Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance

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

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Compounding and Related Documents
Revision 2

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Guidance[1]
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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create any rights for or on 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 as listed in the title page.

I. INTRODUCTION

This guidance announces FDA's intention with regard to enforcement of section 503A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 353a) to regulate entities that compound drugs, now that section 503A has been amended by Congress to remove the advertising and solicitation provisions that were held unconstitutional by the U.S. Supreme Court in 2002 (see section II below). Several parts of section 503A require rulemaking and consultation with a Pharmacy Compounding Advisory Committee to implement. This guidance explains how the provisions will be applied pending those consultations and rulemaking. This guidance also describes some of the possible enforcement actions FDA can bring against individuals or firms that compound drugs in violation of the FD&C Act.

This guidance does not apply to registered *outsourcing facilities* under section 503B of the FD&C Act.[2] Guidance for outsourcing facilities will be issued separately.

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 was prepared by the Office of Compliance, Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] Title I of the Drug Quality and Security Act created a new section 503B of the FD&C Act, entitled "Outsourcing Facilities." *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

II. BACKGROUND

Section 503A was added to the FD&C Act by the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115) (the Modernization Act). Section 503A describes the conditions that must be satisfied for drug products compounded by a licensed pharmacist or licensed physician to be exempt from the following three sections of the FD&C Act: (1) section 501(a)(2)(B) (concerning current good manufacturing practice); (2) section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).[3]

Previously, the conditions of section 503A of the FD&C Act also included restrictions on the advertising or promotion of the compounding of any particular drug, class of drug, or type of drug and the solicitation of prescriptions for compounded drugs. These provisions were challenged in court and held unconstitutional by the U.S. Supreme Court in 2002.[4] Following that decision, in May 2002 FDA issued a compliance policy guide entitled *Pharmacy Compounding* (May 2002 CPG), which described how FDA intended "to address pharmacy compounding of human drugs in the immediate future" as a result of the Supreme Court decision.[5] In 2013, section 503A was amended by the Drug Quality and Security Act (DQSA)[6] to remove the advertising, promotion, and solicitation provisions. As a result, the May 2002 CPG is no longer relevant, and it is necessary to explain FDA's current thinking with regard to section 503A.

The *Federal Register* notice announcing the availability of the draft version of this guidance withdrew the May 2002 CPG as well as the November 1998 guidance for industry entitled *Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act*.[7]

III. POLICY

[3] Section 503A of the FD&C Act and this guidance do not apply to positron emission tomography (PET) drugs as defined in section 201(ii) of the FD&C Act or radiopharmaceuticals (see section 503A(e) of the FD&C Act). Section 503A(e) specifically states that section 503A does not apply to radiopharmaceuticals or to PET drugs as defined in section 201(ii). PET drugs are subject to the current good manufacturing practice requirements of 21 CFR part 212. Section 503A also does not apply to drugs intended for use in animals. The statutory and regulatory provisions governing the compounding of human drug products differ from those governing the compounding of animal drug products. All relevant statutory and regulatory requirements relating to the compounding of animal drug products remain in effect, subject to the requirements of section 512 of the FD&C Act (21 U.S.C. 360b) and 21 CFR part 530.

[4] *See Thompson v. Western States Med. Ctr*., 535 U.S. 357 (2002).

[5] *See* 67 FR 39,409 (June 7, 2002).

[6] *See* Pub. L. No. 113-54 (2013).

[7] 78 FR 72,901 (Dec. 4, 2013).

A drug product intended for use in humans that is compounded in compliance with section 503A and its associated regulations is exempt from the requirements in sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act. However, all other applicable provisions of the FD&C Act remain in effect for compounded drugs, even if the conditions of section 503A are met.

FDA expects state boards of pharmacy to continue their oversight and regulation of the practice of pharmacy, including pharmacy compounding. FDA also intends to continue to cooperate with state authorities to address pharmacy activities that may be violative of the FD&C Act, including section 503A. FDA's enforcement approach with respect to such violations is described in section IV.C., below.

A. Conditions of Section 503A

Under section 503A of the FD&C Act, a compounded drug product is exempt from sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act if it meets the conditions of section 503A of the FD&C Act. Specifically, the compounded drug product qualifies for the exemptions if:

1. The drug product is 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 (section 503A(a) of the FD&C Act).

2. The compounding of the drug product is performed:

    - By a licensed pharmacist in a state licensed pharmacy or a Federal facility, or by 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; or
    - By a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient and:
        - 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
        - those 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 (sections 503A(a)(1) and (2) of the FD&C Act).

3. The drug product is compounded in compliance with the United States Pharmacopoeia (USP) chapters on pharmacy compounding[8] using bulk drug substances, as defined in 21 CFR 207.3(a)(4), that comply with the standards of an applicable USP or National Formulary (NF) monograph, if one exists.

[8] After the Modernization Act was enacted in 1997, the USP moved its chapter on pharmacy compounding to chapter <795> and added chapter <797>, which specifically addresses sterile compounding and is referenced in chapter <795>.

If such a monograph does not exist, the drug substance(s) must be a component of an FDA-approved human drug product. If a monograph does not exist and the drug substance is not a component of an FDA-approved human drug product, it must appear on a list of bulk drug substances for use in compounding developed by FDA through regulation (section 503A(b)(1)(A)(i) of the FD&C Act). See section III.B.2 below for the interim policy for this provision.

4. The drug product is compounded using bulk drug substances that are manufactured by an establishment that is 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) (section 503A(b)(1)(A)(ii) of the FD&C Act).

5. The drug product is compounded using bulk drug substances that are accompanied by valid certificates of analysis for each bulk drug substance (section 503A(b)(1)(A)(iii) of the FD&C Act).

6. The drug product is compounded using ingredients (other than bulk drug substances) that comply with the standards of an applicable USP or NF monograph, if one exists, and the USP chapters on pharmacy compounding[9] (section 503A(b)(1)(B) of the FD&C Act).

7. The drug product does not appear on the list, published at 21 CFR 216.24, that includes drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (section 503A(b)(1)(C) of the FD&C Act). See section III.B.1 below.

8. The licensed pharmacist or licensed physician does not compound regularly or in inordinate amounts any drug products that are essentially copies of commercially available drug products (section 503A(b)(1)(D) of the FD&C Act).

9. The drug product is not a drug product identified by FDA by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product (section 503A(b)(3)(A) of the FD&C Act). See section III.B.3 below.

10. The drug product is compounded in a state that has entered into a memorandum of understanding (MOU) with FDA that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a state agency of complaints relating to compounded drug products distributed outside such state; or, in states that have not entered into such an MOU with FDA, the licensed pharmacist, licensed pharmacy, or licensed physician does not distribute, or cause to be distributed, compounded drug products out of the state in which they are compounded, more than 5% of the total prescription orders dispensed or distributed by such pharmacy

[9] *Id.*

or physician (sections 503A(b)(3)(B)(i) & (ii) of the FD&C Act). See section III.B.4 below for the interim policy for this provision.

B. Provisions of Section 503A That Require Regulations or Other FDA Actions

Specific provisions of section 503A of the FD&C Act require rulemaking or other action by FDA. FDA's policy related to these specific provisions is described below.

1. Withdrawn or Removed List

FDA promulgated a final rule, codified at 21 CFR 216.24, which lists drug products that cannot be compounded because they have been withdrawn or removed from the market because the drug products or components of the drug products have been found to be unsafe or not effective. ***FDA intends to update this list periodically, and expects compounders to comply with the list as it currently exists and with any final updates.***

2. Bulk Drug Substances List

Section 503A(b)(1)(A)(i)(III) of the FD&C Act provides that a drug product can be compounded using bulk drug substances that do not have an applicable USP or NF monograph (section 503A(b)(1)(A)(i)(I) of the FD&C Act) and are not components of FDA-approved drugs (section 503A(b)(1)(A)(i)(II) of the FD&C Act) if the bulk drug substances appear on a list developed by FDA and issued through regulation.

In the Federal Register of April 7, 1998 (63 FR 17,011), FDA invited all interested persons to nominate bulk drug substances for inclusion on the list. In the Federal Register of January 7, 1999 (64 FR 996), FDA published a proposed rule listing bulk drug substances that can be used in pharmacy compounding. In the Federal Register of December 4, 2013 (78 FR 72,841), FDA published a notice withdrawing the 1999 proposed rule and inviting all interested persons to nominate bulk drug substances for inclusion on a list of bulk drug substances that can be used for compounding under section 503A of the FD&C Act. FDA's interim policy concerning bulk drug substances that are not components of drugs approved under section 505 of the FD&C Act or that are not the subject of applicable USP or NF monographs can be found in the guidance, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug and Cosmetic Act*.

3. "Demonstrable Difficulties" for Compounding

Under section 503A(b)(3)(A) of the FD&C Act, a compounded drug product would not qualify for the exemptions provided in subsection (a) if it is identified by FDA through regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of the drug product. In the *Federal Register* of December 4, 2013 (78 FR 72,840), FDA published a notice inviting all interested persons to nominate drug products or categories of drug products for inclusion on a list of drug products that present demonstrable difficulties for compounding (difficult-to-compound list). This provision is not enforceable until FDA promulgates an implementing regulation.

4. Memorandum of Understanding Between FDA and the States

Section 503A(b)(3) of the FD&C Act states that FDA, in consultation with the National Association of Boards of Pharmacy (NABP) will develop a standard MOU for use between FDA and the states that will address the interstate distribution of inordinate amounts of compounded drug products and provide for appropriate investigation by a state agency of complaints relating to compounded drug products distributed outside that state. On January 21, 1999, FDA published a notice in the *Federal Register* announcing the availability of a draft standard MOU, developed in consultation with the NABP. This draft MOU was not finalized. FDA intends to publish a new draft MOU for comment that will replace the January 1999 draft.

Under section 503A(b)(3)(B)(ii), an individual or firm in a state that does not enter into an MOU with FDA that distributes, or causes to be distributed, compounded drug products out of the state in which they are compounded, can compound for interstate distribution outside the state only 5% of the total prescription orders dispensed or distributed by the individual or firm. FDA does not intend to enforce the 5% limit on interstate distribution until after FDA has finalized an MOU and made it available to the states for their consideration and signature. The *Federal Register* notice that will announce the availability of the draft MOU will specify a time period during which the MOU will be made available to the states to sign. After this time period expires, FDA intends to begin enforcing the 5% limit in states that have not signed the MOU.

IV. GUIDANCE ON REGULATORY ACTION

A. Requirements Applicable to Drug Products that Meet the Conditions of Section 503A

As stated above, a compounded drug product intended for use in humans that meets the conditions of section 503A of the FD&C Act and its associated regulations is exempt from the requirements under sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act.

However, individuals and firms may be subject to a warning letter, seizure of product, injunction, and/or criminal prosecution for violations of other requirements of the FD&C Act. Such violations may include, but are not limited to, the following:

1. The drug product must not consist in whole or in part of any filthy, putrid, or decomposed substance, or be prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth or whereby it may have been rendered injurious to health. (Sections 501(a)(1) and (a)(2)(A) of the FD&C Act)

2. If the drug product purports to be a drug that is recognized in an official compendium, its strength must not differ from, and its quality or purity must not fall below, the standards set forth in the compendium, unless the difference is plainly stated on its label. (Section 501(b) of the FD&C Act)

3. For a drug product not subject to section 501(b) of the FD&C Act, the drug's strength must not differ from, and its quality or purity must not fall below, that which it purports to have. (Section 501(c) of the FD&C Act)

4. If the drug product purports to be a drug that is recognized in an official compendium, it must be packaged and labeled as prescribed in the compendium. (Section 502(g) of the FD&C Act)

5. The drug product's labeling, advertising, and promotion must not be false or misleading. (Sections 502(a), 502(bb),[10] and 201(n) of the FD&C Act)

B. Enforcement Action When a Drug Does Not Meet the Conditions of Section 503A

If FDA determines that an individual or firm compounds a drug product that does not meet the conditions of section 503A, then in addition to the violations listed above in section IV.A., the individual or firm that compounds the drug product may also be subject to a warning letter, seizure of product, injunction, and/or criminal prosecution for violations of sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act.[11] Such violations may include, but are not limited to, the following:

1. Producing Adulterated Drugs

In accordance with section 501(a)(2)(B) of the FD&C Act and 21 CFR parts 210 and 211, the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and holding of a drug must conform with current good manufacturing practice (CGMP) requirements. If an individual or firm compounds any drug products that do not meet the conditions of section 503A of the FD&C Act, those drug products would be subject to CGMP requirements.

2. Producing Unapproved New Drugs

In accordance with section 505(a) of the FD&C Act, an individual or firm must not introduce or deliver for introduction into interstate commerce any new drug unless an approved NDA or ANDA is in effect for that drug product. If an individual or firm compounds any drug products that do not meet the conditions of section 503A of the FD&C Act, those drug products would be subject to the new drug approval requirements.

3. Misbranded Drugs

[10] Section 502(bb) was added to the FD&C Act by section 103(b) of the DQSA.

[11] *See Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383, 405 (5th Cir. 2008) ("compounded drugs are in fact 'new drugs' as defined by [21 U.S.C.] § 321(p) but are exempt from the requirements of [21 U.S.C.] §§ 351(a)(2)(B), 352(f)(1), and 355 if and only if they comply with the conditions set forth in [21 U.S.C.] § 353a.").

In accordance with section 502(f)(1) of the FD&C Act and 21 CFR part 201.5, drug products that are not labeled with adequate directions for use are misbranded. If an individual or firm compounds any drug products that do not meet the conditions of section 503A of the FD&C Act, those drug products would be subject to the requirements for adequate directions for use.

In addition to sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act, an individual or firm that compounds any drug products that do not meet the conditions of section 503A of the FD&C Act would be subject to the requirements listed in section IV.A, above, as well as other requirements of the FD&C Act and FDA regulations.

C. Enforcement Approach

Generally, FDA expects to employ a risk-based enforcement approach with respect to violative compounded drugs, giving the highest enforcement priority to compounded drugs and violations of the FD&C Act and FDA regulations that pose the greatest public health risks. However, FDA emphasizes that it need not identify a particular safety problem before pursuing enforcement action.