (RAM) licenses to authorize possession of specific types of radioactive materials and who may use the material under the license.[6] Transport of radioactive materials is regulated by the NRC or the Agreement State and the U.S. Department of Transportation.[7]

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, 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. Compounding, Generally

1. Compounding of Radiopharmaceuticals By an Outsourcing Facility

In 2013, the Drug Quality and Security Act added a new section 503B to the FD&C Act, which describes a new category of compounders called *outsourcing facilities*.[8] Section 503B of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility to qualify for exemptions from the following three sections of the FD&C Act:

- Section 502(f)(1) (concerning labeling with adequate directions for use)
- Section 505 (concerning drug approval requirements)
- Section 582 (concerning drug supply chain security requirements)[9]

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

[5] 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).

[6] See 10 CFR 35.2

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

[8] See Pub..L. 113-54, §102(a), 127 Stat. 587, 587-588 (2013).

[9] In addition to the exemption in section 503B, 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.

A complete list of the conditions that must be met for a drug product to qualify for the exemptions in section 503B appears in the Appendix to this guidance document.

In contrast to drug products compounded under section 503A of the FD&C Act, drug products compounded by outsourcing facilities under section 503B cannot qualify for exemption from current good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act. Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks associated with the drug products they compound.

Section 503B of the FD&C Act defines *compounding* as including "the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug."[10] In contrast to section 503A of the FD&C Act, section 503B does not expressly exclude radiopharmaceuticals, so the conditions of section 503B of the FD&C Act apply to radiopharmaceuticals compounded by an entity that is registered with FDA as an outsourcing facility.

Because section 503B applies to the compounding of radiopharmaceuticals, an entity is eligible to become an outsourcing facility if some or all of its operations consist of compounding radiopharmaceuticals for human use, provided that the entity otherwise meets the definition of an *outsourcing facility* in section 503B(d)(4) of the FD&C Act (e.g., the entity must engage in the compounding of at least some sterile products (radiopharmaceuticals or non-radiopharmaceuticals)).[11]

2. Repackaging

FDA regards *repackaging of radiopharmaceuticals* 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 drug. 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 under this guidance.

Drugs that are repackaged are not subject to section 503B of the FD&C Act. Therefore, repackaged radiopharmaceuticals are not eligible for the exemptions under section 503B. Additionally, an entity that <u>only</u> repackages drugs, including radiopharmaceuticals, does not meet the definition of an *outsourcing facility* in section 503B(d)(4) of the FD&C Act. However, if an entity that meets the definition of an *outsourcing facility* in section 503B(d)(4) also

[10] See section 503B(d)(1).

[11] See Section 503Bf(d)(4)A)(i). Section 503B(d)(4) defines an *outsourcing facility* as a facility at one geographic location or address that is engaged in the compounding of sterile drugs; has elected to register as an outsourcing facility; and complies with all of the requirements of Section 503B. An outsourcing facility is not required to be a licensed pharmacy and may or may not obtain prescriptions for identified individual patients.

repackages radiopharmaceuticals, FDA generally does not intend to take action for violations of sections 505 and 502(f)(1) of the FD&C Act when the outsourcing facility repackages radiopharmaceuticals in accordance with the conditions described below and any other applicable requirements. Further, the outsourcing facility's compounded drugs would be eligible for the exemptions in section 503B if they meet the conditions in that section. We describe our policies with respect to repackaged and compounded radiopharmaceuticals in section III of this guidance document.

III. POLICY

A. Compounding of Radiopharmaceuticals By an Outsourcing Facility

1. Compounding

Outsourcing facilities that compound radiopharmaceuticals must do so in accordance with the conditions of section 503B of the FD&C Act (see the Appendix to this guidance document). If an outsourcing facility fails to compound a drug in accordance with a condition of section 503B, none of the outsourcing facility's compounded drugs, including radiopharmaceuticals and non-radiopharmaceuticals, would qualify for the exemptions in section 503B.[12]

In general, FDA's policies regarding section 503B apply to the compounding of radiopharmaceutical drug products by outsourcing facilities. However, we have developed the following specific policies, applicable only to the compounding of radiopharmaceuticals by outsourcing facilities:

- Bulk drug substances used in compounding radiopharmaceuticals under section 503B (see section III.A.2)
- Compounding radiopharmaceuticals that are essentially copies of approved drugs under section 503B when such compounding is limited to *minor deviations*, as defined below (see section III.A.3).

2. Bulk Drug Substances Used to Compound Radiopharmaceuticals Under Section 503B of the FD&C Act[13]

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for the exemptions provided by 503B is that the outsourcing facility does not compound drug products using a bulk drug substance unless: (1) the bulk drug substance appears on a list developed by FDA of bulk drug substances for which there is a clinical need (503B

[12] See sections 503B(a)(11) and 503B(d)(4) of the FD&C Act.

[13] FDA considers cold kits to be finished drug products. Therefore, preparation of a radiopharmaceutical from the components of a cold kit according to FDA approved labeling is not compounding. However, if an ingredient is added, or if the cold kit is otherwise manipulated in a manner not considered a minor deviation, it would be considered compounding under this guidance.

bulks list);[14] or (2) the drug compounded from such bulk drug substance appears on the drug shortage list in effect under section 506E of the FD&C Act (the FDA's drug shortage list) at the time of compounding, distribution,[15] and dispensing.[16]

FDA solicited nominations for bulk drug substances for inclusion on the 503B bulks list; however, FDA's request for nominations for the 503B bulks list reserved the question of compounded radiopharmaceutical products, and only one radiopharmaceutical was nominated for the 503B bulks list.[17]

At this time, interested parties can nominate substances for inclusion on the 503B bulks list,[18] and they will be evaluated as described in the FDA guidance for industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. FDA has also published draft guidance for industry *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. This guidance, when finalized, will set forth the Agency's interpretation of bulk drug substances for which there is a clinical need and the statutory standard for including a bulk drug substance on the 503B bulks list, including radiopharmaceuticals.

3. Compounded Radiopharmaceuticals That Are Essentially Copies of Approved Drugs

Under section 503B(a)(5) of the FD&C Act, a compounded drug that is essentially a copy of one or more approved drugs is not eligible for the exemptions under section 503B of the FD&C Act.

In some cases, an outsourcing facility might receive a prescription or order for a radiopharmaceutical compounded from an FDA-approved radiopharmaceutical, with one or more *minor deviations* (see 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 that does not adversely affect the quality of the product made when compounding the radiopharmaceutical from an FDA-approved drug product in a patient-ready dose. If the deviation adversely impacts product quality, then such change would not be minor. Examples of *minor deviations* include:

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[14] See section 503B(a)(2)(A)(i) of the FD&C Act.

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

[16] See Section 503B(a)(2)(A)(ii).

[17] See the guidance, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

[18] Nominations of bulk drug substances to be used in compounding radiopharmaceuticals should be submitted to Docket No. FDA-2015-N-3469. See 80 FR 65770 and the guidance, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

- The addition of a supplemental amount of Tc-99m sodium pertechnetate to an FDA-approved kit, so that the radiopharmaceutical can be provided to a patient with a later use time.
- 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.
- A minor deviation in the step-by-step procedures for preparation that may result in the same finished radiopharmaceutical, but incorporates improvements in technology or decreased radiation exposure to pharmacy personnel.
- The use of enhanced quality control procedures that have been shown to be equivalent or superior to the recommended procedures.

A compounded radiopharmaceutical that is prepared with *minor deviations* from the directions contained in FDA-approved labeling provided by the product's manufacturer may meet the definition of *essentially a copy of an approved drug* under section 503B(d)(2).[19] However, FDA recognizes that for practical reasons radiopharmaceuticals might be compounded with *minor deviations* from an approved radiopharmaceutical, including for the reasons listed above. After considering the risks associated with these practices we generally do not intend to focus enforcement on such compounding. Specifically, FDA generally does not intend to take action against an outsourcing facility for compounding a radiopharmaceutical that is essentially a copy of an approved drug and, thus, does not meet the condition of section 503B(a)(5) of the FD&C Act, provided that the outsourcing facility:

- Compounds the radiopharmaceutical from FDA-approved radiopharmaceuticals, and not using bulk drug substances;
- Makes *minor deviations* from the approved product labeling, as defined above; and
- Compounds all of its drugs in accordance with all of the other conditions of section 503B and all other applicable statutory and regulatory requirements.

B. Repackaging of Radiopharmaceuticals

Outsourcing facilities sometimes receive a prescription or order for a radiopharmaceutical product that differs from an approved radiopharmaceutical only in that it has been repackaged. As discussed above, repackaged drug products are not eligible for the exemptions provided under section 503B of the FD&C Act. In addition, repackaged radiopharmaceuticals are generally not exempt from any of the provisions of the FD&C Act related to the production of drugs, including

[19] See FDA guidance for industry *Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. This guidance describes FDA's current thinking on compounding drug products that are essentially copies of approved drugs under section 503B.

the premarket approval, misbranding, and adulteration provisions of the FD&C Act, including sections 505,[20] 502(f)(1), and 501(a)(2)(B).

Below, FDA describes the conditions under which it generally does not intend to take action regarding violations of certain requirements of the FD&C Act, in the context of radiopharmaceutical repackaging. Specifically, FDA generally does not intend to take action for violations of sections 505 and 502(f)(1)[21] if an outsourcing facility repackages radiopharmaceuticals in accordance with the conditions described below, and any applicable requirements other than sections 505, 502(f)(1) of the FD&C Act.[22] The Agency may take other factors into consideration when determining whether enforcement is appropriate in a particular case.

Conditions:

1. The radiopharmaceutical that is being repackaged is a drug product approved under section 505 of the FD&C Act.

2. The radiopharmaceutical is repackaged by or under the direct supervision of a licensed, authorized nuclear pharmacist[23] in an outsourcing facility that holds a RAM license issued by the NRC or by an Agreement State.

3. The radiopharmaceutical is repackaged in accordance with applicable CGMP requirements.[24]

4. The radiopharmaceutical is stored and shipped in a way that consistent with approved drug product labeling.

5. The radiopharmaceutical being repackaged does not appear on a list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness.[25]

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[20] However, see U.S. v. Kaybel, 430 F.2d 1346 (3d Cir. 1970), holding that repackaging of approved Enovid (estrogen) tablets from large bottles into small bottles did not require pre-approval under Section 505 of the FD&C Act.

[21] See footnote 8.

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

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

[24] See FDA draft guidance for industry *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*. Once final, this guidance will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated.

[25] See 21 CFR 216.24.

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

7. The repackaged radiopharmaceutical is distributed only in states in which the production of the radiopharmaceutical meets all applicable state requirements.

8. The radiopharmaceutical is repackaged in accordance with all applicable requirements of the NRC or Agreement State (e.g., labeling requirements[26]) by a facility that meets all applicable requirements of the NRC or Agreement State, and the authorized nuclear pharmacist who repackages or supervises the repackaging of the radiopharmaceutical meets all applicable NRC or Agreement State requirements.

9. The label on the immediate container (primary packaging) of the repackaged radiopharmaceutical includes the following:

    a. The statement "This radiopharmaceutical was repackaged by [name of outsourcing facility]."

    b. The address and phone number of the outsourcing facility that repackaged the radiopharmaceutical.

    c. The established name of the original, approved radiopharmaceutical that was repackaged.

    d. The lot or batch number of the repackaged radiopharmaceutical.

    e. The dosage form and radioactive dose of the repackaged radiopharmaceutical.

    f. A statement of either the quantity or volume of the repackaged radiopharmaceutical, whichever is appropriate.

    g. The date the radiopharmaceutical was repackaged.

    h. The beyond use date (BUD) of the repackaged radiopharmaceutical.

    i. Storage and handling instructions for the repackaged radiopharmaceutical.

    j. The National Drug Code (NDC) number of the repackaged radiopharmaceutical, if available.[27]

[26] See 10 CFR 20.1904.

[27] The NDC number of the original approved drug product should not be placed on the repackaged drug product.

k. The statement "Not for resale" and, if the repackaged radiopharmaceutical is distributed by an outsourcing facility other than pursuant to a prescription for an individual identified patient, the statement "Office Use Only."

l. A list of the active and inactive ingredients, unless such information is included on the label for the container from which the individual units are removed, as described below in condition 9.a.

10. The label on the container from which the individual units are removed for administration (secondary packaging (e.g., the bag, box, or other package in which the repackaged products are distributed)) includes:

    a. The active and inactive ingredients, if the immediate drug product label is too small to include this information

    b. Directions for use, including, as appropriate, radioactive dosage and administration, and the following information to facilitate adverse event reporting: www.fda.gov/medwatch and 1-800-FDA-1088.

11. The radiopharmaceutical is included on a report submitted to FDA each June and December identifying the drug products repackaged by the outsourcing facility during the previous 6-month period, and providing the active ingredient(s); source of the active ingredient(s); NDC number of the source ingredient(s), if available; the dosage form and route of administration; the package description; the number of individual units produced; and the NDC number of the final product, if assigned.[28]

12. The outsourcing facility reports serious adverse events to FDA that may be associated with its repackaged radiopharmaceuticals.[29]

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

[28] FDA has issued guidance for industry *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, which describes how outsourcing facilities are to submit drug product reports to FDA. Once finalized, that guidance will represent the Agency's current thinking on that topic. Although that guidance addresses reporting of compounded drug products, outsourcing facilities should follow the same procedure to electronically report the radiopharmaceuticals they repackaged.

[29] FDA has issued guidance for industry *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, which describes how outsourcing facilities are to submit adverse event reports to FDA and the content and format of the reports that they are required to submit. Although that guidance addresses reporting of adverse events associated with compounded drug products, outsourcing facilities should follow the same procedure to electronically report adverse events associated with the radiopharmaceuticals they repackaged.

under section 510(b) must list its drugs with the Agency. Outsourcing facilities that are state-licensed pharmacies that compound or repackage radiopharmaceuticals may qualify for an exemption from registration and thus also not be required to list their drugs with FDA. 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 outsourcing facilities that do not qualify for the exemptions from registration under section 510 of the FD&C Act,[30] FDA generally 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.

[30] See also 21 CFR 207.10.

APPENDIX

SUMMARY OF STATUTORY CONDITIONS IN SECTION 503B OF THE FD&C ACT

The following are the statutory conditions contained in section 503B that must be met for a compounded drug, including a compounded radiopharmaceutical, to qualify for the exemptions in section 503B of the FD&C Act:

1. The outsourcing facility is in compliance with the registration and reporting requirements of section 503B(b). This includes submitting twice yearly reports regarding the drugs compounded by the outsourcing facility and submitting adverse event reports in accordance with section 503B(b)(5).[31,32]

2. If the outsourcing facility compounds drugs using one or more bulk drug substances, the bulk drug substances meet the requirements of 503B(a)(2). See the policy described in section II.A.2 of this guidance document.

3. If the outsourcing facility compounds using ingredients other than bulk drug substances, those ingredients must meet certain requirements.[33]

4. The outsourcing facility does not compound drugs that appear on a list published by FDA of drugs that have been withdrawn or removed from the market because the drugs or components of such drugs have been found to be unsafe or not effective.[34,35]

5. The outsourcing facility does not compound drugs that are essentially a copy of one or more approved drugs.[36] See the policy described in section II.A.3 of this guidance document.

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[31] See section 301(ccc)(3) of the FD&C Act, which makes it a prohibited act for an entity that is registered in accordance with section 503B(b) to fail to report drugs or adverse events as required.

[32] See sections 503B(a)(1) and (b); FDA final guidance for industry *Registration of Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*, *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, and *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

[33] See section 503B(a)(3).

[34] See section 503B(a)(4).

[35] The list of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (the withdrawn-or-removed list) can be found at 21 CFR 216.24.

[36] See section 503B(a)(5) and FDA guidance for industry *Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

6. The outsourcing facility does not compound drugs that appear on a list published by FDA of drugs that present demonstrable difficulties for compounding.[37]

7. If the outsourcing facility compounds a drug that is the subject of a risk evaluation and mitigation strategy (REMS) approved with elements to assure safe use pursuant to section 505-1, or from a bulk drug substance that is a component of such drug, the outsourcing facility must demonstrate to FDA before beginning to compound that it will use controls comparable to the controls applicable under the REMS.[38]

8. The outsourcing facility's compounded drugs will not be sold or transferred by an entity other than that outsourcing facility.[39]

9. The outsourcing facility has paid all applicable establishment and reinspection fees owed under section 744(k).[40,41]

10. The outsourcing facility includes on the labels and labeling of its compounded drug products the information required under section 503B(a)(10).[42]

11. All of the outsourcing facility's compounded drugs are compounded in accordance with section 503B.[43,44]

[37] See section 503B(a)(6). This list has not yet been developed.

[38] See section 503B(a)(7).

[39] See section 503B(a)(8).

[40] See section 503B(a)(9).

[41] See also sections 744J and 744K of the FD&C Act and FDA guidance for industry *Fees for Human Drug Compounding Outsourcing Facilities Under Sections 503B and 744K of the FD&C Act*.

[42] See section 503B(a)(10).

[43] See section 503B(a)(11).

[44] See FDA guidances for industry *For Entities Considering Whether to Register as Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* and *Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act.*