Guidance

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 the Center for Drug Evaluation and Research (CDER) at the 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)

December 2013
Procedural

Guidance

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

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

or

Office of Policy
Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-4830

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

December 2013
Procedural

TABLE OF CONTENTS

Guidance[1]
Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act

This draft guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the public.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

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 struck down as 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 those provisions will be applied pending those consultations and rulemaking. This guidance also describes some of the possible enforcement actions FDA may 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. Guidance for outsourcing facilities will be issued separately.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents 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 FDA's guidance documents means that something is suggested or recommended, but not required.

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 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

[1] This guidance was prepared by the Office of Compliance, Center for Drug Evaluation and Research at the Food and Drug Administration.

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)).[2]

The conditions of section 503A of the FD&C Act 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.[3] In May 2002, FDA issued a compliance policy guide that described how FDA intended "to address pharmacy compounding of human drugs in the immediate future" as a result of the Supreme Court decision.[4] Now that section 503A has been amended by the Drug Quality and Security Act to remove the advertising, promotion, and solicitation provisions, the May 2002 CPG is no longer relevant, and it is necessary to explain FDA's current thinking with regard to section 503A.

FDA is withdrawing the May 2002 CPG, entitled, *Pharmacy Compounding*, and the November 1998 guidance for industry entitled, *Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act*. FDA had not formally withdrawn the 1998 guidance when the 2002 CPG was issued, but has now done so in the *Federal Register* notice announcing the availability of this guidance.

[2] 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 Code of Federal Regulations (CFR) part 530.

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

[4] *See* 67 Fed. Reg. 39409 (June 7, 2002).

III. POLICY

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. All other applicable provisions of the FD&C Act remain in effect for compounded drugs, however, 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 traditional 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 when:
        - the licensed pharmacist or licensed physician has historically received 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 the 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[5] 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.

   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[6] (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.

[5] 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>.

[6] *Id.*

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

1. Withdrawn or Removed List

FDA promulgated a final rule, codified at 21 CFR 216.24, which lists drug products that may not 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 updates.***

2. Bulk Drug Substances List

Section 503A(b)(1)(A)(i)(III) of the FD&C Act provides that a drug product may 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 Fed. Reg. 17011), FDA invited all interested persons to nominate bulk drug substances for inclusion on the list. In the *Federal Register* of January 7, 1999 (64 Fed. Reg. 996), FDA published a proposed rule listing bulk drug substances that may be used in pharmacy compounding. FDA intends to reconsider the bulk drug substances that were proposed for inclusion on the list and that do not have an applicable USP or NF monograph due to the time lapse since the last proposal. Therefore, FDA plans to seek additional nominations and propose an updated list.

Until a bulk drug substances list is published in the *Federal Register* as a final rule, human drug products should be compounded only using bulk drug substances that are components of drugs approved under section 505 of the FD&C Act, or are the subject of USP or NF monographs.

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. 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 90 days after FDA has finalized an MOU and made it available to the States for their consideration and signature.

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), 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.[7] 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.

[7] *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.").

3. Misbranded Drugs

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.