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BUSINESS, CONSUMER SERVICES AND HOUSING AGENCY
DEPARTMENT OF CONSUMER AFFAIRS
GOVERNOR EDMUND G. BROWN JR.

To: Board Members

Subject: Agenda Item VI. Executive Officer's Report

At the meeting the board will discuss five recent guidance documents released by the FDA -- two are drafts that have been released for public comment, and three are final guidance documents. As part of the discussion, the board will have the opportunity to make a recommendation about whether to submit comments in response to each guidance document.

a. Discussion and Consideration of Possible Board Comments on the FDA's Draft Guidance Documents

1. FDA's Draft Guidance, Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities

Attachment 1

Comments due: February 27, 2017

This guidance document sets forth the FDA's policy regarding compounding and repackaging of radiopharmaceuticals for human use by outsourcing facilities. Below is text paraphrased or copied from the FDA's proposed guidance. This draft guidance describes how FDA intends to apply section 503B of the FD&C Act to radiopharmaceuticals compounded by outsourcing facilities, and it describes the conditions under which FDA does not intend to take action for violations of certain provisions of the FD&C Act when an outsourcing facility repackages radiopharmaceuticals.

The guidance does **not** address:

- Mixing, reconstituting, combing, diluting or repackaging a radiopharmaceutical performed in accordance with directions contained in FDA-approved labeling.
- Positron emission tomography drugs.
- Drug products that are not radiopharmaceuticals.
- Radioactive biological products that are subject to licensure under section 351 of the Public Health Service Act.
- Radiopharmaceuticals for use in animals.
- Compounding or repackaging of radiopharmaceuticals by non-outsourcing facilities,
- Investigational new drugs.

Radiopharmaceuticals are radioactive sterile and nonsterile drugs that are used in nuclear medicine procedures to diagnose, monitor and treat diseases. They are used in diagnostic procedures and typically in larger amounts for therapeutic purposes.

Because radioactive drugs generally have short half-lives (minutes, hours, or up to a few days), they must reach the patient for administration soon after they are produced. Hospitals and imaging centers typically place orders for next day administration.

There are legal restrictions on who may obtain, transport, manipulate and use radioactive drugs. The Nuclear Regulatory Commission has rules to protect workers, patients and the general public. California is a state that has agreements with the NRC to authorize who may possess radioactive materials and the type of material that they may possess. An authorized nuclear pharmacist by be identified on the NRC license which is issued to a nuclear pharmacy where radiopharmaceuticals are prepared. The board also licenses the pharmacies that receive, prepare, repackage and/or dispense radioactive drugs.

Regarding compounding by outsourcers: Section 503B of the federal Food, Drug & Cosmetic Act (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." Section 503B does not exclude radiopharmaceuticals, so the conditions of section 503B of the FD&C Act apply to radiopharmaceuticals compounded by an outsourcing facility. The FDA states that an entity that compounds radiopharmaceuticals may be licensed as an outsourcing facility if it engages in compounding as least some sterile products, whether these sterile products are radiopharmaceuticals or not.

Regarding repackaging by outsourcers: FDA regards repackaging as the act of taking a finished drug product, including a 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 an outsourcing facility repackages radiopharmaceuticals, FDA 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.

Note: Section 505 concerns the approval of drugs under new drug applications or abbreviated new drug applications. Section 502(f)(1) concerns the labeling of drugs with adequate directions for use

The FDA also does not intend to take action against an outsourcing facility for compounding a radiopharmaceutical that is essentially a copy of an approved drug 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, 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.

The guidance also lists a number of conditions that all must apply before the FDA will not take action (pages 8-10).

Staff recommendation: support.

2. FDA's Draft Guidance, Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities

Attachment 2

Comments due: February 2017

This is a companion draft guidance for pharmacies that compound or repackage radiopharmaceuticals.

The FDA states that there are circumstances in which state-licensed nuclear pharmacies and federal facilities compound or repackage radiopharmaceuticals to meet patient needs. This guidance identifies conditions under which the FDA does not intend to take action regarding violations of sections 505, 502(f)(1) and 501(a)(2)(B) the FD&C Act against such facilities.

Note: Section 505 concerns the approval of drugs under new drug applications or abbreviated new drug applications. Section 502(f)(1) concerns the labeling of drugs with adequate directions for use. Section 501(a)(2)(B) concerns requirements for use current good manufacturing practices when preparing medications.

The exemptions are in two categories:

1. Compounding that Involves Manipulation Other Than Minor Deviations, and
2. Radiopharmaceutical Compounding that Constitutes Minor Deviations and Repackaging

Generally, the FDA will require a patient-specific prescription before a nuclear pharmacy can dispense the radiopharmaceutical medication, and while it will permit limited anticipatory compounding by a pharmacy, the FDA expects that the medication will not

be released by the pharmacy until a patient-specific prescription is received. Use of bulk drug substances is very limited and when bulk substances are used, they must be accompanied by a certificate of analysis. The compounded radiopharmaceutical cannot be a copy of a marketed FDA-approved radiopharmaceutical. The radiopharmaceutical cannot appear on a list of drugs that present demonstrable difficulties for compounding. The product cannot be resold or transferred by an entity other than the pharmacy that compounded it. There are 13 total of these restrictions listed in the guidance.

The FDA's guidance for pharmacies also specifies a separate list of conditions that for repackaging of radiopharmaceuticals is permitted:

- The radiopharmaceutical is compounded or repackaged from an FDA approved drug product
- No substances are added unless specified in the FDA approved labeling for the radiopharmaceutical being compounded
- The radiopharmaceutical is compounded pursuant to NRC and state requirements

There are a total of 8 conditions listed for repackaging by nuclear pharmacies.

b. Final Guidance Documents Issued by the FDA:

The board will feature the following final guidance documents in the next *The Script.*

1. FDA Guidance, Prescription Requirement Under Section 503A of the Federal Food, Drug and Cosmetic Act

Attachment 3

Generally this guidance restates the FDA's position that a prescription is required before a pharmacy may compound any medication, except in limited circumstances when it will permit compounding before receipt of a prescription.

The FDA states that while compounded products can serve an important need, they pose a higher risk to patients than FDA approved drugs. This is due to failure to use current good manufacturing practices, failure of pre-market review of the product by FDA, nearly nonexistent inspections by the FDA of pharmacies and physicians that compound, and compounding occurs under unsanitary conditions. As such, the FDA's policy is that pharmacy or physician compounding:

- Is for an identified individual patient
- When compounding of products occurs in advance of receipt of a patient- specific prescription, compounding may occur only in limited quantities
- Drugs are distributed pursuant to a valid patient-specific prescription

The guidance describes valid prescription order for a compounded product, conditions for compounding after receipt of a patient-specific prescription and anticipatory compounding before receipt of a patient- specific order.

The guidance states that: "We recognize that some state boards of pharmacy may authorize the writing of prescriptions that do not include individual patient names. Such prescriptions, however, do not meet the requirement of a patient-specific prescription in section 503A [pharmacies]. Under section 503B, outsourcing facilities can fill such prescription if they meet the requirements of applicable state and federal laws."

Additionally: "Hospitals, clinics and health care practitioners can obtain non-patient-specific compounded drug products from outsourcing facilities under section 503B. Outsourcing facilities, which are subject to CGMP requirements, FDA inspections according to a risk-based schedule, specific adverse event reporting requirements and other conditions that provide greater assurance of the quality of their compounded drug products, may, but need not, obtain prescriptions for identified individual patients prior to distribution of compounded drug products." "Therefore outsourcing facilities can compound and distribute sterile and non-sterile non-patient-specific drug products to hospitals, clinic, and health care practitioners for office use."

2. Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug and Cosmetic Act

Attachment 4

This guidance explains how outsourcing facilities are to report to the FDA the drug products they compound. This "guidance" actually establishes requirements that are binding on outsourcers. An outsourcer is required to provide the FDA at the time it applies for an outsourcing licensure, and twice a year thereafter (June and December) a list anticipating initially, and after operations begin, identifying the drugs that are compounded by the facility during the prior six months. Even if the outsourcer does not produce any products, a report is still due. These items include:

- The active ingredient and strength of active ingredients per unit
- The source of the active ingredient
- The NDC number of the source drug or bulk active ingredient if available
- The dosage form and route of administration
- The package description
- The number of individual units produced
- The NDC number of the final product, if assigned

The report is to be submitted electronically to the FDA. The board will accept copies of this information

3. Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities

Attachment 5

This guidance describes FDA policy with respect to repackaging by state-licensed pharmacies and FDA licensed outsourcers. The guidance pertains to human drug products, excluding radiopharmaceuticals and non-prescription drugs. Repackaging is defined as taking a finished drug product 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. It also includes placing the contents of multiple containers (e.g., vials) of the same product into one container without adding additional ingredients.

Repackaged drug products are subject to the premarket approval, misbranding, adulteration and drug supply chain security provisions of the FD&C Act. Nevertheless, FDA does not intend to take action for violations of sections 505 (new drug applications), 502(f)(1) (labeling with adequate directions for use), section 501(a)(2)(B) (CGMP), and 582 (drug supply chain security) for drug repackaging.

There is a list of more than 13 conditions that will apply when the FDA makes this determination and these appear on pages 5-10 of the guidance.

c. Discussion and Consideration of the Planned Decommissioning of CURES 1.0 by the California Department of Justice on March 5, 2017

Attachment 6

The California Department of Justice recently released a notice that it intends to decommission CURES 1.0 on March 5. This means that the DOJ will no longer operate the initial CURES system, and will solely support CURES 2.0, which was created and released last year. A copy of the DOJ's press release regarding this action is on the board's website and is provided in **Attachment 6.**

d. Discussion and Consideration of a Planned Educational Forum Cohosted by the California State Board of Pharmacy and the Drug Enforcement Administration; Request for Authorization to Award Continuing Education Credits To Attendees

Over the past six years, the board has co-hosted with the Drug Enforcement Administration educational forums for pharmacists on corresponding responsibility, prescription drug abuse and CURES. Board staff has been working on a new program to be offered initially in San Diego in March.

An agenda is under review by the DEA at the time this packet is being prepared. The agenda will be shared with the board during this meeting.

During this meeting, board staff will ask for the board to award CE credit to pharmacists who attend this session.

Attachment 1

Compounding and Repackaging of Radiopharmaceuticals By Outsourcing 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 Sara Rothman, 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 Outsourcing 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

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

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 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 intends to apply section 503B of the FD&C Act to radiopharmaceuticals compounded by outsourcing facilities. It also describes the conditions under which FDA 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), 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 Act. See, for example, *For Entities Considering Whether to Register 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's draft guidance document, *Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities*.
- This guidance does not alter FDA's current regulations and 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 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.

[3] 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.

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.[4] The NRC and those States that have entered into certain agreements with the NRC (Agreement States)[5] 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,[6] 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.[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, 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. Compounding and Repackaging of Radiopharmaceuticals by an Outsourcing Facility

1. Compounding

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)

[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. No.113-54, §102(a), 127 Stat. 587, 587-588 (2013).

- Section 582 (concerning drug supply chain security requirements)[9]

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 and/or non-radiopharmaceuticals)).[11]

2. Repackaging

FDA regards *repackaging* as the act of taking a finished drug product, including a 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.

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[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.

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

[11] See Section 503B(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.

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 only repackages drugs, including radiopharmaceuticals, does not meet the definition of an *outsourcing facility* in section 503B(d)(4) of the FD&C Act. If an entity that meets the definition of an *outsourcing facility* in section 503B(d)(4) also repackages radiopharmaceuticals, FDA 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 of described below and any other applicable requirements. In addition, 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.B of this guidance document.

III. POLICY

A. Compounding of Radiopharmaceuticals

1. General

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. 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

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.

bulks list)[13]; 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, [14] and dispensing.[15]

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. [16]

At this time, interested parties can nominate substances for inclusion on the 503B bulks list,[17] and they will be evaluated as described in FDA's guidance, *Interim Policy for Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. FDA intends to adopt a policy for bulk drug substances nominated for use in compounding radiopharmaceuticals under section 503B that is consistent with the policy described in *Interim Policy for Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

3. Compounded Radiopharmaceuticals that are Essentially Copies of Approved Drugs

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

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 made when compounding the radiopharmaceutical from an FDA-approved drug product in a patient-ready dose. For example:

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[13] See Section 503B(a)(2)(A)(i).

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

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

[16] See the guidance, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf.

[17] 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*.

- 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.
- 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.

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).[18] 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 do not intend to focus enforcement on such compounding. Specifically, FDA does not intend to take action against an outsourcing facility for compounding a radiopharmaceutical that is essentially a copy of an approved drug in violation 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. Repackaged drug products are not eligible for the exemptions provided under section 503B of the 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 the premarket

[18] See FDA's draft guidance, *Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. Once finalized, this guidance will describe FDA's current thinking on compounding drug products that are essentially copies of approved drugs under Section 503B.

approval, misbranding, and adulteration provisions of the FD&C Act, including sections 505,[19] 502(f)(1), and 501(a)(2)(B).

Below, FDA describes the conditions under which it does not intend to take action regarding violations of certain requirements of the FD&C Act, in the context of radiopharmaceutical repackaging. Specifically, FDA does not intend to take action for violations of sections 505 and 502(f)(1)[20] if an outsourcing facility repackages radiopharmaceuticals in accordance with all of the conditions described below, and any applicable requirements.[21]

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[22] 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.[23]

4. 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.[24]

5. 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.

6. The repackaged radiopharmaceutical is distributed only in States in which the production of the radiopharmaceutical meets all applicable State requirements.

[19] But 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.

[20] See footnote 8.

[21] 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.

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

[23] See FDA's draft guidance, *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.

[24] See 21 CFR 216.24.

7. The radiopharmaceutical is repackaged in accordance with all applicable requirements of the NRC (e.g., labeling requirements[25]) by a facility that meets all applicable requirements of the NRC, and the nuclear pharmacist who repackages or supervises the repackaging of the radiopharmaceutical meets all applicable NRC requirements.

8. The label on the immediate container (primary packaging, e.g., the syringe) 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 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[26]
    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.

9. 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.

10. 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

[25] See 10 CFR 20.1904.

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

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.[27]

11. The outsourcing facility reports serious adverse events to FDA that may be associated with its repackaged radiopharmaceuticals. [28]

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. 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,[29] 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.

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[27] FDA has issued a draft 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.

[28] FDA has issued a 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.

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

APPENDIX

The following are the conditions of 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).[30,31]

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.[32]

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.[33,34]

5. The outsourcing facility does not compound drugs that are essentially a copy of one or more approved drugs.[35] See the policy described in section II.A.3 of this guidance document.

6. The outsourcing facility does not compound drugs that appear on a list published by FDA of drugs that present demonstrable difficulties for compounding.[36]

[30] 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.

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

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

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

[34] 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.

[35] See section 503B(a)(5) and FDA's draft guidance document, *Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

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

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.[37]

8. The outsourcing facility's compounded drugs will not be sold or transferred by an entity other than that outsourcing facility.[38]

9. The outsourcing facility has paid all applicable establishment and reinspection fees owed under section 744(k).[39,40]

10. The outsourcing facility includes on the labels and labeling of its compounded drug products the information required under section 503B(a)(10).[41]

11. All of the outsourcing facility's compounded drugs are compounded in accordance with section 503B.[42,43]

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

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

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

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

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

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

[43] See FDA's final guidance, *For Entities Considering Whether to Register as Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, and FDA's draft guidance, *Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act.*

Attachment 2

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
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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

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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.

Attachment 3

Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

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

Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

Additional copies are available from:
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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act

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 concerning certain prescription requirements for compounding human drug products[2] for identified individual patients under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act). It addresses compounding after the receipt of a prescription for an identified individual patient, compounding before the receipt of a prescription for an identified individual patient (anticipatory compounding), and compounding for office use (or office stock).

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 only 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.

[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] This guidance does not apply to drugs compounded for use in animals, to biological products subject to licensure in a biologics license application, or to repackaged drug products. For proposed policies pertaining to compounding drug products from bulk drug substances for use in animals, see FDA's draft guidance, *Compounding Animal Drugs from Bulk Drug Substances*. For proposed policies pertaining to mixing, diluting, and repackaging biological products, see FDA's draft guidance, *Mixing, Diluting, and Repackaging Biological Products Outside the Scope of an Approved Biologics License Application*. For proposed policies pertaining to repackaged drug products, see FDA's draft guidance, *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities*. FDA guidances are available on the FDA website at http://www fda.gov/RegulatoryInformation/Guidances/default htm.

II. BACKGROUND

A. Overview

1. Compounding Under the FD&C Act

Sections 503A and 503B of the FD&C Act address human drug compounding.

Section 503A, added to the FD&C Act by the Food and Drug Administration Modernization Act in 1997, describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from the following three sections of the FD&C Act:

- section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP) requirements);
- section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and
- section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).

A list of the conditions that must be met for a compounded drug product to qualify for the exemptions in section 503A of the FD&C Act appears in the guidance, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

New section 503B, added to the FD&C Act by the Drug Quality and Security Act in 2013, created a new category of compounders called *outsourcing facilities*. 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 three sections of the FD&C Act:

- section 502(f)(1);
- section 505; and
- section 582 (concerning drug supply chain security requirements).

In contrast to drug products compounded under section 503A of the FD&C Act, drug products compounded by outsourcing facilities under section 503B are not exempt from CGMP requirements in section 501(a)(2)(B). 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 of the drug products they compound.

The guidance, *For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, lists the conditions that are set forth in section 503B of the FD&C Act.

2. Compounding, Generally

Compounded drug products can serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product, such as a patient who has an allergy and needs a medication to be made without a certain dye, or an elderly patient or a child who cannot swallow a tablet or capsule and needs a medicine in a liquid dosage form that is not otherwise available, or for appropriate pediatric or weight-based dosing. Drug products for identified individual patients can be compounded consistent with section 503A by licensed pharmacists in State licensed pharmacies and Federal facilities, or by licensed physicians. Drug products can also be compounded by outsourcing facilities under section 503B of the FD&C Act.

In general, when a compounded drug product is clinically necessary for a patient, a prescriber writes a prescription for a compounded drug product, and the patient brings the prescription to a pharmacy, where a licensed pharmacist fills the prescription. In an inpatient setting, such as in a hospital, a prescriber may write an order for a compounded drug product on a patient's health record (e.g., chart). In an office setting, a physician may make an entry or order in a patient's health record that the physician compounded a drug in the office for administration to his or her patient after the patient presents at the physician's office with a clinical need for the compounded drug.

In other cases, based on a history of receiving prescriptions for identified individual patients, in the context of an established relationship with the patient or the practitioner who writes the prescription, a pharmacist may compound a drug product before receipt of a prescription for an identified individual patient in anticipation of receiving such a prescription. The pharmacist then provides the drug product to a patient or a prescriber upon receipt of a prescription. Similarly, based on the amount of the compounded drug that the physician has historically administered or dispensed to his or her patients, a physician may compound a drug product to hold in his or her office in anticipation of patients in his or her practice presenting with a need for the compounded drug,. The physician then administers or dispenses the compounded drug to his or her patients after making an entry in the patients' health records.

Sometimes, it is necessary for health care practitioners in hospitals, clinics, offices, or other settings to have certain compounded drug products on hand that they can administer to a patient who presents with an immediate need for the compounded drug product. For example, if a patient presents at an ophthalmologist's office with a fungal eye infection, timely administration of a compounded antifungal medication may be critical to preventing vision loss. In such a case, the ophthalmologist may need to inject the patient with a compounded drug product immediately, rather than writing a prescription and waiting for the drug product to be compounded and shipped to the prescriber.[3]

In other cases, compounded drug products may need to be administered by a health care practitioner in his or her office because it would not be safe for the patient to take the drug home for self-administration, and it would be more convenient for the physician to have the drug in his

[3] Such compounding would be subject to all of the conditions of section 503A or 503B, including provisions concerning compounding drug products that are essentially copies of commercially available drug products (section 503A(b)(1)(D)) or drug products that are essentially copies of approved drugs (section 503B(a)(5)).

or her office to administer immediately upon diagnosis, rather than asking the physician to order the drug and have the patient return to the health care practitioner for administration.

3. Risks Associated with Compounded Drug Products

Although compounded drugs can serve an important need, they pose a higher risk to patients than FDA-approved drugs. Compounded drug products are not FDA-approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality. In addition, licensed pharmacists and licensed physicians who compound drug products in accordance with section 503A are not subject to CGMP requirements. Furthermore, FDA does not interact with the vast majority of licensed pharmacists and licensed physicians who compound drug products and seek to qualify for the exemptions under section 503A of the FD&C Act for the drug products they compound (see section 3, below) because these compounders are not licensed by FDA and generally do not register their compounding facilities with FDA. Therefore, FDA is often not aware of potential problems with their compounded drug products or compounding practices unless it receives a complaint such as a report of a serious adverse event or visible contamination.

In 2012, contaminated injectable drug products that a compounding pharmacy shipped to patients and health care practitioners across the country caused a fungal meningitis outbreak that resulted in more than 60 deaths and 750 cases of infection.[4] This was the most serious of a long history of outbreaks associated with contaminated compounded drugs. Since the 2012 fungal meningitis outbreak, FDA has investigated numerous other outbreaks and other serious adverse events, including deaths, associated with compounded drugs that were contaminated or otherwise compounded improperly. For example, patients have been hospitalized after receiving compounded non-sterile drugs that were hundreds or even thousands of times their labeled strength.[5]

FDA has also identified many pharmacies that compounded drug products under insanitary conditions whereby the drug products may have been contaminated with filth or rendered injurious to health, and that shipped, sometimes in large amounts, the compounded drug products made under these conditions to patients and health care providers across the country.[6] The longer a compounded sterile drug product that has been contaminated is held by a pharmacist or physician before distribution,[7] or held in inventory in a health care facility before administration, the greater the likelihood of microbial proliferation and increased patient harm. Because of these and other risks, the FD&C Act places conditions on compounding that must be met for compounded drugs to qualify for the exemptions in section 503A. These conditions include:

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[4] See http://www.cdc.gov/HAI/outbreaks/meningitis.html.

[5] See, for example, http://www fda.gov/Drugs/DrugSafety/ucm474552 htm

[6] See FDA actions, including warning letters and injunctions, related to insanitary conditions at compounding facilities, on FDA's website at http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771 htm

[7] *Distribution* means that the compounded drug has left the facility in which it was compounded. As used in this guidance, *distribution* includes dispensing a drug directly to a patient.

- compounding is for an identified individual patient,
- drugs compounded in advance of receiving prescriptions are compounded only in limited quantities, and
- drugs are distributed pursuant to a valid patient-specific prescription.

These conditions are meant to help ensure that compounding under section 503A is based on individual patient needs, and that entities purportedly operating under section 503A are not actually operating as conventional manufacturers.

B. The Prescription Requirement in Section 503A(a) of the FD&C Act

A compounded drug product may be eligible for the exemptions under section 503A of the FD&C Act only if it is, among other things, "compounded for an identified individual patient based on the receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient." To qualify for the exemptions under section 503A, the drug product must also be compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or by a licensed physician (section 503A(a)).

Section 503A(a) describes two situations in which a drug product can be compounded: (1) based on the receipt of a valid prescription order for an identified individual patient (section 503A(a)(1)); or (2) in limited quantities before the receipt of a valid prescription order for an identified individual patient (section 503A(a)(2)). As discussed further in section III.C of this guidance document, section 503A does not provide for distributing a compounded drug product before receiving a valid prescription order for an identified individual patient.

The *prescription requirement* under section 503A is a critical mechanism to distinguish compounding by a licensed pharmacist or licensed physician from conventional manufacturing, and to ensure that drug products compounded under section 503A, which are not FDA-approved, are not subject to the requirement that labeling bear adequate directions for use, and are not subject to CGMP requirements, are provided to a patient only based on individual patient need.

The prescription requirement is also an important factor that distinguishes compounding by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or by a licensed physician under section 503A from compounding by an outsourcing facility under section 503B of the FD&C Act. Section 503B states that an outsourcing facility may or may not obtain prescriptions for identified individual patients (section 503B(d)(4)(C)). Outsourcing facilities, which are subject to CGMP requirements and other important conditions, can compound drug products to fulfill the needs described in section II.A.2 for health care practitioners to have drug products on hand that are not compounded for identified individual patients.

1. Compounding After Receipt of a Valid Prescription Order

As described in section II.A.2, a prescriber may write a prescription for an identified individual patient who needs a compounded drug product. In most cases, either the prescriber or the patient

will then bring or send the prescription to the pharmacy, where the pharmacist will compound the drug product for the patient and provide it to the prescriber or patient according to the prescription. For a patient in an inpatient setting, a prescriber may place an order in the patient's health record (e.g., chart) for a compounded drug product, which will likely be provided by the health care facility pharmacy. In an office setting, a physician may compound a drug after making a notation in the health record of a patient in his practice who presents with a need for the compounded medication. These types of compounding are covered under section 503A(a)(1) of the FD&C Act,[8] which provides for compounding by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or a licensed physician, on the prescription order for an individual patient made by a licensed physician or other licensed practitioner authorized by state law to prescribe drugs.

2. Compounding Before Receipt of a Valid Prescription Order

Sometimes, based on a history of receiving prescriptions for a particular drug product to be compounded for an identified individual patient, and in the context of an established relationship with a particular prescriber or patient, a pharmacist or physician will compound a batch of drugs in anticipation of receiving another patient-specific prescription. The compounder then provides the drugs to a patient or health care provider when a prescription for an identified individual patient is received. This is known as *anticipatory compounding*. Section 503A(a)(2) of the FD&C Act provides for compounding by a licensed pharmacist or licensed physician in "limited quantities before the receipt of a valid prescription order for such individual patient" if:

- The compounding is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the human drug product;

and

- The orders have been generated solely within an established relationship between the licensed pharmacist or licensed physician and either such patient for whom the prescription order will be provided or the physician or other licensed practitioner who will write such prescription order.

Anticipatory compounding can be beneficial because larger batch sizes can increase efficiency and reduce the likelihood of human error that is associated with compounding many small batches of a drug product after the receipt of individual prescriptions for the same drug. However, anticipatory compounding also has risks. For example, if a problem occurs during compounding, such as contaminating a drug product that is supposed to be sterile, or producing subpotent or superpotent sterile or non-sterile drugs, it could affect numerous patients, and not just one. Because drug products compounded in accordance with section 503A are exempt from CGMP requirements, there is an inherently greater chance of a production mistake or

[8] If applicable state and federal requirements are met, outsourcing facilities can also compound drug products pursuant to prescriptions for identified individual patients under section 503B of the FD&C Act. However, that is not the subject of this guidance document.

contamination. Restricting anticipatory compounding to limited quantities serves to limit the number of patients likely to be affected if there are drug product mix-ups or contamination.

The limitations on anticipatory compounding in section 503A (i.e., compounding must be in "limited quantities" and based on an "established relationship") help to protect patients from product quality issues.

These limitations on anticipatory compounding also help to distinguish licensed pharmacists or licensed physicians compounding drug products under section 503A for individual patients from conventional manufacturers, who generally produce larger quantities of drugs that are distributed without a prescription.

The anticipatory compounding limitations also differentiate licensed pharmacists and licensed physicians compounding under section 503A from compounders registered as outsourcing facilities under section 503B of the FD&C Act. As explained above, outsourcing facilities are subject to increased Federal oversight and quality standards, including CGMP requirements, which reduce the risks of quality problems such as production mistakes or contamination. Under section 503B, an outsourcing facility can distribute compounded drug products to health care facilities and health care practitioners without first receiving prescriptions for identified individual patients.

With these principles in mind, FDA sets forth its policy with regard to the prescription requirement in section 503A.

III. POLICY

A. Receipt of a Valid Prescription Order or a Notation Approved by the Prescriber Under Section 503A

For purposes of section 503A(a), a *valid prescription order* for a compounded drug product means a valid prescription order from a licensed physician or other licensed practitioner authorized by state law to prescribe drugs (prescriber). It also includes a valid order or notation made by a prescriber in a patient's health record (e.g., chart) in an inpatient setting, and a valid order or notation by a physician who compounds a drug for his or her own patient documented in that patient's health record.[9]

To meet the prescription requirement, a prescription must identify the patient for whom the drug has been prescribed. If the identity of the patient is not given or is not clear, it will not satisfy

[9] Prescription orders that are not valid would not satisfy the prescription requirement in section 503A and cannot serve as the basis for anticipatory compounding. See, in addition, section 301(ccc)(2), which states that, with respect to a drug to be compounded pursuant to section 503A or 503B, the intentional falsification of a prescription, as applicable, is a prohibited act.

this requirement. For example, a prescription would not satisfy the requirement if it is written for the prescriber, when the prescriber is not also the patient.[10]

B. When a Drug Can Be Compounded Under Section 503A

1. Compounding After Receipt of a Valid Prescription Order

Unless a drug product is compounded in limited quantities before the receipt of a valid prescription order under the conditions described in section 503A(a)(2) of the FD&C Act, which are also described in section III.B.2 of this guidance, to qualify for the exemptions under section 503A, the drug product must be compounded *after* the licensed pharmacist or licensed physician receives a valid prescription order for an individual patient. We understand this to be compounding "on" the receipt of a valid prescription order, as provided in section 503A(a)(1).[11]

2. Compounding Before Receipt of a Valid Prescription Order

If a drug product is not compounded after the receipt of a valid prescription order for an identified individual patient as described in section 503A(a)(1) of the FD&C Act and section III.B.1 of this guidance, the drug product can be compounded under section 503A of the Act by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient (section 503A(a)(2)(A)), if all of the conditions of section 503A are met, including the following conditions:

- The compounding is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the human drug product; and

- The orders have been generated solely within an established relationship between the licensed pharmacist or licensed physician and either such patient for whom the prescription order will be provided or the prescriber who will write such prescription order[12] (see section 503A(a)(2)(B)).

This means that anticipatory compounding under section 503A is done in limited quantities, based on an expectation that the licensed pharmacist or licensed physician will receive a patient-specific prescription for the particular drug product, written for a patient or by a prescriber with whom the compounder has a relationship.

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[10] In addition, for a notation to serve as a basis for compounding under section 503A, the notation must document the prescriber's determination that a compounded drug is necessary for the identified patient (section 503A(a)). FDA intends to describe its policies regarding this provision in a future policy document.

[11] This includes a physician compounding a drug for his or her own patient after writing a prescription order (e.g., an order written in the patient's chart) for the compounded drug.

[12] When a physician compounds drugs for his or her own patients, FDA considers the "established relationship" provision of section 503A(a)(2) to have been satisfied because the licensed physician and the "prescriber who will write such prescription order" are the same individual.

At this time, as an interim compliance policy, we do not intend to consider whether a compounder has exceeded the limited quantity[13] condition in section 503A(a)(2) if:

- The compounder holds for distribution[14] no more than a 30-day supply of a particular compounded drug product (i.e., units of a compounded drug product that the compounder believes it will distribute over a 30-day period) to fill valid prescriptions it has not yet received; and

- The amount of the supply of a particular compounded product is based on the number of valid prescriptions that the compounder has received for identified individual patients in a 30-day period over the past year that the compounder selected.

Under this policy, if a compounder does not exceed the quantities described above, FDA does not intend to determine whether anticipatory compounding was based on the expectation that the compounder would receive another prescription for the drug product for the same patient or from the same prescriber with whom the compounder has a history. FDA also contemplates that a compounded drug product might be distributed to any patient or prescriber who presents a valid prescription for an identified individual patient for the compounded drug product.[15]

The following examples illustrate FDA's policy on anticipatory compounding under section 503A(a)(2):

- A compounder regularly receives valid prescription orders from a particular prescriber or prescribers, or for a particular patient or patients, for compounded drug X. The highest number of units of drug X for which the compounder has received valid patient-specific prescriptions in a 30-day period in the last year is 500 units. Compounding up to 500 units of drug X in advance of receiving prescriptions for the drug, and holding no more than that amount to fill new valid patient-specific prescriptions as the compounder receives them, would be consistent with this policy.[16]

- A compounder regularly receives valid prescription orders from a particular prescriber or prescribers, or for a particular patient or patients, for compounded drug

[13] The *limited quantities* policy, which relates to the amount of inventory held by the compounder, does not alter the product's BUD. For example, if the BUD for the product is 9 days, the compounder should not produce more units than can be distributed pursuant to valid prescriptions and used within 9 days.

[14] A drug product *for distribution* does not include drug product that is being held pending receipt of the results of release testing such as sterility testing.

[15] For example, in an inpatient setting, the "established relationship" may be between the prescriber who writes an order for a compounded drug product in a patient's health record, and the compounder who produces the drug product.

[16] In this example, it would be consistent with FDA's policy if, after distributing 200 units of drug X pursuant to valid patient-specific prescriptions, the compounder produces up to 200 additional units of drug X so that the total number of units that the compounder is holding for distribution returns to 500 units.

X. As of August 1, 2016, the highest number of units of drug X for which the compounder has received such valid patient-specific prescriptions in a 30-day period between August 1, 2015, and August 1, 2016, is 500 units, which were received between July 1, 2016, and July 30, 2016. Based on this 30-day reference period, the compounder produces 500 units of drug X in advance of receiving prescriptions for the drug, and holds no more than that amount to fill new patient-specific prescriptions as the compounder receives them. However, between July 15, 2016, and August 15, 2016, the compounder receives valid patient-specific prescriptions for 750 units of compounded drug X. Therefore, based on this new reference period, on August 16, 2016, the compounder produces up to 750 units of drug X in advance of receiving prescriptions for the drug, and holds no more than that amount to fill new valid patient-specific prescriptions as the compounder receives them. This would be consistent with FDA's policy on anticipatory compounding.

- A physician who compounds drugs for his or her own patients routinely sees patients who need compounded drug X. The highest number of units of drug X that the physician has dispensed or administered to patients after making a notation in the patients' charts in a 30-day period in the last year is 500 units. Compounding up to 500 units of drug X in advance of making such notations in patients' charts (i.e., before patients present at the physician's office with a need for the compounded drug), and holding no more than that amount to dispense or administer to patients, would be consistent with this policy.

C. When a Compounded Drug Product Can Be Distributed Under Section 503A

Compounding under section 503A(a) must be "for an identified patient based on the receipt of a valid prescription order" – either "on the receipt of a prescription order for such individual patient" or, under certain conditions, "before the receipt of a valid prescription order for such individual patient." This means that for each drug compounded under section 503A, the compounder must obtain a valid patient-specific prescription order. We therefore understand that the compounder can distribute compounded drugs under section 503A only pursuant to such a valid patient-specific prescription (i.e., the compounder receives a valid patient-specific prescription before the compounded drug product leaves the compounding facility). We recognize that some state boards of pharmacy may authorize the writing of prescriptions that do not include individual patient names. Such prescriptions, however, do not meet the requirement of a patient-specific prescription in section 503A. Under section 503B, outsourcing facilities can fill such prescriptions if they meet the requirements of applicable state and Federal laws.

D. Compounding Office Stock/ Compounding for Office Use

As discussed in section II.A.2 of this guidance, some compounded drug products are kept as office stock/ for office use by hospitals, clinics, or health care practitioners to administer to patients who present with an immediate need for a compounded drug product. Hospitals, clinics, and health care practitioners can obtain non-patient-specific compounded drug products from

outsourcing facilities registered under section 503B.[17] Outsourcing facilities, which are subject to CGMP requirements, FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that provide greater assurance of the quality of their compounded drug products, may, but need not, obtain prescriptions for identified individual patients prior to distribution of compounded drug products (section 503B(d)(4)(C)).[18] Therefore, outsourcing facilities can compound and distribute sterile and non-sterile[19] non-patient-specific drug products to hospitals, clinics, and health care practitioners for office use.[20]

Section 503A(a)(2) provides a pathway for anticipatory compounding in limited quantities. A licensed pharmacist or licensed physician can compound a drug product in advance of receiving a valid prescription order for an identified individual patient, in accordance with the conditions described in section 503A(a)(2) of the FD&C Act, to have a supply of the drug product ready to provide to a patient or prescriber (or, in the case of a physician, to administer to a patient) when a patient-specific prescription order is presented for the compounded drug product. This can reduce the time it would take for a compounded drug product to be made available to a patient upon receipt of a valid prescription order for that patient.

[17] See also FDA's draft guidance, *Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act*, which, when final, will describe FDA's policies regarding the application of section 503A of the FD&C Act to drug products compounded for use within a hospital or health system.

[18] Although an outsourcing facility may send prescription drugs to health care facilities without obtaining prescriptions for identified individual patients, drugs produced by outsourcing facilities remain subject to the requirements in section 503(b) of the FD&C Act. Therefore, an outsourcing facility cannot dispense a prescription drug to a patient without a prescription.

[19] Section 503B defines *outsourcing facility*, in part, as a facility that is engaged in the compounding of sterile drugs (section 503B(d)(4)(A)(i)). Therefore, an entity that only compounds non-sterile drugs does not meet the definition of *outsourcing facility*. An outsourcing facility may engage in non-sterile compounding provided that it also engages in the compounding of sterile drugs, and provided that it compounds all of its drugs (both sterile and non-sterile) in accordance with the conditions of section 503B.

[20] Distribution of compounded drug products by outsourcing facilities is subject to the limitations described in section 503B(a)(8), among other conditions.

Attachment 4

Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

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

December 2016
Compounding and Related Documents

Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

Additional copies are available from:
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Center for Drug Evaluation and Research
Food and Drug Administration
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Email: 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

December 2016
Compounding and Related Documents

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Guidance for Industry
Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

I. INTRODUCTION

This guidance explains how facilities that elect to register with FDA as outsourcing facilities are to submit drug product reports, consistent with section 503B of the Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b).[1] Section 503B of the FD&C Act provides that a facility that elects to register with FDA as an outsourcing facility must report to FDA certain information about the drugs compounded at that outsourcing facility in the form and manner that FDA may "prescribe by regulation or guidance."[2] This guidance describes who must report and what information they must provide and explains that drug compounding reports must be submitted in structured product labeling (SPL) format using FDA's electronic submissions system.

Because Congress gave FDA explicit statutory authority to establish binding requirements in guidance as to the form and manner in which reports are to be prepared, those portions of this guidance relating to such form and manner are not subject to the usual restrictions in FDA's good guidance practices (GGP) regulations (i.e., the requirements that guidances not establish legally enforceable responsibilities and that guidances prominently display a statement of the document's nonbinding effect).[3]

II. BACKGROUND

The DQSA added new section 503B to the FD&C Act. Under section 503B(b), a compounder can elect to become an outsourcing facility by registering with FDA and meeting the other requirements described in section 503B of the FD&C Act.[4] Outsourcing facilities are inspected by FDA on a risk-based schedule and must comply with other provisions of the FD&C Act, such as current good manufacturing practice (CGMP) requirements. Details on other requirements applicable to outsourcing facilities are the subject of separate guidance documents.[5]
A facility that elects to become an outsourcing facility must, at the time of initial registration and twice each year, in June and December, submit to FDA a report identifying the drugs

[1] Section 503B was added to the FD&C Act by the Drug Quality and Security Act (DQSA), Pub. Law No. 113-54, on November 27, 2013.

[2] See section 503B(b)(2)(B).

[3] See 21 CFR 10.115(d) & (i).

[4] See the guidance for industry *Registration for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act*.

[5] 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.

compounded by the facility during the previous six-month period.[6] For each identified drug, the outsourcing facility must provide certain information, which is listed in section 503B(b)(2)(A)(ii).

III. SCOPE OF THIS GUIDANCE

This guidance addresses the provisions in the DQSA regarding the drug reporting requirements for registered outsourcing facilities. Separate guidance documents provide instructions on which facilities should register with FDA as outsourcing facilities and how to do so. FDA has modified its electronic submission system to accept the electronic reports for drugs compounded by registered outsourcing facilities in SPL format. This guidance provides instructions for outsourcing facilities to report compounded drugs in SPL format using FDA's electronic submission system, and supersedes FDA's draft guidance, *Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*.

IV. SUBMITTING COMPOUNDED PRODUCT REPORTS

A. Who Must Report and What Must They Report

Upon initial registration as an outsourcing facility under section 503B and twice each year (in June and December), each registrant must submit a drug product report to FDA.[7] This means that even if the outsourcing facility has not compounded any drug products during the previous six-month period, it must submit a report to FDA indicating that it has not compounded any drug products during the period.

This report must identify all sterile and non-sterile drugs compounded at the outsourcing facility during the previous six-month period and provide all of the following information for each compounded drug[8]:

- The active ingredient and strength of active ingredient per unit
- The source of the active ingredient
- The National Drug Code (NDC) number of the source drug or bulk active ingredient, if available
- The dosage form and route of administration
- The package description
- The number of individual units produced
- The NDC number of the final product, if assigned[9]

For purposes of drug product reporting under section 503B(b), the *strength of the active ingredient per unit* is the strength of the active ingredient per dose of the product.

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[6] Section 503B(b)(2) of the FD&C Act.

[7] Section 503B(b)(2)(A) of the FD&C Act.

[8] Section 503B(b)(2)(A) of the FD&C Act.

[9] Section 503B(b)(2)(A)(ii) of the FD&C Act.

The *NDC number* for both the source drug or bulk active ingredient and any finished drug product to which an NDC has been assigned must be submitted in the standard format of ten numerical digits with dashes separating the three segments, for example, in a 5-4-1, 5-3-2, or 4-4-2 configuration.

The *package description* refers to the description of the smallest individual saleable package of the product for distribution and must include the type of package (e.g., vial, syringe, bottle) and the volume per package (e.g., 100 ml vial, 5 ml syringe, 100 tablets per bottle).

The *number of individual units produced* refers to the number of the smallest individual saleable packages of product for distribution. For example, if a registered outsourcing facility compounds one thousand 100 ml vials of 5 mg/ml of Drug X, the *strength of the active ingredient per unit* is "5 mg/ml," the *package description* is "100 ml vials," and the *number of individual units produced* is "1,000 vials." Similarly, if a registered outsourcing facility compounds 5 mg tablets of Drug Y in one thousand bottles of 100 tablets each, the *strength of the active ingredient per unit* is "5 mg," the *package description* is "bottles of 100 tablets," and the *number of individual units produced* is "1,000 bottles."

B. When to Report

Registered outsourcing facilities must submit a report upon initial registration under section 503B of the FD&C Act and twice each year thereafter, once in June and once in December.[10] Initial drug product reports must identify products compounded during the previous six month period, not including the month in which the facility registers. Semiannual drug product reports submitted between June 1 and June 30 of each year must report products produced during the previous six month period from December 1 through May 31. Semiannual reports submitted between December 1 and December 31 of each year must report drug products compounded during the previous six month period from June 1 through November 30.[11]

C. How to Report

Section 503B(b)(3) of the FD&C Act requires outsourcing facilities to submit drug reporting information by electronic means, unless FDA grants a request for a waiver of such requirement "because use of electronic means is not reasonable for the person requesting the waiver." FDA has modified its electronic submission system to accept electronic submissions in SPL format for drugs compounded by registered outsourcing facilities. Therefore, a facility that elects to register with FDA as an outsourcing facility must submit drug product reporting information using FDA's electronic reporting system and the SPL format, unless FDA has granted the facility a waiver.

FDA has created a new SPL document type category for outsourcing facilities' drug product report submissions. Outsourcing facilities making electronic submissions must submit drug

[11] Section 503B(b)(2)(A) of the FD&C Act.

product reporting information using the document type "Human Compounded Drug Label."[12] Section IV of the guidance for industry *Providing Regulatory Submissions in Electronic Format — Drug Establishment Registration and Drug Listing* provides detailed instructions on how to submit information using SPL. FDA also offers tools and information for creating and submitting SPL files. Additional information can be found at www.fda.gov/edrls.

Although each compounded product could be reported in a separate SPL submission, techniques can be used to simplify and combine the submissions for products with identical active ingredients, different packaging presentations, formulations, and/or strengths. Multiple strengths, package sizes, and source NDC numbers can be reflected in a single SPL submission, which will reduce the number of SPL submissions that a facility will need to submit to FDA. For example, the following table contains data that could be consolidated into a single product SPL submission:

NDC of Final Product, If Assigned (Use FDA 10 digit format with hyphens)	Active Ingredient(s) (Enter each ingredient on a separate line directly beneath)	Strength of Active Ingredient in Final Product	Source NDC for Active Ingredient (Separate multiple source NDCs for the same active ingredient with a semicolon ";")	Dosage Form	Route of Administration	Package description	Number of units produced between 12/1/14 and 5/31/15 (integers only)
12345-678-90	Hydrocortisone	10%	23456-789-90	Cream	Topical	20oz jar	1000
12345-679-91	Hydrocortisone	5%	34567-8901-2	Cream	Topical	40oz jar	1500
12345-679-92	Hydrocortisone	5%	34567-8901-2	Cream	Topical	20oz jar	1200

Furthermore, SPL submissions can be saved, updated, and resubmitted for subsequent reporting periods instead of creating a new submission each time. In addition, any product that is not compounded in a particular 6 month period does not require an SPL submission, even if the outsourcing facility sent in a submission for that product previously.

Whether the product report is for initial registration or the semiannual reporting period, if an outsourcing facility has not compounded any products for the previous six month period, a report explicitly stating so must be submitted.[13] This can be accomplished by creating a single Human Drug Compounded Drug Label SPL file and indicating "No Products to Report" in the data elements section.

FDA does not anticipate many instances in which electronic submission of reporting information will not be reasonable for a facility because the electronic system for submitting the information is an internet-based system accessible to all facilities seeking to register. It is likely to be easier

[12] The SPL document type name "Human Compounded Drug Label" was chosen by the FDA Data Standards Council to distinguish drug product reporting submissions under section 503B from drug registration and listing submissions under section 510.

[13] Section 503B(b)(2)(A).

to report product information electronically than in paper form. However, to apply for a waiver from the requirement to electronically submit drug reporting information, please provide a written request with a complete explanation of why the use of electronic means is not reasonable to the following:

Drug Registration and Listing System Staff
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

or

Email: edrls@fda.hhs.gov

If you are granted a waiver, you will be instructed on how to submit product reporting information.

D. Confidentiality of Reporting Information

Section 503B(b)(1)(B)(i) provides that outsourcing facility registrations are available for inspection to any person so requesting.

Section 503B(b)(2)(C) specifies that product reports are exempt from inspection under section 503B(b)(1)(B)(i) unless the Secretary finds that such an exemption would be inconsistent with the protection of the public health. FDA finds that exempting from disclosure some of the information submitted in product reports would be inconsistent with the protection of the public health, specifically, for each marketed product: the name of the outsourcing facility, address of the outsourcing facility, name of the active ingredient, strength of the active ingredient per unit, dosage form, package description, and NDC of the final product (if assigned). This information is generally required on product labels or publicly available, but publication of this information will facilitate product recalls when they are necessary, and assist the public in finding outsourcing facilities that have compounded certain drug products, particularly drugs in shortage. FDA intends to publish this information on our Web site. FDA does not intend to publish information about a drug submitted in a product report if an outsourcing facility notes in the report that it has not distributed the drug and has not advised any person of its intent or ability to compound the drug.

Attachment 5

Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities

Guidance for Industry

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

January 2017
Compounding and Related Documents

Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities

Guidance for Industry

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Guidance for Industry[1] Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities[2]

This guidance represents 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 is not binding on FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance.

I. INTRODUCTION AND SCOPE

This guidance sets forth the FDA's policy regarding repackaging by State-licensed pharmacies, Federal facilities, and facilities that register 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 the conditions under which FDA does not intend to take action for violations of sections 505, 502(f)(1), 582, and where specified, section 501(a)(2)(B) of the Act, when a State-licensed pharmacy, a Federal facility, or an outsourcing facility repackages human prescription drug products.

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

- Biological products that are subject to licensure under section 351 of the Public Health Service (PHS) Act. The repackaging of biological products subject to licensure under section 351 is addressed in a separate guidance document.[3]
- Repackaging drug products for use in animals.
- Repackaging non-prescription drug products.
- Radiopharmaceuticals.[4]

[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 Federal Food, Drug, and Cosmetic Act.

[3] FDA has issued a draft guidance entitled, *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application*. Once finalized, that guidance will represent FDA's thinking on this topic.

All FDA guidances are available on the Agency's guidance website at http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm. FDA updates guidances regularly. To ensure that you have the most recent version, please check this web page.

[4] FDA has issued draft guidances entitled, *Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Pharmacies and Federal Facilities* and *Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities*. Once finalized, those guidances will represent FDA's thinking on that topic.

- Repackaging by entities that are not State-licensed pharmacies, Federal facilities, or outsourcing facilities (e.g., repackers registered with FDA under section 510 of the FD&C Act).
- Removing a drug product from the original container at the point of care (e.g., patient's bedside) for immediate administration to a single patient after receipt of a valid patient-specific prescription or order for that patient (e.g., drawing up a syringe to administer directly to the patient). FDA does not consider this to be "repackaging," for purposes of this guidance document.
- Upon receipt of a valid patient-specific prescription, a licensed pharmacy removing from one container the quantity of non-sterile drug products[5] (e.g., oral dosage forms) necessary to fill the prescription and placing it in a different container to dispense directly to the patient.
- Investigational new drugs being studied under an investigational new drug application. This guidance does not alter FDA's existing approach to regulating 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 only 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. Repackaging, Generally

FDA regards repackaging as the act of taking a finished drug product 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.[6] 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 drug is manipulated in any other way, including if the drug is reconstituted, diluted, mixed, or combined with another ingredient, that act is not considered repackaging.[7]

Repackaging is performed by a range of entities, including pharmacies and other facilities that specialize in repackaging drug products. FDA is aware that repackaging is done for a variety of

[5] For purposes of this guidance, a sterile drug is a drug that is intended for parenteral administration, an ophthalmic or oral inhalation drug in aqueous format, or a drug that is required to be sterile under Federal or State law.

[6] For example, if tablets are removed from a blister pack and placed into a different container, that would be repackaging. However, if the blister packs containing tablets are placed into a different container for later use (without opening the individual blister packs), that would not be repackaging.

[7] This guidance does not apply to the compounding of drug products. Compounding is addressed in other guidance documents. *See*, for example, the guidances *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act* and *For Entities Considering Whether to Register as Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

reasons including: to meet the needs of specific groups of patients (e.g., pediatric patients or patients receiving drugs for ophthalmic use) who require smaller doses of approved sterile drug products that may not be available commercially; to reduce medication errors associated with drawing up a dose from a vial at the point of patient care; to reduce the availability of drug products that could be abused when controlled substances are left over in a vial after a dose is drawn out; to provide a particular sized container to fit into a particular device to administer the drug (such as a particular pain medication pump); for convenience for the practitioner administering an injection to a patient; to reduce waste and conserve drug supplies; and in some cases to reduce cost. Some repackagers repackage both sterile and non-sterile drug products. Examples of repackaging include tablets and capsules that are repackaged from large containers into smaller containers or blister packs, and creams and lotions are sometimes purchased in bulk and repackaged into smaller tubes or containers.

As part of the drug application review and approval process, FDA evaluates the container closure system and the packaging into which the drug will be placed, as well as the conditions under which the drug will be packaged. The container closure system and packaging can affect the quality of the drug product when it is on the market. In particular, during the approval process, FDA reviews whether the container closure system and the packaging are appropriate for maintaining the stability of the drug product through its expiration date, as long as the container-closure and package are not breached, and the drug is stored according to the conditions specified in the application. For drug products required to be sterile, FDA also considers whether the container closure system and packaging are adequate to ensure that the drug product will remain sterile until its expiration date, as long as the container closure is not breached and the drug product is stored appropriately.

When a drug product is repackaged, its characteristics may change in ways that have not been evaluated during the FDA approval process and that could affect the safety and efficacy of the drug product. Improper repackaging of drug products can cause serious adverse events. Of particular concern is repackaging of sterile drug products, which are susceptible to contamination and degradation. For example, failure to properly manipulate sterile drug products under appropriate aseptic conditions could introduce contaminants that could cause serious patient injury or death. Repackaging practices that conflict with approved product labeling could result in drug product degradation and adverse events associated with impurities in the product or lack of efficacy because the active ingredient has deteriorated.

B. Regulatory Framework for Repackaging

Repackaged drug products are generally not exempt from any of the provisions of the FD&C Act related to the production of drugs. For example, repackaged drug products are generally subject to the premarket approval, misbranding, adulteration, and drug supply chain security provisions of the FD&C Act, including section 505 (concerning new drug applications),[8] section 502(f)(1)

[8] *But 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).

(concerning labeling with adequate directions for use), section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP)), and section 582 (concerning drug supply chain security).

Drugs that are repackaged are not subject to sections 503A and 503B of the FD&C Act.[9] Therefore, drug products repackaged by State-licensed pharmacies, Federal facilities, or outsourcing facilities are not eligible for the exemptions provided under those sections. In this guidance, FDA describes the conditions under which it does not intend to take action regarding violations of certain requirements of the FD&C Act, in the context of drug repackaging.

III. POLICY

A. General Policy[10]

As discussed above, repackaged drug products are generally subject to the adulteration, misbranding, and approval provisions of the FD&C Act.[11] FDA does not intend to take action for violations of sections 505, 502(f)(1), and 582 if a State-licensed pharmacy, a Federal facility, or an outsourcing facility repackages drug products in accordance with the conditions described below, and any applicable requirements.[12, 13] In addition, FDA does not intend to take action for violations of section 501(a)(2)(B) of the FD&C Act if the drug product is repackaged by a State-licensed pharmacy or a Federal facility in accordance with the conditions described below, and any applicable requirements.[14]

The conditions referred to in the preceding paragraph are as follows:

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[9] Section 503A of the FD&C Act exempts compounded drug products from sections 505, 502(f)(1), and 501(a)(2)(B) of the FD&C Act provided certain conditions are met, including that the drug product is compounded pursuant to a valid prescription for an individually identified patient from a licensed practitioner. The Drug Quality and Security Act added a new section 503B to the FD&C Act. Under section 503B(b), a compounder can register as an outsourcing facility with FDA. Drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility qualify for exemptions from the FDA approval requirements in section 505 of the FD&C Act, the requirement to label drug products with adequate directions for use under section 502(f)(1) of the FD&C Act, and the Drug Supply Chain Security Act requirements in section 582 of the FD&C Act, if the conditions in section 503B are met. Drug products compounded in outsourcing facilities are not exempt from CGMP requirements under section 501(a)(2)(B).

[10] Portions of this guidance are shaded in gray to indicate that they constitute collections of information that are subject to review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

[11] *See* footnote 8.

[12] 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.

[13] FDA is considering the applicability of the policies described in this guidance to hospitals and health systems and intends to address these issues in separate guidance.

[14] For purposes of the applicability of the conditions in this guidance document, references to a State-licensed pharmacy or Federal facility do not include a facility that is registered as an outsourcing facility under section 503B of the FD&C Act.

1. The drug product that is being repackaged is a prescription drug product that:

   a. is approved under section 505 of the FD&C Act, or

   b. is an unapproved drug product that appears on the drug shortage list in effect under section 506E of the FD&C Act, and the repackaged drug product is distributed during any period in which it is listed on that drug shortage list or during the 30 days following such period.

2. The drug product is repackaged in a State-licensed pharmacy, a Federal facility, or an outsourcing facility.

3. The drug product is repackaged by or under the direct supervision of a licensed pharmacist.

4. If the drug product is repackaged in a State-licensed pharmacy or a Federal facility, it is distributed[15] only after the receipt of a valid prescription for an identified, individual patient (including a written order or notation in a patient's chart in a health care setting) directly from the prescribing practitioner or patient.[16] This condition does not apply to drug products repackaged in an outsourcing facility.[17]

5. Except as provided below for a single-dose vial, the drug product is repackaged, stored, and shipped in a way that does not conflict with approved drug product labeling.[18]

   For a drug product that is packaged in a single-dose vial that is repackaged into multiple units, the drug product is repackaged in a way that does not conflict with the

[15] "Distributed" means that the repackaged drug product has left the facility in which it was repackaged.

[16] FDA is considering the applicability of this condition to certain non-sterile drug products repackaged by State-licensed pharmacies for distribution to long-term care facilities, and intends to revise this guidance or issue separate guidance to address this issue. During this interim period, FDA does not intend to apply this condition to non-sterile drug products repackaged by State-licensed pharmacies for use in long-term care facilities.

[17] Note, however, that drugs produced by outsourcing facilities remain subject to the requirements in section 503(b) of the FD&C Act. Therefore, a prescription drug cannot be dispensed to a patient without a prescription.

[18] If the approved labeling contains instructions for handling or storage of the product, the drug product is repackaged in accordance with those instructions. Otherwise, the repackaging would be considered to be in conflict with the approved labeling. For example, the approved labeling for propofol states that "propofol undergoes oxidative degradation in the presence of oxygen and is therefore packaged under nitrogen to eliminate this degradation path", and it states, "Do not freeze." Therefore, exposing propofol to oxygen during the repackaging process or freezing it would be in conflict with the approved labeling. In contrast, the labeling of propofol is silent on the type of container into which it can be packaged. Therefore, packaging it into an appropriate container would not conflict with the approved labeling. Also note that section 502(g) of the FD&C Act states that a drug is misbranded if it is a drug that is recognized in an official compendium and among other things it is not packaged as prescribed therein.

approved labeling, except for the statements designating the product as a single-dose or single-use product and related language (e.g., discard remaining contents).[19]

6. The container into which the drug product is repackaged is suitable for storage of the drug product through its beyond-use-date (BUD).[20]

7. If the labeling for the approved drug product being repackaged includes storage and/or handling instructions (e.g., protect from light, do not freeze, keep at specified storage temperature), the labeling for the repackaged drug product specifies the same storage conditions.

8. The repackaged drug product is assigned a BUD[21,22] as described below, unless literature or other scientific information suggests that a shorter BUD would be appropriate, in which case a shorter BUD is assigned consistent with such scientific information. The BUD timeframes in this condition begin from the time in which the container of the original drug product to be repackaged is punctured or otherwise opened.

    a. **Sterile drug products repackaged by State-licensed pharmacies or Federal facilities:**

        i. **FDA-approved drug product with a specified in-use time**: If the drug product being repackaged is an FDA-approved drug product that specifies in the labeling a time within which the opened product is to be used (an "in-use" time), the repackaged drug product is assigned a BUD (1) that is established in accordance with the in-use time on the drug product being repackaged; or (2) that is the expiration date on the drug product being repackaged, whichever is shorter.[23]

[19] This condition would not be satisfied if a drug product repackaged from a single-dose vial is repackaged in a way that conflicts with other language in the approved labeling (e.g., regarding storage conditions).

[20] For example, for State-licensed pharmacies and Federal facilities, information provided by the container's manufacturer could indicate that the container is suitable for drug products repackaged in accordance with this condition. For outsourcing facilities, CGMP requirements address container suitability and drug stability.

[21] The BUD is the date beyond which a drug product should not be used.

[22] FDA does not intend to take action against an outsourcing facility for assigning a BUD to be used as an expiration date in lieu of conducting stability studies required under 21 CFR part 211 for its repackaged drug products if the outsourcing facility assigns a BUD consistent with this condition.

[23] For example, if an approved drug product that includes a 3-day in-use time and an expiration date of January 15, 2017, on the label is repackaged on January 1, 2017, the applicable BUD for the repackaged drug product would be January 4, 2017, because the labeled in-use time of 3 days is shorter than the time until the labeled expiration date of the drug product (14 days). If the drug product is repackaged on January 14, 2017, the applicable BUD for the repackaged drug product would be January 15, 2017, because the time until the labeled expiration date of the approved drug product is 1 day, which is shorter than the labeled 3-day in-use time.

ii. **FDA-approved drug product without an in-use time or unapproved drug product**: If the drug product being repackaged is an FDA-approved drug product whose labeling does not specify an in-use time, or if it is an unapproved drug product on the FDA drug shortage list (which does not have an in-use time reviewed by FDA as part of the drug approval process), the repackaged drug product is assigned a BUD (1) that is established in accordance with the proposed revision to USP Chapter <797> published in the Pharmacopeial Forum (PF) 41(6) [Nov.–Dec. 2015] on November 2, 2015,[24] or (2) that is the expiration date on the drug product being repackaged, whichever is shorter.

b. **Sterile drug products repackaged by outsourcing facilities:**

The outsourcing facility assigns a BUD as described in the guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*.[25]

c. **Non-sterile drug products repackaged by State-licensed pharmacies, Federal facilities, or outsourcing facilities:**[26]

i. **FDA-approved drug product with a specified in-use time**: If the drug product being repackaged is an FDA-approved drug product that specifies in the labeling an "in-use" time, the repackaged drug product is assigned a BUD (1) that is established in accordance with the in-use time on the drug product being repackaged; or (2) that is the expiration date on the drug product being repackaged, whichever is shorter.

ii. **FDA-approved drug product without an in-use time or unapproved drug product**:[27]

[24] Once USP has considered the public comments that it received and finalizes the revised Chapter <797>, FDA intends to evaluate whether condition 8 should refer to the updated chapter or BUDs that are different than those included in final Chapter <797>. Although USP Chapter <797> addresses *compounded* sterile preparations, many of the same principles for conditions and practices to assure sterility and stability of compounded drug products, such as the requirement to maintain a sterile environment, engage in appropriate sterile processing techniques, and assign the appropriate BUD to the product, also apply to repackaged sterile drug products to help assure their quality is not compromised during and after the repackaging operation.

[25] The longer BUDs set forth for outsourcing facilities reflect that conditions maintained to comply with CGMP requirements provide greater assurance of the quality of manufacturing operations and the products that are produced at the facility, and that outsourcing facilities are subject to FDA inspections on a risk-based schedule.

[26] In lieu of the BUDs set forth in this condition, outsourcing facilities may establish BUDs for non-sterile drug products that they repackage based on stability studies conducted in accordance with 21 CFR Part 211.

[27] The BUDs in this condition are based on the BUDs applicable to non-sterile compounded preparations in USP Chapter <795>.

- For nonaqueous formulations, the BUD does not exceed six months or the expiration date of the drug product being repackaged, whichever is shorter.

- For water-containing oral formulations, the BUD does not exceed 14 days or the expiration date of the drug product being repackaged, whichever is shorter.

- For water-containing topical/dermal and mucosal liquid and semisolid formulations, the BUD does not exceed 30 days or the expiration date of the drug product being repackaged, whichever is shorter.

9. The drug product is repackaged in accordance with the following[28]:

    a. If the drug product is repackaged in a State-licensed pharmacy or a Federal facility:

        i. If it is a non-sterile drug product, it is repackaged in accordance with USP Chapter <795>, except the BUD is as specified in condition 8; or

        ii. If it is sterile drug product, it is repackaged in accordance with USP Chapter <797>, except the BUD is as specified in condition 8.

    b. If the drug product is repackaged in an outsourcing facility, repackaging is conducted in accordance with CGMP requirements.[29]

10. The drug product that is being repackaged 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 ineffective. For purposes of this provision, repackagers should refer to the list of drug products in 21 CFR 216.24, developed for use with sections 503A and 503B of the FD&C Act.

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

12. The repackaged drug product is distributed only in States in which the facility repackaging the drug product meets all applicable State requirements.

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[28] The intention is that the BUDs are set in accordance with condition 8.

[29] *See* the guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*.

13. If the drug product is repackaged by an outsourcing facility:

    a. The label on the immediate container (primary packaging, e.g., the syringe) of the repackaged product includes the following:
        i. The statement "This drug product was repackaged by [name of outsourcing facility]"
        ii. The address and phone number of the outsourcing facility that repackaged the drug product
        iii. The established name of the original drug product that was repackaged
        iv. The lot or batch number of the repackaged drug product
        v. The dosage form and strength of the repackaged drug product
        vi. A statement of either the quantity or volume of the repackaged drug product, whichever is appropriate
        vii. The date the drug product was repackaged
        viii. The BUD as the expiry date for the repackaged drug product
        ix. Storage and handling instructions for the repackaged drug product
        x. The National Drug Code (NDC) number of the repackaged drug product, if available[30]
        xi. The statement "Not for resale," and, if the drug product is distributed by an outsourcing facility other than pursuant to a prescription for an individual identified patient, the statement "Office Use Only", and
        xii. If included on the label of the drug product from which the drug product is being repackaged, 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 11.b.i.

    b. 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:
        i. The active and inactive ingredients, if the immediate drug product label is too small to include this information
        ii. Directions for use, including, as appropriate, dosage and administration
        iii. The following information to facilitate adverse event reporting: www.fda.gov/medwatch and 1-800-FDA-1088.

    c. The drug product 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; strength of the active ingredient(s) per unit; the dosage form and route of administration; the package description; the number

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

of individual units produced; and the NDC number of the repackaged drug product, if assigned.[31]

d. The outsourcing facility reports serious adverse events to FDA that are associated with its repackaged drug products.[32]

B. 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. A drug is misbranded under section 502(o) of the FD&C Act if it was manufactured, prepared, propagated, compounded, or processed in an establishment that is not registered under section 510, or if it was not included on a list required by section 510(j). Pharmacies that repackage drug products 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 of section 510 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,[33] FDA does not intend to take action for violations of section 502(o) of the

[31] FDA has issued a guidance for industry, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. This guidance describes how outsourcing facilities submit drug product reports to FDA. Although that guidance addresses reporting of compounded drug products, outsourcing facilities should follow the same procedure to electronically report the drug products they repackaged.

[32] FDA has issued a 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 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 procedure described in that guidance to electronically report adverse events associated with the drug products they repackaged.

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

FD&C Act for failure to register and list drugs under section 510 for drugs that are repackaged in accordance with this guidance.[34]

[34] FDA has developed this policy because outsourcing facilities that repackage drug products in accordance with this guidance are registered with FDA under section 503B of the FD&C Act and report repackaged drug products to FDA in accordance with condition 13.c.

Attachment 6

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December 30, 2016

RE: CURES 1.0 Decommission

The Department of Justice and the Department of Consumer Affairs are pleased to provide the following update regarding California's Controlled Substance Utilization Review and Evaluation System (CURES).

On **Sunday, March 5, 2017,** the legacy "CURES 1.0" system will no longer be available to users attempting to access the database with unsupported browser software. In December 2015, Attorney General Harris sent a letter to members of the medical community outlining the risks of using unsupported web browsers to access confidential and sensitive patient records. Decommissioning CURES 1.0 is a necessary step towards protecting this information.

The CURES 2.0 system has been live since January 2016 and currently accounts for over 90% of patient activity report requests. As such, the retirement of CURES 1.0 should only affect a small number of CURES users who have unsecure web browsers that do not meet the CURES 2.0 minimum security requirements. The CURES 2.0 system features a significantly improved user experience, cutting-edge analytics for flagging at-risk patients, and other enhancements. This state-of-the-art system requires the use of a modern web browser to help protect against cyber security threats.

To ensure continued access to the CURES database, all remaining 1.0 users must update their web browsers prior to March 5. Users who have *not* updated their browsers will no longer be redirected to the old system but will instead view a message containing information as to why they cannot access the site with an unsecure browser.

The secure browser requirements for CURES 2.0 are as follows:

- Microsoft Internet Explorer, version 11.0 or higher
- Mozilla Firefox
- Google Chrome
- Apple Safari

To learn more, visit oag.ca.gov/cures-pdmp/faqs
For assistance, contact the CURES helpdesk at (916) 227-3843 or cures@doj.ca.gov