
Guidance for Industry

Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Procedural 10

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*Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
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DRAFT GUIDANCE FOR INDUSTRY¹

Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act

I. INTRODUCTION

This document provides guidance to drug compounders on how the Food and Drug Administration (FDA) intends to enforce section 503A of the Federal Food, Drug, and Cosmetic Act during the transition to full implementation of that provision.

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) (the Modernization Act). Section 127 of the Modernization Act, which adds section 503A to the Federal Food, Drug, and Cosmetic Act (the act), clarifies the status of pharmacy compounding under Federal law. Under section 503A, drug products that are compounded by a pharmacist or physician on a customized basis for an individual patient may be entitled to exemptions from three key provisions of the act: (1) the adulteration provision of section 501(a)(2)(B) (concerning the good manufacturing practice requirements); (2) the misbranding provision of section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (concerning the approval of drugs under new drug or abbreviated new drug applications). To qualify for these statutory exemptions, a compounded drug product must satisfy several requirements, some of which are to be the subject of FDA rulemaking or other actions.

Section 503A of the act takes effect on November 21, 1998, one year after the date of the enactment of the Modernization Act. FDA is working on several rules and other documents necessary to implement certain provisions of section 503A. This guidance describes FDA's policy

¹ This guidance has been prepared by the Pharmacy Compounding Steering Committee, which operates under the direction of the Office of the Center Director in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on enforcement of section 503A of the Federal Food, Drug, and Cosmetic Act. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, (Internet) <http://www.fda.gov/cder/guidance.htm>.

on enforcement of section 503A until these preliminary implementation efforts, described below, are completed. The provisions of section 503A that are not discussed in this guidance document may be implemented and subject to enforcement beginning on November 21, 1998. However, in the future, FDA intends to provide general regulations to further clarify some of these provisions.

II. THE AGENCY'S ENFORCEMENT PLAN FOR STATUTORY PROVISIONS REQUIRING IMPLEMENTING REGULATIONS OR OTHER AGENCY ACTION

A. Bulk Drug Substances List: Section 503A(b)(1)(A)

Section 503A(b)(1)(A) restricts the universe of bulk drug substances that a compounder may use. The section provides, in relevant part, that every bulk drug substance used in compounding (1) must comply with an applicable and current United States Pharmacopeia (USP) or National Formulary (NF) monograph, if one exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, the bulk drug substance must be a component of an FDA-approved drug; or (3) if a monograph does not exist and the bulk drug substance is not a component of an FDA-approved drug, it must appear on a list of bulk drug substances that may be used in compounding that is developed and issued by FDA through regulation (the bulk drugs list).

To date, 30 bulk drug substances have been nominated and are under consideration for inclusion on the bulk drugs list: bismuth citrate; caffeine citrate; cantharadin; choline bitartrate; diloxanide furoate; dimercapto-1-propanesulfonic acid; ferric subsulfate; ferric sulfate hydrate; glutamine; guaiacol; iodoform; metronidazole benzoate; myrrh gum tincture; phenindamine tartrate; phenyltoloxamine dihydrogen citrate; piracetam; sodium butyrate; taurine; thymol iodide; tinidazole; 4-aminopyridine; betahistine dihydrochloride; cyclandelate; 3,4-diaminopyridine; dinitrochlorobenzene; diphenylcyclopropanone; hydrazine sulfate; pentylenetetrazole; silver protein mild; and squaric acid dibutyl ester. Other bulk drug substances may be nominated in the future for inclusion on the bulk drugs list (see April 7, 1998, call for nominations, 63 FR 17011).

FDA will not have addressed all of the substances nominated for inclusion on the list by the time section 503A of the act becomes effective. In addition, FDA also anticipates that for a period of time after section 503A takes effect, as the compounding community becomes more familiar with the requirements of this provision, additional bulk drug substances will be nominated for inclusion on the list. To make the transition easier for patients and health care practitioners, FDA is adopting the enforcement policy described below.

1. Substances Nominated On or Before November 21, 1999.

For bulk drug substances that have already been nominated for inclusion on the list (the 30 bulk drug substances listed above), or for bulk drug substances that are nominated on or before November 21, 1999 (see April 7, 1998, call for nominations, 63 FR 17011), FDA intends to exercise its enforcement discretion. FDA will not normally take regulatory action against a drug product that has been compounded with a bulk drug substance that has been nominated for inclusion on the bulk drugs list while the substance is being evaluated, as long as the compounding complies with the other effective requirements in section 503A and does not appear to present a significant safety risk. FDA will consider a substance to be under evaluation from the time it is nominated until FDA takes final action by either including the substance on the list published as a final regulation or issuing a letter to the nominator indicating that FDA has decided that the substance should not be included on the list. If FDA determines that a nominated substance should not be used in compounding while it is under evaluation because it appears to present a significant safety risk, the Agency will provide notice that the substance cannot be used in compounding prior to a final determination on its acceptability for use in compounding.

2. Substances Rejected by the Agency and Then Renominated

This exercise of enforcement discretion will not apply to substances that have been nominated and have been determined by the Agency to be unacceptable for use in compounding. Although the Agency will continue to entertain renominations supported by additional information not previously considered by the Agency, the substance may not be used in compounding during the second and subsequent evaluations of the nomination unless and until the substance is added to the bulk drugs list through a final rule.

3. Substances Nominated after November 21, 1999

FDA will continue to entertain nominations for additional bulk drug substances after November 21, 1999. However, drug products compounded using such substances will not qualify for the exemptions described under section 503A of the act unless and until the substance is added to the bulk drugs list through a final rule. FDA believes that this policy strikes an appropriate balance among the needs of patients, the healthcare practitioners, the compounding community, and congressional intent. FDA believes it is appropriate to allow ample time for the compounding community to become aware of the limitations in section 503A(b)(1) concerning the use of bulk drug substances and to nominate those substances that are likely to be included on the bulk drugs list. A one-year period to submit additional nominations, in addition to the year that has already passed, should be sufficient for this purpose. FDA also recognizes that Congress intended that, at some point in time, the requirements for use of bulk drug substances in section 503A(b)(1) would take effect and be enforced. FDA believes that this enforcement policy

appropriately balances these competing considerations.

B. Withdrawn/Removed List: Section 503A(b)(1)(C)

Section 503A(b)(1)(C) of the act prohibits a licensed pharmacist or licensed physician from compounding a drug product using drug products or components of drug products that appear on a list, published by the Agency in the *Federal Register*, of drug products that have been withdrawn or removed from the market because the drug products or the components of the drug products have been found to be unsafe or not effective.

In the *Federal Register* of October 8, 1998 (63 FR 54082), the Agency published a proposed rule listing drug products that have been withdrawn or removed from the market because they were found to be unsafe or not effective. Until this list is finalized and published in the *Federal Register* as a final rule, section 503A(b)(1)(C) of the act will not be implemented or enforced.

C. Demonstrable Difficulties in Compounding: Section 503A(b)(3)(A)

Section 503A(b)(3)(A) of the act provides that a drug product may only be compounded if it is not a drug product identified by 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 products. The Agency is presently developing proposed regulations covering difficult-to-compound drug products. Until final regulations identifying demonstrably difficult-to-compound drug products are issued by the Agency, the provision will not be implemented or enforced by the Agency.

D. Memorandum of Understanding: Section 503A(b)(3)(B)

Section 503A(b)(3)(B) of the act provides that the compounded drug product must be compounded in accordance with either of the following:

1. It is compounded in a State that has entered into a memorandum of understanding with FDA addressing the interstate distribution of inordinate amounts of compounded drug products and providing for investigation by a State agency of complaints related to compounded drug products distributed outside such state.

or

2. It is compounded in a State that has no such memorandum of understanding but the licensed pharmacist, pharmacy, or physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

The section also directs FDA, in consultation with the National Association of Boards of Pharmacy (NABP), to develop a standard memorandum of understanding (MOU) for use by States in complying with these provisions.

In consultation with the NABP, the Agency is currently developing a draft standard MOU on pharmacy compounding that would establish a cooperative program between FDA and State agencies that choose to enter into the MOU regarding the regulation of interstate distribution of compounded drug products. When this process is completed, the Agency will make the draft standard MOU available to the public for comment through publication in the *Federal Register*. Once the comment period has expired, the Agency will finalize the MOU and make it available to the States for their signature. Until at least 90 days after the standard MOU is finalized and made available to the States for their consideration and signature, the Agency intends to exercise its enforcement discretion and will not normally take regulatory action regarding the requirement in section 503A(b)(3)(B) that a licensed pharmacist, pharmacy, or physician distribute or cause to be distributed out of State no more than 5 percent of the total prescription orders dispensed or distributed.